

Flufenacet is not registered for use on any sites that would result in residential exposure.

4. *Cumulative exposure to substances with a common mechanism of toxicity.* Section 408(b)(2)(D)(v) of the FFDCA requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide's residues and "other substances that have a common mechanism of toxicity."

EPA does not have, at this time, available data to determine whether flufenacet has a common mechanism of toxicity with other substances or how to include this pesticide in a cumulative risk assessment. 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 this tolerance action, therefore, EPA has not assumed that flufenacet 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 final rule for Bifenthrin Pesticide Tolerances (62 FR 62961, November 26, 1997).

D. Safety Factor for Infants and Children

1. *In general.* Section 408 of the FFDCA provides that EPA shall apply an additional tenfold margin of safety for infants and children in the case of threshold effects to account for prenatal and postnatal toxicity and the completeness of the data base on toxicity and exposure unless EPA determines that a different margin of safety will be safe for infants and children. Margins of safety are incorporated into EPA risk assessments either directly through use of a MOE analysis or through using uncertainty (safety) factors in calculating a dose level that poses no appreciable risk to humans.

2. *Prenatal and postnatal sensitivity.* No increase in susceptibility was seen in rat and rabbit developmental studies, but qualitative and/or quantitative increases in susceptibility were seen in the rat reproduction study and in the rat developmental neurotoxicity studies.

3. *Conclusion.* The toxicology data base for flufenacet is complete except for a special comparative assay on thyroid hormone levels in neonatal and adult rats and a 28-day inhalation

toxicity study in rats. The exposure data are complete or are estimated based on data that reasonably accounts for potential exposures.

The Agency evaluated the potential for increased susceptibility of infants and children from exposure to flufenacet. The Agency concluded that there is a low degree of concern and lack of residual uncertainties for pre- and post-natal toxicity in the rat reproduction study and the rat and rabbit developmental toxicity studies. The Agency determined that the concern is also low for susceptibility seen in the developmental neurotoxicity (DNT) study. Multiple offspring effects were seen at the mid- and high doses, and no adverse maternal effects were seen at any dose. However, the only effect seen at the lowest dose in offspring was a transient decrease in body weight. The concern for the decrease in the offspring weights was reduced because no decrease in body weight was seen in the offspring in the reproduction study.

The Agency considered the lack of comparative data for thyroid hormone levels in adult and neonatal animals. Available data support the possibility of decreases in thyroid hormones in adult animals (decreases were observed in several studies conducted in rats, mice, rabbits, and dogs) at dose levels similar to those used in the submitted DNT study. Because of the above concern, a special comparative study on thyroid hormone levels in neonatal and adult rats is being requested by the Agency as a condition of registration. The Agency also noted that morphometric measurements could be incorporated into the comparative thyroid assay to confirm the findings observed in adult female offspring in the DNT (data for this endpoint were not available at the low dose).

Due to the concerns regarding the possibility of decreases in thyroid hormones and the need for comparative susceptibility data on this issue as well as the lack of a NOAEL in the DNT, EPA found no basis to remove the 10X FQPA safety for the protection of infants and children. EPA considers this additional 10X factor to be an uncertainty factor to address the deficiencies in the database.

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 (EECs). 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.* Using the exposure assumptions discussed in this unit for acute exposure, the acute dietary exposure from food to flufenacet will occupy 23% of the aPAD for the U.S. population, 17 % of the aPAD for females 13 years and older, 23% of the aPAD for all infants and 48% of the aPAD for children 1-2 years. In addition, there is potential for acute dietary exposure to flufenacet in drinking water. Table 4 of this unit presents the EECs and DWLOCs for the major populations subgroups.