

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

Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics	Pyraflufen-ethyl was readily absorbed and excreted within 96 hours following a single or repeated oral dose of 5 mg/kg (plasma $t_{1/2}$ of 3–3.5 hours). However, at a dose of 500 mg/kg, absorption was saturated as indicated by C_{max} values which did not reflect the 100-fold dose differential (2.7–2.8 Fg eq/g for the low-dose group and 100–107 Fg eq-hr/g for the high-dose group). Following single or multiple oral low doses (5 mg/kg) of pyraflufen ethyl, urinary excretion accounted for 27–33% of the administered radioactivity suggesting that a multiple exposure regimen did not affect the absorption/excretion processes. Urinary excretion was reduced to only 5–7% following a single 500 mg/kg dose. Excretion via the feces accounted for the remainder of the administered radioactivity in all treatment groups. Analysis of biliary excretion following a single 5 mg/kg dose showed that 36% of the administered dose appeared in the bile. Based upon the excretion data, total bioavailability of a low dose was approximately 56%. Biliary excretion data were not available for a high-dose group which prevented a definitive assessment of bioavailability. Excretory patterns did not exhibit gender-related variability. However, plasma and blood clearance was more rapid in females than in males as shown by plasma/blood radioactivity time-course and the greater AUC values for males (32.3 vs 18.4 Fg eq-hr/g for the low-dose group and 2,738 vs 1,401 Fg eq-hr/g for the high-dose group). Radioactivity concentrations indicated tissue concentrations at or near detection limits (generally <0.01 Fg eq/g and never exceeding 0.02 Fg eq/g) at 96 hours postdose for any tissues. Therefore, neither pyraflufen-ethyl nor its metabolites appear to undergo significant sequestration. Tissue burden data following compound administration did not suggest a specific target beyond those tissues, namely liver and kidney, which are associated with absorption and elimination of orally administered xenobiotics.

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 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 intraspecies differences.

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 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 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 pyraflufen-ethyl used for human risk assessment is shown in Table 2.

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

Exposure Scenario	Dose (mg/kg/day) UF/MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute dietary	Not applicable	Not applicable	No adverse effect attributable to a single exposure (dose) was observed in oral toxicity studies, including the developmental toxicity studies in rats and rabbits.