

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

Guideline No.	Study Type	Results
870.3800	1-Generation reproduction and fertility effects (rat)	<i>Parental/systemic</i> NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified <i>Reproductive</i> NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified <i>Offspring</i> NOAEL = 139.4 - 151.7 mg/kg/day LOAEL not identified
870.4300	Combined chronic toxicity/carcinogenicity rodents (rat)	NOAEL = 778.8/1024.7 mg/kg/day M/F LOAEL was not established No evidence of carcinogenicity
870.4200	Carcinogenicity rodents (mouse)	NOAEL = 39.9 - 43.7 mg/kg/day M/F LOAEL = 401.8 - 447.9 mg/kg/day M/F, based on liver toxicity in both sexes and mild anemia in males No evidence of carcinogenicity
870.5100	Bacterial gene mutation assay	Flufenpyr-ethyl was tested up to concentrations limited by cytotoxicity. There was no evidence of mutagenicity at any dose levels tested. Positive controls induced appropriate response
870.5100	Bacterial gene mutation assay S-3153 acid-4-OH	There was no evidence of a cytotoxic, mutagenic or dose-response trend in any tester system \pm S9. Positive controls induced appropriate response
870.5300	<i>In vitro</i> mammalian cell gene mutation assay	The compound was tested up to an upper concentration limited by solubility and cytotoxicity. Flufenpyr-ethyl was negative for inducing mutations at the TK locus in mouse L5178Y \pm S9
870.5395	Mammalian erythrocyte micronucleus assay	No clinical signs of toxicity was observed. Flufenpyr-ethyl did not induce micronucleated polychromatic erythrocytes after any treatment
870.7485	Metabolism and pharmacokinetics - rat	There is no difference in the metabolic profile of flufenpyr-ethyl attributable to gender or radiolabel position

B. Toxicological Endpoints

The dose at which no observed adverse effects levels (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 (aRfD or cRfD) 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} = point of departure/exposures) is calculated. A summary of the toxicological endpoints for flufenpyr-ethyl used for human risk assessment is shown in the following Table 2: