

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

Guideline No.	Study Type	Results
870.6200	Subchronic neurotoxicity screening battery	NOAEL = 30 mg/kg/day for males and 37 mg/kg/day for females LOAEL = 150 mg/kg/day for males and 180 mg/kg/day for females based on increased incidence of clinical signs; decreased body weight, body weight gains, and food consumption in females; and increased motor activity in females. At 5,000 ppm, included increased mortality; decreased body weights, and body weight gains in males; decreased hindlimb grip strength and increased tail flick latency in males at week 8; distended bladders with red fluid and enlarged spleen. No evidence of neuropathology at 2,500 and 5,000 ppm.
870.7485	Metabolism and pharmacokinetics (rats)	Sulfentrazone (Phenyl -14C - sulfentrazone) was readily absorbed and 84 to 104% of the administered dose was excreted in urine and feces within 72 hours. There were no major sex differences in the pattern of excretion. Almost all the radioactivity in the urine was 3-hydroxy-methyl-F6285 (84 - 104% of the administered dose). In the feces, HMS accounted for 1.26 to 2.55% of the administered dose. The proposed metabolic pathway appeared to be conversion of the parent compound mainly to 3-hydroxymethyl-F6285 (excreted in the urine). A small amount of 3-hydroxymethyl-F6285 was also converted to 3-carboxylic acid-F6285 (excreted in the urine and 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 factor (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 sulfentrazone used for human risk assessment is shown in Table 2 of this unit: