

### 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. A UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intraspecies differences. Acceptable developmental toxicity studies were performed in rats and rabbits, with evidence of neurotoxicity in the rat study, and an acceptable 2-generation reproduction study in rats. The developmental toxicity rabbit study did not exhibit either quantitative or qualitative susceptibility. Neurotoxicity studies are not available. Although, the Agency has concluded that there is a concern for prenatal and/or postnatal toxicity resulting from exposure to sethoxydim, the concern is reduced

because the fetal effects in the developmental rat study were seen only at the high dose. Concern is also low because the LOAEL for offspring toxicity for the 2-generation reproduction rat study is based on conservative determinations of offspring toxicity. However, due to lack of subchronic and developmental neurotoxicity studies with evidence of developmental (tail) abnormalities in the rat developmental and reproductive studies the additional 10X FQPA safety factor (SF) in the form of a data base UF was retained.

For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (aRfD or cRfD) where the reference dose (RfD) is equal to the NOAEL divided by the appropriate UF (RfD = NOAEL/UF). Where an additional 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  $1 \times 10^{-6}$  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 ( $\text{MOE}_{\text{cancer}} = \text{point of departure/exposures}$ ) is calculated. A summary of the toxicological endpoints for sethoxydim used for human risk assessment is shown in the following Table 2:

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

Exposure Scenario	Dose Used in Risk Assessment, UF	Special FQPA SF* and Level of Concern for Risk Assessment <sup>k</sup>	Study and Toxicological Effects
Acute dietary (Females 13–50 years of age and including infants and children)	NOAEL = 180 mg/kg/day UF = 1,000 Acute RfD = 0.18 mg/kg/day	Special FQPA SF = 1X aPAD = acute RfD ÷ Special FQPA SF = 0.18 mg/kg/day	Rat developmental toxicity <i>Developmental</i> LOAEL = 650 mg/kg/day based on decreased fetal body weight, tail abnormalities, delayed ossification
Acute dietary (General population)	NOAEL = 180 mg/kg/day UF = 1,000 Acute RfD = 0.18 mg/kg/day	Special FQPA SF = 1X aPAD = acute RfD ÷ Special FQPA SF = 0.18 mg/kg/day	Rat developmental toxicity <i>Maternal</i> LOAEL = 650 mg/kg/day based on irregular gait that was observed in 12/34 dams on the first day of dosing
Chronic dietary (All populations)	NOAEL = 14 mg/kg/day UF = 1,000 Chronic RfD = 0.014 mg/kg/day	Special FQPA SF = 1X cPAD = chronic RfD ÷ Special FQPA SF = 0.014 mg/kg/day	Mouse carcinogenicity study LOAEL = 41 mg/kg/day based on liver hypertrophy and fatty degeneration
Short-term Incidental oral (1–30 days)	NOAEL = 180 mg/kg/day	<i>Residential</i> LOC for MOE = 1,000	Rat developmental toxicity <i>Maternal</i> LOAEL = 650 mg/kg/day based on irregular gait that was observed in 12/34 dams on the first day of dosing
Intermediate-term Incidental oral (1–6 months)	NOAEL = 45.6 mg/kg/day	<i>Residential</i> LOC for MOE = 1,000	90-Day mouse oral toxicity LOAEL = 137 mg/kg/day based on increased liver weight and hepatocellular hypertrophy