

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

Guideline No.	Study Type	Results
870.5300	Gene Mutation	DPX-MP062 negative for mutagenic activity for the following concentration ranges: 3.1–250 µg/mL (-S9); 3.1–250 µg/mL (+S9) DPX-JW062 negative for mutagenic activity for the following concentration ranges: Negative; 100–1,000 µg/mL (-S9); 100–1,000 µg/mL (+S9), precipitate ≥1,000 µg/mL
870.5375	Cytogenetics	DPX-MP062 no evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 15.7–1,000 µg/mL (±S9) DPX-JW062 no evidence of chromosomal aberrations induced by the test article over background for the following concentration ranges: 19–300 µg/mL (- S9), 19–150 µg/mL (+S9); partial insoluble and cytotoxicity ≥150 µg/mL
870.5395	Cytogenetics	DPX-MP062 no evidence of mutagenicity for the following dose ranges: 3,000–4,000 mg/kg - males; 1,000–2,000 mg/kg - females DPX-JW062 no evidence of mutagenicity at 2,500 or 5,000 mg/kg
870.5550	Other Effects	DPX-MP062 no evidence of mutagenic activity at the following concentration range: 1.56–200 µg/mL; cytotoxicity was seen at concentrations of ≥100 µg/mL DPX-JW062 No evidence of mutagenic activity at the following concentration range: 0.1–50 µg/mL, cytotoxicity observed at ≥50 µg/mL
870.6200	Acute neurotoxicity screening battery	DPX-MP062 NOAEL = M 100, F 12.5 mg/kg LOAEL = M 200 mg/kg based on decreased body weight gain, decreased food consumption, decreased forelimb grip strength, and decreased foot splay. F 50 mg/kg based on decreased body weight, body weight gain, and food consumption DPX-JW062 NOAEL = M > 2,000 mg/kg = F < 500 mg/kg LOAEL > M 2,000 mg/kg F < 500 mg/kg based on clinical signs, decreased body weight gains and food consumption, and FOB effects
870.6200	Subchronic neurotoxicity screening battery	DPX-MP062 NOAEL = M 0.57, F 0.68 mg/kg/day LOAEL = M 5.6, F 3.3 mg/kg/day based on decreased body weight and alopecia
870.7485	Metabolism and pharmacokinetics	Both DPX-MP062 and DPX-JW062 were extensively metabolized and the metabolites were eliminated in urine, feces, and bile. The metabolite profile for DPX-JW062 was dose dependent and varied quantitatively between males and females. Differences in metabolite profiles were also observed for the different label positions (indanone and trifluoromethoxyphenyl rings). All biliary metabolites undergo further biotransformation in the gut. The proposed metabolic pathway for both DPX-MP062 and DPX-JW062 has multiple metabolites bearing one of the two ring structures (see 870–4100 chronic toxicity rodents above).

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 intra species 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 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 Safety Factor (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