

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

Guideline No.	Study Type	Results
870.5395	Micronucleus Assay	No clastogenic response at any dose or sacrifice time
870.5550	Unschedule DNA synthesis	No clear evidence of genotoxicity. However, study not acceptable
870.7485	Metabolism and pharmacokinetics	<p>Single dose of 1 or 100 mg/kg bwt: Urinary excretion - 76–88% of administered radioactivity with 59–72% excreted within first 24 hours. Fecal excretion ranged from 13–32%. 83–91% of administered dose excreted (urine and feces) by 24 hours and 91 to &gt; 99% excreted by 48 hours. At least 68–88% of administered dose absorbed. Recovery in tissues/animal: 0.24% of administered radioactivity (range: 0.07 – 0.51%). General order of concentration plasma &gt; whole blood &gt; lungs &gt; subcutaneous fat &gt; heart &gt; kidneys &gt; retroperitoneal fat &gt; liver &gt; gonads &gt; pancreas &gt; skeletal muscle. No volatile radioactivity detected 0–24 hours after dosing. Between 100–106% of administered radioactivity recovered.</p> <p>Single dose of 1 or 100 mg/kg bwt: Radioactivity rapidly excreted: total of 78–92% excreted by 48 hours. Renal excretion predominant route of elimination (65–72% by 48 hours), indicating that at least 65–72% of the administered dose was absorbed. None of test material found in its original form in urine. Three metabolites identified in urine: 13–26% of the radioactivity was recovered in the feces by 48 hours. The same three metabolites identified in urine were also present in the feces: Proposed metabolic steps: Consecutive hydrolysis (saponification) of the two carboxylic acid ester groups and a decarboxylation of one of the carboxylic groups, resulting in an aromatization of the pyrazoline ring. Enterohepatic circulation is unlikely to play a major role. In males, there appears to be either lower intestinal absorption or a higher biliary excretion when compared to females.</p>

### 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). 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 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 mefenpyr-diethyl used for human risk assessment is discussed in this unit: The Agency has determined that there is no acute toxicological concern. No appropriate endpoint was identified from oral toxicity studies including the developmental toxicity studies in rats and rabbits. No short-term or intermediate-term dermal or systemic toxicity was observed up to 1,000 mg/kg/day and no development effects were observed in the developmental rat study at 1,000 mg/kg/day. Therefore, no endpoint was identified for risk assessment for the short- and intermediate-term risk assessments. Based on the current use-pattern (i.e. one application per season) long-term exposure via the dermal route is not expected. Therefore, a long-term dermal end-point was not identified. Similarly, no endpoint was identified for carcinogenicity since this chemical is not classified as a human carcinogen.

For chronic dietary risk assessment the NOAEL of 57.3 mg/kg/day in a 2-generation reproduction toxicity study was identified as an appropriate endpoint. Taking into account the UF of

100, the chronic RfD is 0.57 mg/kg/day (NOAEL 57.3/ UF 100 = 0.57). The Agency has used a FQPA Factor of 1 and therefore, the chronic population adjusted dose (PAD) is 0.57 mg/kg/day (RfD 0.57/FQPA 1 = 0.57) for mefenpyr-diethyl.

### C. Exposure Assessment

1. *Dietary exposure from food and feed uses.* Tolerances have been previously established (40 CFR 180.509(b)) under FIFRA section 18, the Emergency Exemption Program, for the combined residues of mefenpyr-diethyl. To establish permanent tolerances, risk assessments were conducted by EPA to assess dietary exposures from mefenpyr-diethyl in food as follows:

i. *Acute exposure.* Acute dietary risk assessments are performed for a food-use pesticide if a toxicological study has indicated the possibility of an effect of concern occurring as a result of a 1-day or single exposure.

An acute dietary risk assessment was not performed because no appropriate acute toxicological endpoint could be identified in any of the oral toxicity studies including the developmental studies in rats and rabbits.

ii. *Chronic exposure.* The chronic dietary exposure assessment was conducted using the Dietary Exposure Evaluation Model software with the