

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

Guideline No.	Study Type	Results
870.5500	Mutagenic-Reverse Mutation	Positive direct acting mutagen. Both batches tested were equally mutagenic. Effect of metabolic activation not assessed.
870.5500	Mutagenic-DNA Repair Test	Positive for DNA damage without metabolic activation.
870.5550	Unscheduled DNA Synthesis in WI 38 Fibroblasts:	Positive in the presence of metabolic activation only.
870.5500	Reverse Mutation	Positive for reverse mutations in <i>Salmonella</i> TA100, TA1535 & TA1538, & in <i>E. coli</i> WP2. Rat liver S-9 had no effect on mutagenicity
870.5575	Mutagenic-Recomb/Convers Assay	Positive for recombinants with/without metabolic activity.
870.6200	Acute neurotoxicity screening battery	Not available.
870.6200	Subchronic neurotoxicity screening battery	Not available.
870.6300	Developmental neurotoxicity	Not available.
870.7485	Metabolism and pharmacokinetics	Doses: 50 and 5,000 ppm. Results: The 5,000 ppm level had been shown to cause the tumors in mice but not in rats. The studies suggested that folpet was tumorigenic in the mouse and not in the rat because: Greater intake in the mouse and greater target tissue exposure to active metabolites that the mouse could not detoxify; greater local effects on mouse upper gastrointestinal tract; and greater reliance by the mouse on glutathione for detoxification of folpet.
870.7485	Metabolism and pharmacokinetics	C ¹⁴ -Folpet was administered orally to Sprague-Dawley rats in 3 studies: 1. Single dose of 10 mg/kg; 2. Single dose of 500 mg/kg; and 3. On day 15, 10 mg/kg of C ¹⁴ -Folpet after 14 consecutive days of unlabeled folpet at 10 mg/kg. Samples were examined for radioactivity for up to 120 hours post C ¹⁴ -dosing. Results: 1. Single C ¹⁴ -Folpet at 10 mg/kg was absorbed > 90% of the dose, there was rapid urinary excretion and by 120 hours, there was little detectable radioactivity. 2. Single C ¹⁴ -Folpet at 500 mg/kg was about 60% absorbed with the urinary excretion rate being slower than after the 10 mg/kg dose (possibly due to rate-limiting absorption). 3. Single C ¹⁴ -Folpet at 10 mg/kg following 14 daily non-labeled doses of 10 mg/kg yielded results similar to those observed after a single C ¹⁴ dose. 4. No accumulation of folpet was detected during the 5 days after dosing; concentrations of radioactivity in measured tissues were generally below the limit of detection at 10 mg/kg or were detected at very low levels at 500 mg/kg. 5. Phthalamic acid was determined to be the single active metabolite found in urine & it was suggested that its formation from Folpet may have been by trichloromethylthio groups loss and hydrolytic cleavage of the maleimide ring. At 10 mg/kg, the major fecal metabolite was phthalamic acid and at 500 mg/kg, the radioactivity was primarily associated with unchanged C ¹⁴ -folpet (assumed to be unabsorbed test article).
870.7600	Dermal penetration	Doses: C ¹⁴ -Folpet was administered dermally to male doses of 10, 1, 0.1, and 0.01 mg/rat (200 uL volume of test suspension to 18.9 cm ² of clipped skin) for up to 24 hours. Blood, urine, feces, carcass and skin radioactivity was measured (up to 24 hrs). Results: 1. Rapid absorption into the skin and carcass; 2. Low blood levels; 3. Primary excretion by urine with rate apparently inversely related to quantity applied; and 4. Minor bile involvement in excretion as little in feces.