

IV. Aggregate Risk Assessment and Determination of Safety

EPA performs a number of analyses to determine the risks from aggregate exposure to pesticide residues. For further discussion of the regulatory requirements of section 408 of the FFDCA and a complete description of the risk assessment process, see the final rule on Bifenthrin Pesticide Tolerances November 26, 1997 (62 FR 62961) (FRL-5754-7).

Consistent with section 408(b)(2)(D) of the FFDCA, EPA has reviewed the available scientific data and other relevant information in support of this action. EPA has sufficient data to assess the hazards of imidacloprid and to make a determination on aggregate exposure, consistent with section 408(b)(2) of the FFDCA, for a time-limited tolerance for combined residues of imidacloprid in or on soybean seed at 1.0 ppm. EPA's assessment of the dietary exposures and risks associated with establishing the tolerance follows.

A. Toxicological Endpoints

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological endpoint. However, the lowest dose at

which adverse effects of concern are identified (the LOAEL) is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (aRfD or cRfD) where the RfD is equal to the NOAEL divided by the appropriate UF (RfD = NOAEL/UF). Where an additional safety factor is retained due to concerns unique to the FQPA, this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA SF.

For non-dietary risk assessments (other than cancer) the UF is used to determine the level of concern (LOC). For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for

intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) = NOAEL/exposure) is calculated and compared to the LOC.

The linear default risk methodology (Q*) is the primary method currently used by the Agency to quantify carcinogenic risk. The Q* approach assumes that any amount of exposure will lead to some degree of cancer risk. A Q* is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (e.g., risk is expressed as 1×10^{-6} or one in a million). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a "point of departure" is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure ($\text{MOE}_{\text{cancer}} = \text{point of departure/exposures}$) is calculated. A summary of the toxicological endpoints for imidacloprid used for human risk assessment is shown in the following Table 1:

TABLE 1.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR IMIDACLOPRID FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute dietary (all populations including infants and children)	NOAEL = not determined LOAEL = 42 milligrams/kilogram/day (mg/kg/day) UF = 300 Acute RfD = 0.14 mg/kg/day	FQPA SF = 1 aPAD = acute RfD FQPA SF = 0.14 mg/kg/day	Acute neurotoxicity - rats LOAEL = 42 mg/kg/day based on decreased motor activity in female rats
Chronic dietary (all populations)	NOAEL = 5.7 mg/kg/day UF = 100 Chronic RfD = 0.057 mg/kg/day	FQPA SF = 1 cPAD = chronic RfD FQPA SF = 0.057 mg/kg/day	Combined chronic toxic/carcinogenicity - rat LOAEL = 16.9 mg/kg/day, based upon increased incidence of mineralized particles in thyroid colloid in males
Short-term oral (1–30 days)	Oral study NOAEL = 10 mg/kg/day	LOC for MOE = 100 (residential, includes the FQPA SF)	Developmental toxicity - rat Maternal LOAEL = 30 mg/kg/day, based upon decreased body weight gain and corrected body weight gain
Intermediate-term oral (1–6 months)	Oral study NOAEL = 9.3 mg/kg/day	LOC for MOE = 100 (residential, includes the FQPA SF)	Subchronic neurotoxicity - rat LOAEL = 63.3 mg/kg/day, based upon decreased body weight gain
Short-term dermal (1–30 days)	Oral study NOAEL = 10 mg/kg/day (dermal absorption rate = (7.2%))	LOC for MOE = 100 (occupational) LOC for MOE = 100 (residential, includes the FQPA SF)	Developmental toxicity - rat Maternal LOAEL = 30 mg/kg/day, based upon decreased body weight gain and corrected body weight gain