

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

Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics (mouse)	Of the administered radioactivity, 98.7–99.2% was recovered. Readily absorbed and excreted within 168 hours following a single oral dose of 5 mg/kg bwt
870.7600	Dermal Penetration - monkey	Dermal absorption as the sum of urinary and fecal excretion and Cage/Pan/Chair Wash, Debris was 0.24 (+ 0.11) as percent of dose. Adjustment of the direct absorption determination was not necessary because recovery from the dermal dose was $\leq 90\%$. A value of 1% dermal absorption was considered appropriate for use in risk assessment. This estimation takes into account any variability that would have likely occurred with testing several dose levels
	Special study: Neurotoxicity and pharmacology mouse	NOAEL: 25 mg/kg/day (male/female) LOAEL: 50 mg/kg bw mg/kg/day (transient signs of decreased spontaneous motor activity, tremors, and deep respirations)

B. Toxicological Endpoints

The dose at which 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 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. EPA has concluded that the toxicology database for clothianidin is not complete. Due to evidence of effects on the immune system and that juvenile rats appear to be more susceptible to these effects, EPA has determined that testing should be conducted to assess immune system function in adults and in young animals following developmental exposures. Therefore, a

10X database UF is to be applied to all dietary exposure endpoints for the lack of a developmental immunotoxicity study.

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) = $NOAEL/exposure$) 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 ($MOE_{cancer} = \text{point of departure}/\text{exposures}$) is calculated. A summary of the toxicological endpoints for clothianidin used for human risk assessment is shown in Table 2 of this unit:

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

Exposure Scenario	Dose Used in Risk Assessment, UF ¹	Special FQPA SF ² and LOC for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13–50 years of age)	Developmental NOAEL = 25 UF = 1000 ¹ Acute RfD = 0.025 mg/kg	FQPA SF = 1 aPAD = acute RfD \div FQPA SF = 0.025 mg/kg	Developmental rabbit study Developmental LOAEL = 75 mg/kg/day based on an increased litter incidence of a missing lobe of the lung
Acute Dietary (General population)	NOAEL = 25 UF = 1000 ¹ Acute RfD = 0.025 mg/kg	FQPA SF = 1 aPAD = acute RfD \div FQPA SF = 0.025 mg/kg	Special Neurotoxicity/Pharmacology Study in Mice and Rats LOAEL = 50 mg/kg based on transient signs of decreased spontaneous motor activity, tremors and deep respirations