

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

Guideline No.	Study	Results
870.3700	Prenatal developmental in nonrodents—rabbit	Maternal NOAEL = 200 mg/kg/day LOAEL = not established; the dosing in this study are considered adequate based on the results of a range finding study in which a treatment-related increase in the number of does aborting was seen at 250 mg/kg/day and above. Developmental NOAEL = 200 mg/kg/day LOAEL = not established
870.3800	Reproduction and fertility effects—rat	Parental/Systemic NOAEL = 1.6 mg/kg/day in males, 1.8 mg/kg/day in females. LOAEL = 6.5 mg/kg/day in males and 7.4 mg/kg/day in females based on decreased body weight, body weight gain, and food consumption in both sexes. Reproductive NOAEL = 16.4 mg/kg/day in males, 18.3 mg/kg/day in females. LOAEL = not established. Offspring NOAEL = 16.4 mg/kg/day in males, 18.3 mg/kg/day in females. LOAEL = not established
870.4100	Chronic toxicity dogs	NOAEL = 1.01 mg/kg/day in males, 1.05 mg/kg/day in females LOAEL = 8.95 mg/kg/day in males, 10.42 mg/kg/day in females based on changes in hematological and clinical chemistry parameters in both sexes and histopathological effects in bone marrow, liver, and kidney in both sexes.
870.4300	Chronic/Carcino-genicity rats	NOAEL = 3.9 mg/kg/day in males, 4.8 mg/kg/day in females. LOAEL = 9.7 mg/kg/day in males and 9.7 mg/kg/day in females based on decreased body weight, body weight gain, and food consumption in both sexes. No evidence of carcinogenicity
870.4300	Carcinogenicity mice	NOAEL = 1.5 mg/kg/day in males, 19.7 mg/kg/day in females. LOAEL = 15.4 mg/kg/day in males, 35.7 mg/kg/day in females based on decreased body weight and body weight gain in females and hematological effects and decreased kidney weight in males. No evidence of carcinogenicity
870.5265	Gene Mutation	Non-mutagenic when tested up to 5000 ug/plate, in presence and absence of activation, in <i>S. typhimurium</i> strains TA98, TA100, TA1535, and TA1537 and <i>E.coli</i> strain WP2uvra.
870.5300	Gene Mutation	Non-mutagenic at the TK locus in L5178Y mouse lymphoma cells tested up to cytotoxic concentrations or limit of solubility, in presence and absence of S-9 activation.
870.5375	Chromosome aberration	Did not induce structural chromosome aberration in CHO-K1 cell cultures in the presence and absence of activation up to cytotoxic concentrations.
870.5385	Chromosomal aberration	Non-mutagenic in ICR mouse bone marrow micronucleus chromosomal aberrations assay up to cytotoxic concentrations.
870.7485	Metabolism and pharmacokinetics—rat	Total recovery of the administered dose was <93% for all treatment groups. Fecal excretion was the major route of elimination (66–83% of the dose), with eight primary metabolites detected. These metabolites, as well as those identified in the urine and bile, were the result of metabolic reactions including hydrazine oxidation, demethylation, ring hydroxylation, and molecular scission with the loss of hydrazinecarboxylic acid portion with subsequent conjugation.

In its objection to a separate bifentazate tolerance action, NRDC, asserts that developmental toxicity is a data gap for bifentazate. NRDC appears to be referring to language in the Table 1, Unit III.A. of the **Federal Register** final rule of February 1, 2002, that states that a clear assessment of developmental toxicity was not possible in the range finding study used to choose the dose levels for the developmental toxicity study in rabbits. The Agency concludes there are acceptable developmental toxicity studies conducted with bifentazate in rats and in rabbits, and an

acceptable 2-generation reproduction study in rats, which are described in Table 1. of this unit.

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. An 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 factors