

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

Guideline No.	Study Type	Results
870.7485	Metabolism in rats	Extensively and rapidly metabolized. Metabolizes 79–86% of administered dose. Profiles similar for males and females for both oral and intravenous dosing. Three to seven percent of dose recovered in urine and feces as unchanged test article. Urinary and fecal metabolites from 15-day repeat dose experiment only showed minor differences from single-dose test. Initial Phase I biotransformation: Demethylation of parent. 6-chloronicotinic acid most prevalent metabolite. Phase II metabolism shown by increase in glycine conjugate.
870.7485	Metabolism in mice, rats, and rabbits (Special study)	Male mice, rats or rabbits were administered single doses of acetamiprid by gavage, intraperitoneal injection (i.p.) or intravenous injection (i.v.) up to 60 mg/kg. The animals were assessed for a variety of neurobehavioral parameters. <i>In vitro</i> experiments were also done using isolated ileum sections from guinea pigs to assess contractile responses in the absence and presence of agonists (acetylcholine, histamine diphosphate, barium chloride and nicotine tartrate). Acetamiprid was also assessed via i.v. in rabbits for effects on respiratory rate, heart rate and blood pressure; via gavage in mice for effects on gastrointestinal motility; and via i.p. in rats for effects on water and electrolyte balance in urine, and blood coagulation, hemolytic potential and plasma cholinesterase activity. Based on a number of neuromuscular, behavioral and physiological effects of acetamiprid in male mice, under the conditions of this study, a overall NOAEL of 10 mg/kg (threshold) and LOAEL of 20 mg/kg could be estimated for a single dose by various exposure routes.
870.7600	Dermal absorption	The majority of the dose was washed off with the percent increasing with dose. Skin residue was the next largest portion of the dose with the percent decreasing with dose. In neither case was there evidence of an exposure related pattern. Absorption was small and increased with duration of exposure. Since there are no data to demonstrate that the residues remaining on the skin do not enter the animal, then as a conservative estimate of dermal absorption, residues remaining on the skin will be added to the highest dermal absorption value. The potential total absorption at 24 hours could be approximately 30%.

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 intraspecies 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