

TABLE 2.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR FAMOXADONE FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13–50 years of age)	Not applicable	Not applicable	No appropriate endpoint attributable to a single-oral dose was identified in the available toxicology studies on famoxadone.
Acute Dietary (General population including infants and children)	Not applicable	Not applicable	No appropriate endpoint attributable to a single-oral dose was identified in the available toxicology studies on famoxadone.
Chronic Dietary (All populations)	LOAEL = 1.4 mg/kg/day UF = 1,000 ^a Chronic RfD = 0.0014 mg/kg/day	FQPA SF = 1 cPAD = chronic RfD/FQPA SF Chronic PAD = 0.0014 mg/kg/day	13-Week feeding study in dogs. ^b LOAEL = 1.4 mg/kg/day based on microscopic lens lesions (cataracts) in eyes of female dogs.
Cancer (Oral, dermal, and inhalation)	Not applicable	Not applicable	Classification: Not Likely to be carcinogenic to humans.

* The reference to the FQPA SF refers to any additional SF retained due to concerns unique to the FQPA.

^a The UF of 1,000 includes the conventional 100 and an additional 10 for the use of the LOAEL and dose from a subchronic (13-week) study for chronic risk assessment.

^b Regarding the chronic RfD for famoxadone, a 1-year chronic feeding study in dogs is available, but was determined to not be an appropriate study for use in chronic risk assessment at this time. Although the testing laboratory reported a NOAEL of 1.2 mg/kg/day for treatment-related lens lesions (cataracts) in the eyes of the male and female dogs, a subsequent evaluation by a consulting pathologist of the microscopic sections of the eyes from all dogs in this study strongly suggested that a serious fixation artifact affected all the eye sections such that only prominent cataracts were detectable and as a consequence, a NOAEL could not be reliably determined with any degree of confidence. Considering this second evaluation, the Agency concluded that this fixation artifact may have had a profound effect on the interpretation of the histopathological findings in the eyes of all dogs in this study. In view of the considerable uncertainty relating to the microscopic findings in the eyes of all dogs in this study and the resulting uncertainty with regard to determining a NOAEL for eye effects, the Agency decided to not use the results from this 1-year study for the purpose of determining a chronic RfD for famoxadone at this time. Based on a consideration of findings in the eyes of dogs in both the 13-week and 1-year feeding studies, it was determined that the lowest dose at which evidence of cataracts was actually observed was in the female dogs in the 13-week study at the lowest dose tested of 1.4 mg/kg/day (the LOAEL). This 13-week study, rather than the 1-year study, was selected to be the most appropriate study for chronic risk assessment at this time. Since a LOAEL, rather than a NOAEL, and a subchronic study, rather than a chronic study, were used to determine the chronic RfD, an additional 10x UF was added to the conventional UF of 100x. The chronic RfD (LOAEL of 1.4 mg/kg/day/UF of 1,000) for famoxadone was determined to be 0.0014 mg/kg/day.

The comment received from WWF concerned a toxicity issue in particular: The potential for famoxadone to be an endocrine disruptor. WWF quoted the notice of filing which was written by Dupont. "Chronic, lifespan and multi-generational bioassays in mammals and acute and subchronic studies on aquatic organisms and wildlife did not reveal endocrine effects. Any endocrine related effects would have to have been detected in this definitive array of required tests. The probability of any such effects due to agricultural uses of famoxadone is negligible." WWF stated that pursuant to FQPA, the Agency is establishing a new endocrine disruptor screening and testing program because existing toxicology protocols are not adequate to detect endocrine disruption. Therefore, Dupont's evaluation of the endocrine disruptor potential is incomplete and consequently misleading. WWF also urges the Agency to consider not only evidence of increased susceptibility, but also the significance of endocrine disruptor data gaps when determining the FQPA SF for famoxadone.

In response to the WWF the Agency notes that FQPA requires EPA 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 such other endocrine effect... EPA has been working with interested stakeholders to develop a screening and testing program as well as a priority-setting scheme. In the available toxicity studies on famoxadone, no evidence of endocrine-related effects was observed. However, famoxadone may be subjected to further screening and/or testing to better characterize potential effects related to endocrine disruption when additional appropriate screening and/or testing protocols have been developed by the Agency's Endocrine Disruptor and Testing Advisory Committee (EDSTAC).

C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* Tolerances are being established for (40 CFR 180.587) for the residues of famoxadone, in or on a variety of raw agricultural commodities. Risk assessments were conducted by EPA to assess dietary exposures from famoxadone 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. No toxicological endpoint attributable to a single-oral dose was identified in the available toxicology studies on famoxadone that would be applicable to females (13–50 years) or to the general population (including infants and children). Therefore, famoxadone is not expected to pose an acute dietary risk.

ii. *Chronic exposure.* In conducting this chronic dietary risk assessment the Dietary Exposure Evaluation Model (DEEMTM) analysis evaluated the individual food consumption 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: Anticipated residues based upon average field trial values and assumptions that 100% of each crop is treated with famoxadone.

iii. *Cancer.* The Agency has classified famoxadone as not likely to be