

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

Guideline No.	Study Type	Results
870.6300	Developmental neurotoxicity (rat)	No study performed. Not Required.
870.7485	Metabolism and pharmacokinetics (rat)	Rapidly absorbed and excreted. Most (>87%) of the administered dose (AD) was excreted within 24 hours. After 7 days, very little ($\leq 0.3\%$ of AD) remained in the tissues. Urine was the primary route of excretion in males (50-61% of AD) and in females (70-80% of AD). Unchanged parent in males (11-20% of AD) and in females (37-47% of AD) was excreted almost entirely in the urine and only trace amounts were found in the feces. With the exception of the parent, the metabolite profile was similar between the urine and feces. The 2 primary metabolites in both urine and feces were Metabolite J (desmethyl parent, up to 26% of AD) and Metabolite K (5'-hydroxy-pyrimidine of parent, up to 19% of AD). Other metabolites were Metabolites X, N, F, A and D, each up to 8.2% of the AD in males and up to 4.7% of the AD in females. Several minor metabolites were also identified as Metabolite Q, Metabolite P, guanidine, CGA-382997 and CGA-368732 (each $\leq 4.4\%$ of the AD).
870.7485	Biliary metabolism (rat)	In bile duct cannulated rats, absorption was 84-88% of the Administered Dose (AD) at 48 hours. Nearly all of the AD was excreted within 48 hours. Excretion in urine ranged from 58-76%, in bile from 5-27%, and in feces was about 6% of the AD. There was no evidence for an enterohepatic circulation. Biotransformation was similar to that in the conventional rat metabolism study. The metabolite profiles in urine, bile fluid and feces were all similar.
870.7600	Dermal penetration (rat)	No study performed. Not Required.

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 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 trifloxysulfuron used for human risk assessment is shown in Table 2 of this unit: