

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

Guideline No.	Study Type	Results
870.6200	Acute neurotoxicity screening battery (rats)	NOAEL = M: 1,000 mg/kg F: 2,000 mg/kg. LOAEL = M: 2,000 mg/kg based on decreased body weight gain and food consumption (on days 1–2); and palpebral (eyelid) closure (on day 1 only). F: none (>2,000 mg/kg).
870.6200	Subchronic neurotoxicity screening battery (rats)	NOAEL = M: 11.7 mg/kg/day F: 14.4 mg/kg/day. LOAEL = M: 47 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency. F: 59 mg/kg/day based on decreased body weight, body weight gain, food consumption and food efficiency. No evidence of neurotoxicity in M or F.
870.7800	Immunotoxicity study, rats (28-days)	NOAEL = M: 14 mg/kg/day. F: 16 mg/kg/day. LOAEL = M: 55 mg/kg/day based on decreased body weight, body weight gain, food consumption, and food efficiency; and increased spleen weights (probably due to increased pigment in spleen). F: 57 mg/kg/day based on decreased body weight, body weight gain, food consumption, and food efficiency; and increased spleen weights (probably due to increased pigment in spleen). No evidence of immunotoxicity in M or F.
870.7800	Immunotoxicity study, mice (28-days)	NOAEL = M: 1186 mg/kg/day. F: 417 mg/kg/day. LOAEL = M: none (>1,186 mg/kg/day). F: 1,664 mg/kg/day based on increased spleen weights (probably due to increased pigment in spleen). No evidence of immunotoxicity in M or F.
870.7485	Metabolism and pharmacokinetics, rats	Only about 40% of the administered dose was absorbed. Most of the administered dose (87–6%) was eliminated in the feces within 24 hours; very little (3–12%) was eliminated in the urine. Unchanged parent (51–84% of administered dose) and 2 hydroxylated metabolites (IN-KZ534 and IN-KZ007) were the major components recovered in the feces. No significant qualitative or quantitative differences were observed for sex, dose level, or repeated dosing.
870.7485	Metabolism and pharmacokinetics, dogs (males only)	Absorption was limited. Most of the administered dose (62%) was eliminated in the feces within 24 hours; very little (about 8%) was eliminated in the urine. Initially, unchanged parent (94–97% of radioactivity in feces) was recovered in the feces, but later (>24 hrs) unchanged parent (12–35% of radioactivity in feces), IN-KZ007 (21–3% of radioactivity in feces) and IN-ML815 (4–9% of radioactivity in feces) were recovered. Even later (>48 hrs), trace amounts of the hydroxylated metabolites IN-KZ532 and IN-KZ534 were also identified in the feces.

### 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  $1 \times 10^{-6}$  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 famoxadone used for human risk assessment is shown in Table 2 of this unit: