

### III. Aggregate Risk Assessment and Determination of Safety

Consistent with section 408(b)(2)(D) of the FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of and to make a determination on aggregate exposure, consistent with section 408(b)(2) of the FFDCA, for tolerances for residues of pyriproxyfen on atemoya, biriba, cherimoya, custard apple, ilama, soursop, and sugar apple at 0.20 ppm (PP 2E6416); avocado, black sapote, canistel, mamey sapote, mango, papaya, sapodilla and star apple at 1.0 ppm (PP 2E6428); okra at 0.02 ppm (PP 2E6436); fig at 0.30 ppm (PP 2E6425); and fig, dried at 1.0 ppm (2E6425). EPA's assessment of exposures and risks associated with establishing the tolerances follows.

#### A. Toxicological Profile

EPA has evaluated the available toxicity data and considered its validity, completeness, and reliability as well as the relationship of the results of the studies to human risk. EPA has also considered available information concerning the variability of the sensitivities of major identifiable subgroups of consumers, including infants and children. The no observed adverse effect level (NOAEL) and the lowest observed adverse effect level (LOAEL) from the toxicity studies reviewed as well as the nature of the toxic effects caused by pyriproxyfen are discussed in Unit III.A. of the **Federal Registers** of June 5, 2001 (66 FR 30065) (FRL-6782-5), August 28, 2002 (67 FR 55150) (FRL-7195-7), and March 7, 2003 (68 FR 10972) (FRL-7289-6).

#### B. Toxicological Endpoints

The dose at which the NOAEL from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). However, the LOAEL is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference

dose (acute RfD or chronic RfD) where the RfD is equal to the NOAEL divided by the appropriate UF ( $RfD = NOAEL / UF$ ). Where an additional safety factor (SF) is retained due to concerns unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA SF.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) =  $NOAEL / \text{exposure}$ ) is calculated and compared to the LOC.

The linear default risk methodology ( $Q^*$ ) is the primary method currently used by the Agency to quantify carcinogenic risk. The  $Q^*$  approach assumes that any amount of exposure will lead to some degree of cancer risk. A  $Q^*$  is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (e.g., risk is expressed as  $1 \times 10^{-6}$  or one in a million). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a "point of departure" is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure ( $MOE_{\text{cancer}} = \text{point of departure} / \text{exposures}$ ) is calculated. A summary of the toxicological endpoints for pyriproxyfen used for human risk assessment is shown in Unit III.B. of the **Federal Register** of March 7, 2003 (68 FR 10972).

#### C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* Tolerances have been established (40 CFR 180.510) for the residues of pyriproxyfen, in or on a variety of raw agricultural commodities. There are no significant livestock feed items associated with this action, thus the proposed uses will not result in the transfer of additional pyriproxyfen residues to livestock. Risk assessments were conducted by EPA to assess dietary exposures from pyriproxyfen in food as follows:

i. *Acute exposure.* Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has

indicated the possibility of an effect of concern occurring as a result of a one day or single exposure. An acute dietary exposure analysis was not conducted since no acute doses or toxicological endpoints were selected for the general U.S. population (including infants and children) or the females 13–50 years old population subgroup.

ii. *Chronic exposure.* In conducting this chronic dietary risk assessment EPA used the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID®) which incorporates food consumption data as reported by respondents in the USDA 1994–1996 and 1998 nationwide Continuing Surveys of Food Intake by Individuals (CSFII) and accumulated exposure to the chemical for each commodity. The following assumptions were made for the chronic exposure assessments: The chronic dietary exposure assessment was performed using published and proposed tolerance levels, DEEM® default processing factors, and 100% crop treated (PCT) assumptions for all commodities. Some of the crops (atemoya, custard apple, ilama, birba, sapodilla, black and white sapote, star apple, and ugli fruit) considered in this risk assessment are not included in the present version of DEEM-FCID® due to their low consumption. In these cases, the DEEM-FCID® program underestimates the exposure to pyriproxyfen residues from these crops; however, because the consumption levels of these crops is so low (on a national basis), inclusion of these crops in a future version of DEEM-FCID® would likely make no difference in the overall predicted exposures to pyriproxyfen residues.

iii. *Cancer.* Pyriproxyfen was classified by the EPA (June, 1995) as a "Group E" chemical - no evidence of carcinogenicity to humans based on the absence of carcinogenicity in mice and rats.

2. *Dietary exposure from drinking water.* The Agency lacks sufficient monitoring exposure data to complete a comprehensive dietary exposure analysis and risk assessment for pyriproxyfen in drinking water. Because the Agency does not have comprehensive monitoring data, drinking water concentration estimates are made by reliance on simulation or modeling taking into account data on the physical characteristics of pyriproxyfen.

The Agency uses the FQPA Index Reservoir Screening Tool (FIRST) or the Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS), to produce estimates of