

TABLE 1.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY—Continued

Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics rat	Methylene-labeled imidacloprid was rapidly absorbed. There were no biologically significant differences between sexes, dose levels, or route of administration. Urinary excretion was the major route of elimination, with a lesser amount eliminated in feces. Total tissue burden after 48 hours accounted for only approximately 0.5% of the recovered radioactivity, with major sites of accumulation being the liver, kidney, lung, skin, and plasma and minor sites being the brain and testes. There were two major evident routes of biotransformation. The first included an oxidative cleavage of the parent compound to give 6-CNA and its glycine conjugate. Dechlorination of this metabolite formed the 6-hydroxynicotinic acid and its mercapturic acid derivative. The second included the hydroxylation of imidazolidine followed by elimination of water of the parent compound to give NTN 35884. In a comparison between [Methylene-14C] Imidacloprid and [Imidazolidine-4,5-14C] Imidacloprid, the rates of excretion were similar; however, the renal portion was higher with the imidazolidine-labeled test material. The imidazolidine-labeled test material also demonstrated higher accumulation in the tissues, with the major sites of accumulation being the liver, kidney, lung, and skin, and the minor sites being brain and muscle.

B. 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 level of concern (LOC). 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 intra species differences.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) where

the RfD is equal to the NOAEL divided by the appropriate UF ($RfD = NOAEL / UF$). Where an additional safety factors (SF) 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 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) = $NOAEL / \text{exposure}$) 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 ($MOE_{\text{cancer}} = \text{point of departure} / \text{exposures}$) is calculated. A summary of the toxicological endpoints for imidacloprid used for human risk assessment is shown in Table 2 of this unit:

TABLE 2.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR IMIDACLOPRID FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	* Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary all populations	LOAEL = 42 mg/kg/day UF = 300 Acute RfD = 0.14 mg/kg	FQPA SF = 1X aPAD = aRfD/ FQPA SF = 0.14 mg/kg	Acute neurotoxicity - rat LOAEL = 42 mg/kg, based upon the decrease in motor and locomotor activities observed in females.
Chronic Dietary all populations	NOAEL = 5.7 mg/kg/day UF = 100 Chronic RfD = 0.057 mg/kg/day	FQPA SF = 1X cPAD = cRfD/FQPA SF = 0.057 mg/kg/day	Combined chronic tox/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.