

mechanism on EPA's website at <http://www.epa.gov/pesticides/cumulative/>.

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.* Based on the available data, there is no quantitative and qualitative evidence of increased susceptibility observed following *in utero* pyriproxyfen exposure to rats and rabbits or following pre/post natal exposure in the 2-generation reproduction study.

3. *Conclusion.* There is a complete toxicity data base for pyriproxyfen and exposure data are complete or are estimated based on data that reasonably accounts for potential exposures. EPA determined that the 10X safety factor to protect infants and children should be reduced to 1X because there was no evidence of prenatal or postnatal extra sensitivity or increased susceptibility in developmental studies in rats and rabbits, and in reproduction studies in rats. Likewise, there was no quantitative or qualitative evidence of increased susceptibility to rat or rabbit fetuses identified in the guideline prenatal developmental toxicity studies for rats and rabbits. Additionally, in the 2 non-guideline studies that evaluated perinatal and prenatal development, there was no evidence of quantitative or qualitative increased susceptibility. In 1-study, when pregnant rats were treated from gestation day 17 to lactation day 20, the resulting toxicity was comparable between adults (clinical signs, decreased body weight gain and food consumption) and offspring (decreased body weight and dilation of the renal pelvis) at the same dose. In the other study, when rats were exposed to

pyriproxyfen prior to and in the early stages of pregnancy, no developmental toxicity was seen at the limit dose. Lastly, in the reproduction toxicity study, offspring toxicity (decreased body weight on pups during lactation days 14 to 21) occurred only in the presence of decreases in body weight in parental animals at the same dose level (i.e., comparable toxicity in adults and offspring).

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 milligrams/kilogram/day (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 EPA's 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 ground water are less than the calculated DWLOCs, EPA concludes with reasonable certainty that exposures to the pesticide in drinking water (when considered along with other sources of

exposure for which EPA has reliable data) would not result in unacceptable levels of aggregate human health risk at this time. Because EPA 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, EPA 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.* An acute dietary RfD for females 13–50 and the general U.S. population, including infants and children, was not selected because an acute oral endpoint attributable to a single-dose exposure could not be identified; therefore, acute dietary risk is not expected.

2. *Chronic aggregate risk.* Using the exposure assumptions described in this unit for chronic (long-term) exposure, EPA has concluded that exposure to pyriproxyfen from food will utilize 1.1% of the cPAD for the U.S. population, 2% of the cPAD for all infants, less than 1 year old and 3.9% of the cPAD for children 1 to 2 years old, the subpopulation at greatest exposure. Pyriproxyfen is an active ingredient in pesticide products registered for residential use. Based on the use patterns, the residential risk assessment was performed for toddlers since they are anticipated to have the higher chronic residential exposure to residues of pyriproxyfen. EPA considered background chronic-dietary exposure (food + water), long-term, residential non-dietary oral exposures (hand-to-mouth exposures by toddlers following applications around the home and on pets for flea and tick control-carpet powder and pet shampoo), and long-term dermal exposure to toddlers. The total chronic food and residential aggregate MOEs were calculated. As these MOEs are greater than 100, the chronic aggregate risk does not exceed EPA's level of concern. In addition, there is potential for chronic dietary exposure to pyriproxyfen in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate chronic exposure to exceed the Agency's level of concern, as shown in Table 1 of this unit: