



United States
Environmental Protection
Agency

Prevention, Pesticides
and Toxic Substances
(7508C)

EPA 738-R-06-001
January 2006

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

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

Approved By:

Debra Edwards, Ph. D.
Director, Special Review and
Reregistration Division

Date

I. Regulatory Determination

The Federal Food, Drug and Cosmetic Act (FFDCA), as amended by 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 tridemorph must be reassessed in accordance with FFDCA, as amended by FQPA.

Tridemorph (active ingredient number 121401) is a systemic fungicide used to treat black and yellow sigatoka on banana and plantain plants. There are no U.S. registrations for tridemorph use, and as such, the existing tolerance is commonly referred to as an import tolerance. Because there are no U.S. registrations, 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 tridemorph; therefore, only a dietary (food) risk assessment was conducted for this TRED.

The Agency has evaluated the human health risks associated with tridemorph 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 tridemorph 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 tridemorph is summarized in *Tridemorph HED Risk Assessment for Tolerance Reassessment Eligibility Decision (TRED) Document*, dated November 7, 2005. For further details, please refer to this risk assessment and other technical documents pertaining to the tridemorph TRED, which are available on the internet at www.regulations.gov under Docket # EPA-HQ-OPP-2005-0505 and in the public docket for viewing.

The Agency is issuing this TRED document for tridemorph 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 tridemorph tolerance meets the new safety standards established by FFDCA, as amended by FQPA. This risk assessment for tridemorph includes evaluation of potential susceptibility to infants and children and dietary exposure to adults and children. EPA also considered potential cumulative risks for tridemorph and other substances sharing a common mechanism of toxicity, as well as potential endocrine effects associated with tridemorph.

EPA has determined that risk from exposure to tridemorph is within its own “risk cup.” In other words, EPA is able to conclude today that the tolerance for tridemorph 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 exposure. Because there are no existing registrations for the use of tridemorph in the U.S., only acute and chronic dietary (food) assessments were conducted for potential exposure to tridemorph *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 tridemorph “fit” within the individual risk cup for this chemical. The Agency’s risk assessment conclusions are summarized below.

FQPA Safety Factor Considerations. The FFDCA, as amended by the FQPA, directs the Agency to use an additional tenfold (10X) safety factor to take into account potential pre- and post-natal 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 demonstrate that the resulting level of exposure would be safe for infants and children.

The available developmental toxicity information indicates increased quantitative and qualitative susceptibility (increased incidence for developmental anomalies) in rats and increased quantitative susceptibility (reduction in fetal weight) in mice since the developmental findings occurred in the absence of maternal toxicity.

The degree of concern for the prenatal susceptibility effects in rabbits and post-natal susceptibility effects in rats could not be determined when the risk assessment was completed due to data gaps in the toxicological database. Thus, during the preparation of this TRED, to address the potential degree of concern for infants and children, an FQPA safety factor of 10X was retained for both the acute and chronic reference dose derivations to account for uncertainty due to these data gaps. Although a series of toxicity studies, which may address the identified data gaps, were submitted after the risk assessment was completed, the Agency has not conducted a complete review of these data. However, based on a preliminary review of the data,

the Agency is confident that the 10X FQPA safety factor is adequately protective of potential effects to infants and children.

Dietary Risks (food). Acute and chronic dietary (food) risk assessments were conducted using the Dietary Exposure Evaluation Model (DEEM-FCID™, Version 2.03), which use food consumption data from the USDA's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998. In these analyses, the dietary exposure and risk estimates resulting from food intake were determined for the general U.S. population and various population subgroups. The acute and chronic dietary exposure analyses for tridemorph were conducted using unrefined Tier 1 dietary exposure assumptions for all uses. The Tier 1 analysis assumes tolerance level residues, 100% crop treated for all commodities, and DEEM-FCID™ default processing factors for the processed commodities.

Dietary risk to each population group is measured by a population adjusted dose (PAD), which is the reference dose (RfD) adjusted for the FQPA safety factor. RfD is defined as the estimated human exposure level believed to have no adverse impact on human health. For tridemorph, the acute RfD is the No Observed Adverse Effects Level (NOAEL) divided by 1,000X (10X for interspecies extrapolation, 10X for intraspecies variation, and 10X FQPA safety factor due to toxicity data gaps). The acute RfD for tridemorph is based on developmental effects observed in the rat developmental study. An acute RfD was selected for the subpopulation females 13-49 only. An acute RfD was not selected for the U.S. general population or other population subgroups, because no effect attributable to a single (or few) day(s) oral exposure was observed in available animal studies.

Since no acceptable chronic dietary study was available when the risk assessment was completed, the chronic RfD is based on the NOAEL established by a subchronic dietary dog study, which included clinical signs such as change in body weight and histopathology. Since the endpoint is based on the subchronic study, an additional 3X uncertainty factor (UF) was applied for the extrapolation from subchronic to chronic study effects. The chronic population adjusted dose (cPAD) for tridemorph is the RfD divided by the 3,000X (10X for interspecies extrapolation, 10X for intraspecies variation, 10X FQPA safety factor due to toxicity data gaps, and 3X uncertainty factor for the extrapolation of subchronic to chronic study 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 tridemorph residues in food are low and below the Agency's level of concern. At the 95th percentile, the acute dietary risk estimate for the population subgroup females 13-49 years is 9% of the aPAD. The mean chronic dietary exposure estimate for the highest exposed population subgroup, children 1-2 years of age, is 18% of the cPAD.

Because there are no tridemorph 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 tridemorph and any other substances, and tridemorph 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 tridemorph 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).

Based on the available information, tridemorph was reported to cause degeneration of the testes with oligospermia and azospermia in the subchronic rat and cryptorchidism (testes failed to descend), dysplasia and atrophy of the testes in the subchronic dog study. However, these findings are preliminary and need to be confirmed. When additional appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, tridemorph 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 § 180.372

A tolerance has been established for residues of tridemorph in or on imported bananas at 0.1 ppm, which includes the same allowance for residues in or on plantains. The tolerance for residues of tridemorph in/on plant commodities is expressed in terms of residues of tridemorph *per se* (2,6-dimethyl-4-tridecylmorpholine). New foreign residue data indicates the established tolerance must be increased to 1.0 ppm. Since there are no U.S. registrations, the tolerance should be footnoted to so indicate.

Table 1: Tolerance Summary for Tridemorph (40 CFR § 180.372)			
Commodity	Current Tolerance (ppm)	Reassessed Tolerance (ppm)	Comments
Bananas	0.1 ppm	1.0 ppm	The tolerance should be footnoted to indicate that there are no U.S. registrations associated with tridemorph.

There are no Codex maximum residue levels (MRLs) for tridemorph. Therefore, no questions of compatibility with U.S. tolerances exist.

III. Data Gaps and Confirmatory Data Requirements

The Agency concluded that the database for tridemorph is adequate for tolerance reassessment purposes, but identified some data gaps during the preparation of the risk assessment. To account for the uncertainty associated with the lack of these data, a 10X FQPA safety factor was used in both chronic and acute dietary assessments to account for the absence of these data, and an additional 3X UF was used in the chronic dietary assessment for extrapolation of subchronic to chronic effects. Further, highly conservative exposure assumptions were used in the unrefined Tier I dietary risk assessment (i.e. 100% crop treated, default processing factors, and tolerance level residues).

Recently, after completion of the risk assessment, the registrant submitted a series of toxicity studies (acute battery, subchronic oral toxicity in rats, chronic oral toxicity in rats, mice and dogs, developmental toxicity studies and a two generation reproduction study in rats, and a battery of mutagenic tests). Although these studies may address the identified data gaps, the Agency has not conducted a complete review of these data at this time. However, based on a preliminary review, the Agency is confident that the 10X FQPA safety factor, which was retained to account for uncertainty due to toxicity data gaps, in addition to the 3X UF applied to account for extrapolation from subchronic to chronic effects in the chronic risk assessment, as well as highly conservative exposure assumptions, are adequately protective of all populations, including infants and children. If, following a complete review of these data, information indicates that additional measures are necessary to ensure that the tridemorph tolerance meets the required safety standards, the Agency will amend this TRED accordingly.