

B. Toxicological Endpoints

The dose at which 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 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 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 ($MOE_{cancer} = \text{point of departure/exposures}$) is calculated. A summary of the toxicological endpoints for folpet used for human risk assessment is shown in Table 2 of this unit:

TABLE 2.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR FOLPET FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (Females 13-50 years of age)	NOAEL = 10 mg/kg/day UF = 100 Acute RfD = 0.1 mg/kg/day	FQPA SF = 1X aPAD = acute RfD/FQPA SF = 0.1 mg/kg/day	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day based on an increased number of fetuses and litters with hydrocephaly and related skull malformations
Chronic Dietary (All populations)	NOAEL = 9 mg/kg/day UF = 100 Chronic RfD = 0.09 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD/FQPA SF = 0.09 mg/kg/day	Chronic Toxicity Study in Rat LOAEL = 35 mg/kg/day based on hyperkeratosis/acanthosis and ulceration/erosion of non-glandular stomach epithelium in both sexes
Short-Term Dermal (1 to 7 days) (Residential)	oral study NOAEL = 10 mg/kg/day (dermal absorption rate = 2.7%)	LOC for MOE = 100 (Residential)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day based on an increased number of fetuses and litters with hydrocephaly and related skull malformations
Intermediate-Term Dermal (1 week to several months) (Residential)	oral study NOAEL = 10 mg/kg/day (dermal absorption rate = 2.7%)	LOC for MOE = 100 (Residential)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day based on an increased number of fetuses and litters with hydrocephaly and related skull malformations
Short-Term Inhalation (1 to 7 days) (Residential)	oral study NOAEL = 10 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100 (Residential)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day based on an increased number of fetuses and litters with hydrocephaly and related skull malformations
Intermediate-Term Inhalation (1 week to several months) (Residential)	oral study NOAEL = 10 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100 (Residential)	Developmental Toxicity Study in Rabbits LOAEL = 20 mg/kg/day based on an increased number of fetuses and litters with hydrocephaly and related skull malformations
Cancer (oral, dermal, inhalation)	Cancer potency factor (Q1*) is 1.86×10^{-3} .		Based on increased incidences of adenomas and carcinomas in the duodenum of male and female mice in two strains

*The reference to the FQPA SF refers to any additional SF retained due to concerns unique to the FQPA.