

TABLE 2.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY—Continued

Guideline No.	Study Type	Results
870.5450	Rodent Dominant Lethal	Reported as negative (though unacceptable).
870.5550	Unscheduled DNA synthesis (RPH)	Reported as negative (though unacceptable).
870.7485	Metabolism and pharmacokinetics (rat)	No sex-related differences in absorption were apparent. Within 48 hours of treatment, >90% of the administered dose was recovered in the excreta suggesting that elimination of the labeled test material was rapid. No specific sequestering tissues or organs were identified. Seven days after treatment, essentially all the test material had been eliminated. Rats that received the test material by intravenous injection excreted 87-95% of the administered dose in the urine and approximately 6% into the feces. This suggests that 15-28% of the administered dose recovered in the feces represents unabsorbed material. Metabolite characterization studies show that essentially all of the test material was excreted unchanged. Two minor metabolites CL 252,974 and CL 60,032 were detected in the urine or feces of treated rats; however, their contribution combined was <0.5% of the administered dose. Up to 12 additional unidentified metabolites were isolated, but they constituted >3% of the administered dose. Based on the results, the study author suggests that what limited metabolism of CL 243,997 occurs, proceeds through hydrolysis to form the 2-carbonyl derivatives: CL 252,974 and CL 60,032.
870.7600	Dermal penetration	NA

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 margin of exposure (MOE). A 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 factor (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.

A summary of the toxicological endpoints for imazapyr used for human risk assessment is shown in Table 3 of this unit:

TABLE 3.—SUMMARY OF TOXICOLOGICAL DOSE AND ENDPOINTS FOR IMAZAPYR 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 (Females 13-50 years of age and General population including infants and children)	none	none	An acute dietary endpoint was not selected based on the absence of an appropriate endpoint attributable to a single dose.
Chronic Dietary (All populations)	Oral Study NOAEL= 250 mg/kg/day UF = 100 Chronic RfD= 2.5 mg/kg/day	FQPA SF = 1X cPAD = chronic RfD/FQPA SF = 2.5 mg/kg/day	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog imazapic
Short- and Intermediate- Term Incidental Oral (1-30 days and 1-6 months)	Oral Study NOAEL= 250 mg/kg/day	LOC for MOE= NA (Occupational) LOC for MOE =100 (Residential, includes the FQPA SF - At present time no residential uses)	1-Year Dog [feeding] Study No LOAEL was demonstrated with imazapyr at doses up to 250 mg/kg/day (HDT); HIARC recommended this dose for RA for imazapyr, based on skeletal muscle effects seen in dogs with structural analog imazapic