

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  $1 \times 10^{-6}$  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 dimethomorph used for human risk assessment is shown in Table 1 of this unit:

TABLE 1.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR DIMETHOMORPH FOR USE IN HUMAN RISK ASSESSMENT

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Endpoint for Risk Assessment	Study and Toxicological Effects
Acute dietary females 13-50 years of age	Not applicable	Not applicable	No endpoint attributable to a single dose was identified.
Acute dietary general population including infants and children	Not applicable	Not applicable	No endpoint attributable to a single dose was identified
Chronic dietary all populations	NOAEL= 11 mg/kg/day UF = 100 Chronic RfD = 0.1 mg/kg/day	Special FQPA SF = 1 cPAD = chronic RfD/Special FQPA SF = 0.1 mg/kg/day	Carcinogenicity study in the rat LOAEL = 46.3 mg/kg/day based on decreased body weight and statistically significant increases in liver lesions in female rats
Short-term dermal (1 to 7 days)	Oral study NOAEL= 60 mg/kg/day (dermal absorption factor = 5 %)	LOC for MOE = 100	Developmental toxicity study in the rat LOAEL = 160 mg/kg/day based on decreased body weight, decreased body weight gain, and decreased food consumption
Intermediate-term dermal (1 week to several months)	Oral study NOAEL= 15 mg/kg/day (dermal absorption factor = 5 %)	LOC for MOE = 100	Subchronic feeding study in dogs LOAEL = 43 mg/kg/day based on decreased absolute and relative prostate weight and possible threshold liver effects
Long-term dermal (several months to lifetime)	Not applicable	Not applicable	The current use pattern does not indicate a concern for long-term exposure/risk
Short-term inhalation (1 to 7 days)	Oral study NOAEL= 60 mg/kg/day (inhalation absorption factor = 100 %)	LOC for MOE = 100	Developmental toxicity study in the rat LOAEL = 160 mg/kg/day based on decreased body weight, decreased body weight gain, and decreased food consumption
Intermediate-term inhalation (1 week to several months)	Oral study NOAEL= 15 mg/kg/day (inhalation absorption rate = 100%)	LOC for MOE = 100	Subchronic feeding study in dogs LOAEL = 43 mg/kg/day based on decreased absolute and relative prostate weight and possible threshold liver effects
Long-term inhalation (several months to lifetime)	Not applicable	Not applicable	The current use pattern does not indicate a concern for long-term exposure/risk