

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

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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations)	NA	NA	An appropriate endpoint attributable to a single dose (exposure) of cyromazine was not observed in oral toxicity studies. Thus, an acute dietary endpoint was not chosen.
Chronic Dietary (All populations)	NOAEL = 7.5 mg/kg/day UF = 100 Chronic RfD = $NOAEL / UF$ = 0.075 mg/kg/day	FQPA SF = 1x cPAD = chronic RfD + FQPA SF = 0.075 mg/kg/day	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Short-Term Incidental Oral (1–30 days)	NOAEL = 10 mg/kg/day	Residential LOC for MOE = 100	Developmental Toxicity study in rabbits. LOAEL = 30 mg/kg/day based on decreases in body weight gain and food consumption.
Intermediate-Term Incidental Oral (1–6 months)	NOAEL = 7.5 mg/kg/day	Residential LOC for MOE = 100	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Short-, Intermediate- and Long-Term Dermal	NA	NA	No hazard was identified via the dermal route of exposure.
Short-Term Inhalation (1 to 30 days)	Inhalation (oral) study NOAEL = 10 mg/kg/day (inhalation absorption rate = 100%)	Residential LOC for MOE = 100	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.
Intermediate-Term Inhalation (1 to 6 months)	Inhalation (or oral) study NOAEL = 7.5 mg/kg/day (inhalation absorption rate = 100%)	Residential LOC for MOE = 100	Chronic Oral Toxicity in Dogs. LOAEL = 75 mg/kg/day based on alterations in hematological parameters [hematocrit and hemoglobin (males)], decreased body weight/body weight gain and increases in several organ weights.