

per doe. In the rabbit study, maternal toxicity (does) and developmental toxicity (fetuses) are considered to be equally sensitive to the test material. Therefore, based on the results in these two developmental toxicity studies in rats and rabbits, no increased susceptibility of the fetuses (as compared to adults) was demonstrated for famoxadone.

In the 2-generation reproduction study in rats, the NOAEL for parental toxicity was 200 ppm (equal to 11.3/14.2 mg/kg/day, M/F) and the LOAEL was 800 ppm (44.7/53.3 mg/kg/day, M/F), based on decreased body weight, body weight gain, and food consumption; and hepatotoxicity in the liver. Also, at 800 ppm, adaptive hepatocellular responses indicating enzyme induction were observed. No reproductive toxicity was observed in this study. The NOAEL for reproductive toxicity was 800 ppm (44.7/53.3 mg/kg/day, M/F), the highest dose tested. In this same study, the NOAEL for offspring toxicity was 200 ppm (equal to 11.3/14.2 mg/kg/day, M/F) and the LOAEL was 800 ppm (44.7/53.3 mg/kg/day, based on decreased body weights for F<sub>1</sub> and F<sub>2</sub> pups throughout their respective lactation periods.

3. *Neurotoxicity.* The Agency concluded that there is not a concern for developmental neurotoxicity resulting from exposure to famoxadone and that a developmental neurotoxicity study is not required.

Although clinical signs of neurotoxicity were observed in dogs in the 13-week study at the highest dose tested (>20 mg/kg/day), this effect was not observed at lower doses of about 10 mg/kg/day in the same 13-week study or in a subsequently performed 1-year feeding study in dogs. Also, toxicologically significant signs of neurotoxicity were not observed in any of the other studies on famoxadone in any species (including rats, mice, or monkeys) at any time. In addition, pre- and postnatal studies in rats and rabbits demonstrated no increased susceptibility of fetuses or neonates to famoxadone as compared to adults. Toxicologically significant neurotoxic effects would not be expected to occur in an additional study in rats. The clinical signs of neurotoxicity (muscle twitches) observed only in dogs, only in males, and only at the highest dose

tested, would not be anticipated to occur in a developmental neurotoxicity study in rats.

4. *Conclusion.* The Agency concluded that the toxicology database was complete for FQPA purposes and that there are no residential uncertainties for pre-/postnatal toxicity. Based on the hazard data, the Agency recommended the special FQPA SF be reduced to 1x. The famoxadone risk assessment team evaluated the quality of the exposure data; and, based on these data, recommended that the special FQPA SF be reduced to 1x. The recommendation is based on the following:

i. There is no quantitative or qualitative evidence of increased susceptibility of rat and rabbit fetuses to *in utero* exposure in developmental studies. There is no quantitative or qualitative evidence of increased susceptibility of rat offspring in the multi-generation reproduction study.

ii. The chronic dietary food exposure assessment utilizes average field trial residue data and for all proposed uses, 100% crop treated is assumed. The chronic assessment is somewhat refined and based on reliable data derived from studies designed to produce worst-case residues and unlikely to underestimate exposure.

#### *E. Aggregate Risks and Determination of Safety*

To estimate total aggregate exposure to a pesticide from food, drinking water, and residential uses, the Agency calculates DWLOCs which are used as a point of comparison against the model estimates of a pesticide's concentration in water. DWLOC values are not regulatory standards for drinking water. DWLOCs are theoretical upper limits on a pesticide's concentration in drinking water in light of total aggregate exposure to a pesticide in food and residential uses. In calculating a DWLOC, the Agency determines how much of the acceptable exposure (i.e., the PAD) is available for exposure through drinking water e.g., allowable chronic water exposure (mg/kg/day) = cPAD - (average food + residential exposure). This allowable exposure through drinking water is used to calculate a DWLOC.

A DWLOC will vary depending on the toxic endpoint, drinking water consumption, and body weights. Default body weights and consumption values

as used by the USEPA Office of Water are used to calculate DWLOCs: 2 liter (L)/70 kg (adult male), 2L/60 kg (adult female), and 1L/10 kg (child). Default body weights and drinking water consumption values vary on an individual basis. This variation will be taken into account in more refined screening-level and quantitative drinking water exposure assessments. Different populations will have different DWLOCs. Generally, a DWLOC is calculated for each type of risk assessment used: Acute, short-term, intermediate-term, chronic, and cancer.

When EECs for surface water and groundwater are less than the calculated DWLOCs, OPP concludes with reasonable certainty that exposures to the pesticide in drinking water (when considered along with other sources of exposure for which OPP has reliable data) would not result in unacceptable levels of aggregate human health risk at this time. Because OPP considers the aggregate risk resulting from multiple exposure pathways associated with a pesticide's uses, levels of comparison in drinking water may vary as those uses change. If new uses are added in the future, OPP will reassess the potential impacts of residues of the pesticide in drinking water as a part of the aggregate risk assessment process.

1. *Acute risk.* No appropriate endpoint attributable to a single-oral dose was identified in the available toxicology studies on famoxadone. Therefore, no acute risk from famoxadone is not expected.

2. *Chronic risk.* Using the exposure assumptions described in this unit for chronic exposure, EPA has concluded that exposure to famoxadone from food will utilize 36% of the cPAD for the U.S. population, 76% of the cPAD for Children ages 1–2 and 68% of the cPAD for Children ages 3–5. Children ages 1–2 are expected to be the most highly exposed subpopulation to famoxadone. There are no residential uses for famoxadone. In addition, there is potential for chronic dietary exposure to famoxadone in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate exposure to exceed 100% of the cPAD, as shown in Table 3 of this unit:

TABLE 3.—AGGREGATE RISK ASSESSMENT FOR CHRONIC (NON-CANCER) EXPOSURE TO FAMOXADONE

Population Subgroup	cPAD mg/kg/day	% cPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
U.S. Population	0.0014	36%	0.47	0.23	31