

#### *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.* Developmental studies did not show either qualitative or quantitative susceptibility. There is no increase in quantitative susceptibility demonstrated in the rat developmental neurotoxicity, rabbit developmental or rat reproduction studies. There is an apparent qualitative increase in susceptibility in the rat developmental toxicity study as indicated by increases in resorptions, increases in skeletal variations and retardations and malformations, and decreases in fetal body weight that occurred at the same dose showing a decrease in maternal body weight, but the concern is low since:

- i. There is a well characterized dose response with a clear NOAEL and LOAEL;
- ii. The fetal effects were noted in the presence of maternal toxicity; and
- iii. There are no residual uncertainties.

3. *Conclusion.* In evaluating whether to retain the 10X SF to protect infants and children or to select a different safety factor, EPA considered the following factors:

- i. There are no special concerns regarding pre- or post-natal toxicity exposure;
- ii. The exposure databases (food and drinking water) are complete and/or employ conservative assumptions;
- iii. There is no residential exposure;
- iv. The risk assessments cover or approximate all the metabolites and degradates of concern;
- v. The assessments do not underestimate the potential risk for infants and children; and
- vi. The toxicity database is complete except that there is a lack of morphometric assessments for the low- and mid-dose group animals in the developmental neurotoxicity study (DNT).

Although the lack of morphometric assessments in the DNT raised some uncertainty, EPA determined that there were sufficient reliable data to select an additional safety factor of 3X instead of 10X. The FQPA safety factor of 3X is in the form of a database uncertainty factor of 3X. A 3X factor was judged to be adequate because the dose selected for overall risk assessments is already based on the most sensitive end points for acute (i.e. clinical signs indicative of neurotoxicity) and chronic (i.e. liver and thyroid effects) dietary and non-dietary exposure scenarios, and the available data indicate that the full characterization of brain morphometrics from the DNT study would not be expected to lower the dose used for risk assessments by more than 3-fold.

To elaborate, since the magnitude (4-14%) of the morphometric histopathology changes seen in the offspring at the highest dose (40.8 mg/kg/day) in the developmental neurotoxicity study were considered to be at or near the limit of detection for differences in morphometric measurements, it is unlikely that measurable morphometric changes will be seen at lower doses. Any possible slight effects at lower doses are highly unlikely to change the regulatory level. The actual doses used to establish the acute RfD (3.1 mg/kg/day) and the chronic RfD (1.2 mg/kg/day) are 13 and 34 fold lower, respectively, than the 40.8 mg/kg/day dose where the effects of minimal magnitude were seen. Applying the 3 X factor further renders the adjusted doses 39 and 102-fold lower than the dose level where the effects of minimal magnitude were seen. Moreover, even if the slight morphometric changes are seen at the mid, and even the low, dose of the DNT, a RfD calculated on such findings is highly unlikely to be lower than current acute and chronic RfDs adjusted by 3X given that the effects seen at the high dose were marginal. Therefore it is concluded that 3X is adequate to account for any possible morphometric effects that may be noted in the lower doses for which the additional readings are being sought.

#### *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 thiacloprid will occupy 20% of the aPAD for the U.S. population, 8.5 % of the aPAD for females 13 years and older, 51 % of the aPAD for all infants and 47 % of the aPAD for children 1-2 years old. In addition, there is potential for acute dietary exposure to thiacloprid 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 aPAD, as shown in Table 4 of this unit: