

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.* Neither quantitative nor qualitative evidence of increased susceptibility of fetuses to *in utero* exposure to acetamiprid was observed in the developmental toxicity studies in rats and rabbits. In the multigeneration reproductive study, qualitative evidence of increased susceptibility of rat pups is observed since the offspring effects are considered to be more severe than the parental effects. However, quantitative evidence of increased susceptibility of rat pups was not observed since the parental and offspring NOAELs and LOAELs are at the same doses.

Since there is qualitative evidence of increased susceptibility of the young following exposure to acetamiprid in the rat reproduction study, EPA performed a Degree of Concern analysis to determine the level of concern for the effects observed when considered in the context of all available toxicity data, and to identify any residual uncertainties after establishing toxicity endpoints and traditional uncertainty factors to be used in the risk assessment of this chemical. If residual uncertainties are identified, EPA examines whether these residual uncertainties can be addressed by a special FQPA safety factor and, if so, the size of the factor needed.

The multigeneration reproduction study in rats was used for the Degree of Concern analysis. In that rat reproduction study, qualitative susceptibility was evidenced as significant reductions in pup weights in both generations, reductions in litter size, and viability and weaning indices among F₂ offspring as well as significant delays in the age to attain vaginal opening and preputial separation in the presence of lesser maternal toxicity (reductions in body weight, body weight gain and food consumption) at the highest dose tested. Considering the overall toxicity profile and the doses

and endpoints selected for risk assessment for acetamiprid, the EPA characterized the degree of concern for the effects observed in this study as low, noting that there is a clear NOAEL for the offspring effects observed and that these effects occurred in the presence of parental toxicity and only at the highest dose tested. No residual uncertainties were identified. The NOAEL for offspring effects in this reproduction study (17.9 mg/kg/day) is used as the basis for short- and intermediate-term dermal and inhalation exposure scenarios. For all other toxicity endpoints established for acetamiprid, a NOAEL lower than this offspring NOAEL is used.

For the reasons stated above, EPA has concluded that there is low concern for prenatal and/or postnatal toxicity resulting from exposure to acetamiprid.

3. *Conclusion.* The toxicology data base is not complete for FQPA purposes. EPA has determined that a developmental neurotoxicity study in rats should be conducted. The need for a developmental neurotoxicity study is based on the consideration that clinical signs of neurotoxicity were observed on the day of dosing in the acute neurotoxicity study in rats. In addition, acetamiprid is structurally related to thiamethoxam and imidacloprid, both of which are neonicotinoids. Imidacloprid is a chloronicotinyl compound and is an analog to nicotine. Studies in the published literature suggest that nicotine, when administered causes developmental toxicity, including functional deficits, in animals and/or humans that are exposed *in utero*. With imidacloprid, there is evidence that administration causes clinical signs of neurotoxicity following a single oral dose in the acute study and alterations in brain weight in rats in the 2-year carcinogenicity study. With thiamethoxam, there was also evidence of clinical signs of neurotoxicity in the acute neurotoxicity study. There are also indications that thiamethoxam may affect the endocrine system.

Recently, EPA has received objections to tolerances for residues of acetamiprid from the Natural Resources Defense Council (NRDC). NRDC asserted that EPA is missing data bearing on oral exposure to acetamiprid from residential uses of the pesticide. The **Federal Register** notice on the contested acetamiprid tolerance notes that "incidental oral exposure is an insignificant pathway of exposure" for acetamiprid (67 FR 14649, 14657; March 27, 2002). As noted above, little or no incidental oral exposure is expected since acetamiprid's residential uses are limited to ornamentals, flowers,

vegetable gardens, and fruit trees. Incidental oral exposure to pesticides can occur when young children engage in "mouthing" behavior (i.e. repeatedly placing their hands or other objects in their mouth) in a location where a pesticide is present. EPA assumes that incidental oral exposure to a pesticide may occur when a pesticide is used to treat a home lawn because young children frequently play on home lawns. EPA, however, considers it unlikely that young children would spend an extended time in flower, vegetable, or ornamental gardens, and thus treatment of such gardens with a pesticide is not likely to lead to a significant exposure to children by the incidental oral route.

The NRDC also claimed that a 10X safety factor should be used to account for the lack of the developmental neurotoxicity study. However, it has been noted that reliable developmental neurotoxicity data received and reviewed for other structurally-related compounds in this chemical class (neonicotinoids), including thiacloprid, clothianidin, and imidacloprid, demonstrated that the developmental neurotoxicity had no effect on the regulatory endpoint for those pesticides. Therefore, EPA believes that the results of the required developmental neurotoxicity study will not likely impact the regulatory doses selected for acetamiprid. It is further noted that the requirement of a developmental neurotoxicity study is not based on criteria reflecting special concern for the developing fetuses or young (e.g., neuropathy in adult animals; CNS malformations following prenatal exposure; brain weight or sexual maturation changes in offspring; and/or functional changes in offspring). On this basis, EPA concluded that a data base uncertainty factor is not needed to account for the lack of the developmental neurotoxicity study with acetamiprid, and that reliable data support removing the additional safety factor for the protection of infants and children.

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