

feed consumption declines common to both dams and offspring as well as developmental delays which were noted in the offspring (eye opening, preputial separation). No evidence of specific neurobehavioral effects in the offspring were observed at dietary concentrations of up to 404 ppm.

C. Aggregate Exposure

1. *Dietary exposure.* Flufenacet is an herbicide with currently registered uses on corn and soybean. Section 18 emergency exemptions for use on wheat have been approved in several states. Also, time limited tolerances exist for inadvertent or indirect residues on alfalfa, clover, and crop groups 15, 16 and 17. Tolerances are proposed for use on Crop Group 1C, tuberous and corm vegetables, which includes potatoes and sweet potatoes. There are no residential uses for flufenacet, therefore aggregate exposure would consist of any potential exposure to flufenacet residues in the registered and proposed crops and in drinking water.

i. *Food.* Acute and Chronic dietary exposure assessments were conducted using the Dietary Exposure Evaluation Model (DEEM®, Version 7.76) from Exponent, Inc. and the 1994–1996, 1998 CSFII consumption database. Dietary exposure values were compared to the acute RfD of 0.083 milligrams/kilogram of body weight per day (mg/kg bw/day) based on a LOEL from an acute neurotoxicity study in rats and a 900-fold uncertainty factor. The chronic RfD of 0.004 mg/kg bw/day is based on a LOEL from a combined chronic toxicity/carcinogenicity study in the rat with a 300-fold uncertainty factor.

The refined acute and chronic dietary risk assessments were performed using anticipated residues for all registered and proposed crops and crop groups. Adjustments were made to account for percent of crop treated and processing factors where available. The Tier 2 acute analysis resulted in the U.S. population using 0.00437 mg/kg bw/day or 5.2% of the acute RfD. The highest exposed subpopulation was non-nursing infants at 0.00893 mg/kg bw/day utilized or 10.7% of the acute RfD.

For the Tier 3 chronic analysis the U.S. population utilized 0.000087 mg/kg bw/day or 2.2% of the chronic RfD. The highest exposed subpopulation was children 1–6 at 0.000179 mg/kg bw/day or 4.5% of the chronic RfD.

ii. *Drinking water.* The EPA has calculated drinking water level of comparison (DWLOCs) for acute exposure to flufenacet in drinking water as 2.87 ppm for the U.S. population and 813 ppb for children (1–6 years old). The Agency's screening concentration

in ground water (SCI-Grow) model estimates peak levels of flufenacet and its metabolite thiadone in groundwater to be 15.3 ppb. EPA's Pesticide Root Zone Model/Exposure Analysis Modeling System (PRZM/EXAMS) estimates peak levels of flufenacet and its metabolite thiadone in surface water to be 17 ppb. EPA's acute drinking water levels of comparison are well above the estimated exposures for flufenacet in water for the U.S. population and the subgroup with highest estimated exposure.

The EPA has calculated the drinking water level of comparison for chronic exposure to flufenacet in drinking water as 136 ppb for the U.S. population assuming that an adult weighs 70 kg and consumes a maximum of 2 liters of water per day. For children (1–6 years old), the DWLOC was 37.7 ppb assuming that a child weighs 10 kg and consumes a maximum of 1 liter of water per day. The drinking water estimated concentration (DWECS) for groundwater (parent flufenacet and degradate thiadone) calculated from modeling data is 0.03 ppb for chronic concentrations which does not exceed the DWLOC of 37.7 ppb for children (1–6 years old). The DWECS for surface water based on the computer models PRZM 2.3 and EXAMS 2.97.5 was calculated to be 14.2 ppb for chronic concentration (parent flufenacet and degradate thiadone) which does not exceed the DWLOC of 37.7 ppb for children (1–6 years old). The EPA has concluded that there is a reasonable certainty that no harm will result from aggregate exposure to flufenacet residues.

2. *Non-dietary exposure.* There are no non-food uses of flufenacet currently registered under the Federal Insecticide, Fungicide and Rodenticide Act, as amended. No non-dietary exposures are expected for the general population.

D. Cumulative Effects

Flufenacet is structurally a thiadiazole. EPA is not aware of any other pesticides with this structure. For flufenacet, EPA has not yet conducted a detailed review of common mechanisms to determine whether it is appropriate, or how to include this chemical in a cumulative risk assessment. After EPA develops a methodology to address common mechanism of toxicity issues to risk assessments, the Agency will develop a process (either as part of the periodic review of pesticides or otherwise) to reexamine these tolerance decisions. Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, flufenacet does not appear to produce a toxic metabolite

produced by other substances. For the purposes of these tolerance actions; therefore, EPA has not assumed that flufenacet has a common mechanism of toxicity with other substances.

E. Safety Determination

1. *U.S. population.* Using the assumptions and data described above, it is concluded that chronic dietary exposure to all registered and proposed uses of flufenacet will utilize at most 2.2% of the chronic RfD for the U.S. population. The acute dietary exposure assessment results in the U.S. population utilizing 5.2% of the acute RfD. EPA generally has no concern for exposures below 100% of the acute or chronic reference dose. Drinking water levels of comparison based on the dietary exposure are greater than the highly conservative drinking water estimated concentrations as shown above. Therefore, there is a reasonable certainty that no harm will occur to the U.S. population from aggregate exposure (food and drinking water) to residues of flufenacet.

2. *Infants and children.* In assessing the potential for additional sensitivity of infants and children to residues of flufenacet, EPA considered data from developmental toxicity studies in the rat and rabbit and a two-generation reproduction study in the rat. The developmental toxicity studies are designed to evaluate adverse effects on the developing organism resulting from pesticide exposure during prenatal development to one or both parents. Reproduction studies provide information relating to effects from exposure to the pesticide on the reproductive capability of mating animals and data on systemic toxicity. FFDCA section 408 provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for pre- and post-natal toxicity and the completeness of the data base unless EPA determines that a different margin of safety will be safe for infants and children. Although there is no indication of increased sensitivity to young rats or rabbits following pre- and/or post-natal exposure to flufenacet in the standard developmental and reproductive toxicity studies, an additional developmental neurotoxicity study, which is not normally required, is needed to access the susceptibility of the offspring in function/neurological development. Therefore, EPA has required that a developmental neurotoxicity study be conducted with flufenacet and a threefold safety factor for children and infants will be used in the aggregate dietary acute and chronic