

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

Guideline No.	Study Type	Results
870.5395	Cytogenetics/ <i>In vivo</i> bone marrow micronucleus	In an <i>in vivo</i> bone marrow micronucleus assay, cyprodinil was negative when administered orally (gavage) at 5,000 mg/kg(HDT) to both sexes of Tif:MAGF mice. No signs of overt toxicity or clear evidence of cytotoxicity for the target organ were noted at any dose or sacrifice time.
870.5550	Unscheduled DNA Synthesis	In an Unscheduled DNA Synthesis(UDS) assay in primary rat hepatocytes, cyprodinil was negative up to a cytotoxic concentration (80μg/mL).
870.7485	Metabolism and pharmacokinetics	Single oral doses (0.5 or 100 mg/kg bw) of phenyl or pyrimidyl-radiolabelled cyprodinil (purity ≥98%) were administered toTif:RAIf(SPF) rats, with one low-dose group receiving unlabelled cyprodinil (purity ≥99%) for 2 weeks prior to treatment with radiolabelled compound. Absorption was very rapid (t _{cm} = 0.3 hours) with rapid clearance (t _{cm} /2=1.2 hours). A minimum of 75% of the administered dose was absorbed. Excretion was rapid and almost complete, with urine as the principle route of excretion (48–68%), and >90%of the administered dose detected in the urine and feces within 48 hours. Excretion, distribution and metabolite profiles were essentially independent of dose level, pretreatment, and type of label, although there were some quantitative differences sex-dependent qualitative differences in two urinary metabolite fractions.
870.7485	Metabolism and pharmacokinetics	Excreta (Group D1 and D2) and bile (Group G1) from radiolabelled cyprodinil-treated Tif:RAIf(SPF) rats were used to characterize, isolateand identify cyprodinil metabolites. Eleven metabolites were isolated from urine, feces and bile, and the metabolic pathways in the rat were proposed. All urinary and biliary metabolites (with the exception of 7U) were conjugated with glucuronic acid or sulfonated, and excreted. Cyprodinil was almostcompletely metabolized by hydroxylation of the phenyl ring (position 4) or pyrimidine ring (position 5), followed by conjugation. An alternative pathwayinvolved oxidation of the phenyl ring followed by glucuronic acid conjugation. A quantitative sex difference was observed with respect to sulfonation ofthe major metabolite that formed 6U. The monosulfate metabolite (1U) was predominant in females, whereas equal amounts of mono- and disulfate (6U) conjugates were noted in males. Most of the significant metabolites in feces were exocons of biliary metabolites (2U, 3U, 1G). These were assumed to be deconjugated in the intestines, partially reabsorbed into the generalcirculation, conjugated again, and eliminated renally. The major metabolic pathways of cyprodinil were not significantly influenced by the dose, treatment regimen, or sex of the animal.

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