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Report of the Food Quality
Protection Act (FQPA)
Tolerance Reassessment Progress
and Risk Management Decision (TRED)
for Bitertanol

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Date

I. Regulatory Determination

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by the Food Quality Protection Act (FQPA), requires the Environmental Protection Agency (the Agency or EPA) to reassess all the tolerances for registered chemicals in effect on the day before enactment of the FQPA on August 3, 1996. In reassessing these tolerances, the Agency must consider, among other things, aggregate risks from non-occupational sources of pesticide exposure, whether there is increased susceptibility to infants and children, and the cumulative effects of pesticides with a common mechanism of toxicity. When a safety finding has been made that aggregate risks are not of concern, the tolerances are considered reassessed. Existing tolerances associated with bitertanol must be reassessed in accordance with FFDCA, as amended by FQPA.

Bitertanol (active ingredient number 121601) is a postemergence fungicide used to treat black sigatoka leaf spot on banana and plantain. There are no U.S. registrations for bitertanol use; however, there is a tolerance for imported bananas/plantains treated with bitertanol. Therefore, there are no expected ecological, drinking water, occupational or residential exposures in the U.S. Dietary (food) residues on imported bananas and plantains are expected to be the only source of potential exposure to bitertanol; thus, only a dietary (food) risk assessment was conducted for this TRED.

The Agency has evaluated the human health risks associated with bitertanol residues on commodities and has determined that there is a reasonable certainty that no harm will result from exposure to these residues. In making this determination, EPA has considered dietary exposure from food sources of pesticide exposure (the only exposure route) for which there is reliable information. Therefore, the one (1) tolerance for residues of bitertanol on banana (including plantain) is now considered reassessed as safe under Section 408(q) of FFDCA, as amended by FQPA.

The Agency's human health safety finding for the pesticide bitertanol is summarized in *Bitertanol. Revised HED Chapter of the Tolerance Reassessment Eligibility Decision Document (TRED)*, dated November 30, 2005. For further details, please refer to this risk assessment and other technical documents pertaining to the bitertanol TRED, which are available on the Internet at www.regulations.gov under docket number EPA-HQ-OPP-2005-0491 and in the public docket for viewing.

The Agency is issuing this TRED document for bitertanol as announced in a Notice of Availability published in the *Federal Register*. The Agency is providing a 30-day comment period for stakeholders to respond to this risk management decision. If substantive information is received during the comment period that indicates a need to refine any of EPA's assumptions or a need for risk mitigation, then this decision will be modified as appropriate through an amendment to the TRED.

II. Tolerance Reassessment

A. FQPA Assessment Supporting Tolerance Reassessment Decision

The Agency has conducted a human health risk assessment to ensure that the bitertanol tolerance meets the new safety standards established by FFDCA, as amended by FQPA. This risk assessment for bitertanol includes evaluation of potential susceptibility to infants and children, and dietary exposure to adults and children. EPA also considered potential cumulative risks for bitertanol and other substances sharing a common mechanism of toxicity, as well as potential endocrine effects associated with bitertanol.

EPA has determined that risk from exposure to bitertanol is within its own “risk cup.” In other words, EPA is able to conclude today that the tolerance for bitertanol meets the FQPA safety standards. Although the toxicological database had some deficiencies, the database as a whole is adequate for tolerance reassessment. In reaching this determination, the Agency has considered the available information on the potential sensitivity of infants and children, as well as acute and chronic food exposures. Because there are no existing registrations for the use of bitertanol in the U.S., only acute and chronic dietary (food) assessments were conducted for potential exposure to bitertanol *per se* residues in/on imported bananas/plantains. Results of both dietary assessments indicate that the human health risks from these exposures are considered to be within acceptable levels; that is, all assessed risks from exposure to bitertanol “fit” within the individual risk cup for this chemical. The Agency’s risk assessment conclusions are summarized below.

FQPA Safety Factor and Database Considerations. The FFDCA, as amended by the FQPA, directs the Agency to use an additional tenfold (10X) safety factor (SF) to take into account potential pre- and postnatal toxicity and completeness of the database with respect to exposure and toxicity to infants and children. FFDCA authorizes the Agency to modify the 10X safety factor only if reliable data demonstrates that the resulting level of exposure would be safe for infants and children.

In submitted developmental toxicity studies, effects were seen at the same dose levels as maternal toxicity. There was evidence of malformations and post-implantation loss at high doses in developmental toxicity studies, but no quantitative susceptibility and No Observed Adverse Effect Levels (NOAELs) were clearly defined. In rabbits there were three developmental studies which, when combined, clearly delineated developmental toxicity in the rabbit. Although there were some deficiencies in the rat reproduction study, the study is considered acceptable and indicates that there are adequately defined NOAELs and no evidence of susceptibility. There is no residual uncertainty for pre- and postnatal toxicity based on the submitted developmental and reproduction studies.

Because there is no residual uncertainty with respect to pre- and postnatal toxicity based on the submitted developmental and reproduction studies, the Special FQPA SF is reduced to 1X. There is some uncertainty for potential neurotoxicity based on some literature studies. Because acute and subchronic neurotoxicity studies are not available, a 10X database uncertainty factor (UF_{DB}) is retained to account for the lack of data.

Dietary Risks (food). Acute and chronic dietary (food) risk assessments were conducted using Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03). These Tier 1 assessments are based on an assumption of 100% crop treated, the proposed maximum residue tolerance of 0.5 parts per million (ppm) on whole bananas, and a default processing factor of 3.9x (DEEM, Version 7.81) to assess concentration of potential bitertanol residues in dried bananas. Risk to each population group is measured by a population adjusted dose (PAD), which is the dose predicted to result in no unreasonable health effects to any human subpopulation, including sensitive members of such subpopulations. The acute PAD (aPAD) is the dose at which a person could be exposed on any given day, and the chronic PAD (cPAD) is the dose at which a person could be exposed over the course of a lifetime, with no expected adverse health effects. A dietary risk estimate that is less than 100% of the aPAD or cPAD does not exceed EPA's level of concern.

The Agency's Tier 1 acute and chronic dietary risk assessments indicate that dietary risk from bitertanol residues in food are low and below the Agency's level of concern. An acute dietary risk assessment was conducted only for females 13-49 years old, with estimated exposures representing 2% of the aPAD at the 95th exposure percentile. For the general population, no acute dietary endpoint was selected because effects attributable to a single dose were not seen in the available data. Chronic dietary risk assessments were conducted for the general U.S. population and various population subgroups, including exposure to infants and children. The resulting chronic dietary exposure estimates were 9% of the cPAD for the general U.S. population, and 43% of the cPAD for the highest-exposed population subgroup, children 1-2 years old.

Because there are no bitertanol registrations in the U.S., drinking water, occupational and residential exposures to the U.S. population are not anticipated. Therefore, drinking water, occupational, residential and aggregate risk assessments were not conducted.

B. Cumulative Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to bitertanol and any other substances, and bitertanol does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance reassessment action, therefore, EPA has not assumed that bitertanol has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanisms determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

C. Endocrine Disruptor Effects

EPA is required under FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) "may have an effect in humans that is similar to an effect produced by a naturally-occurring estrogen,

or other such endocrine effects as the Administrator may designate.” Following recommendations of its Endocrine Disruptor and Testing Advisory Committee (EDSTAC), EPA determined that there was a scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC’s recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

In the available toxicity studies on bitertanol, there was no estrogen, androgen, and/or thyroid-mediated toxicity. A potential hormonal effect was seen in a subchronic dog study, but not in chronic dog studies. The hormonal effect in the chronic dog studies suggests that the effect was specific to the dogs tested in the subchronic study, and not as a result of bitertanol exposure. However, the reason for the difference in hormonal effect between the dog studies is unknown. When additional appropriate screening and/or testing protocols being considered under the Agency’s EDSP have been developed, bitertanol may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption.

D. Tolerance Summary

Tolerances Listed in 40 CFR §180.457

The existing tolerance for residues of bitertanol *per se*, established under 40 CFR §180.457 is listed in Table 1. The current tolerance expression listed in 40 CFR §180.457 is “beta-([1,1’-biphenyl]-4-yloxy)-alpha-(1,1-dimethylethyl)-1*H*-1,2,4-triazole-1-ethanol.” The Codex Alimentarius Commission has established a maximum residue level (MRL) for bitertanol *per se* in/on bananas at 0.5 ppm. The Agency recommends that the U.S. tolerance expression be revised to 0.5 ppm, to harmonize its tolerances with those established by the Codex Alimentarius Commission. The proposed increased tolerance of 0.5 ppm was included in the dietary assessment, and did not result in any risks of concern. It is EPA’s policy to harmonize its tolerances with the levels established by Codex provided that the Agency has sufficient information to make a determination that the Codex MRLs will be protective of the health of the U.S. public and meet FFDCA standards.

Table 1: Tolerance Summary for Bitertanol			
Commodity	Established Tolerance (ppm)	Reassessed Tolerance (ppm)	Comments [Correct Commodity Definition]
Banana (whole)	0.2 ppm	0.5 ppm	Tolerance should be increased to 0.5 ppm to harmonize with Codex MRLs. [Banana]

III. Data Gaps

The Agency has concluded that the database for bitertanol is substantially complete, but has identified some data gaps. There are no U.S. registrations for bitertanol. A Data Call-In notice for this additional data will not be issued because these data are not expected to change the regulatory conclusions of the bitertanol TRED described in this document.

Although acute and subchronic neurotoxicity data gaps exist, a 10X UF_{DB} has been used in both chronic and acute dietary assessments to account for the absence of these data. Additional missing data pertain to residue field trials. However, the Agency does not view these data as critical to the continuation of the existing tolerance because exposure assumptions used in the risk assessments were highly conservative (i.e., 100% crop treated; default residue concentration factor of 3.9x for dried bananas; and assumption of residues at 0.5 ppm to harmonize with Codex, even though available field trials indicate that maximum residues were detected at less than 0.2 ppm).