

TABLE 1A.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY FOR METOLACHLOR (PC CODE 108801)—Continued

Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics Unacceptable	Conclusions: Single low (1.5 mg/kg), single high (300 mg/kg) and repeated low (1.5 mg/kg/day for 15 days) oral doses of metolachlor were readily absorbed and eliminated by male and female rats. Urinary and fecal elimination of radioactivity associated with orally administered ^{14}C metolachlor was essentially complete within 48 to 72 hours after dosing. Low- and high-dose females eliminated ^{14}C more rapidly ($p < 0.003$, half-lives of elimination, 16.6 and 15.6 hours, respectively) than low- and high-dose males and repeated-dose animals of both sexes (half-lives, 18.2 and 20.0 hours). Elimination by all animals followed first-order kinetics. Approximately one-half to two-thirds (48 to 64 percent) of the ^{14}C administered was recovered from the urine within 7 days; similar amounts were present in the feces. Low-dose males eliminated slightly more of the radioactive dose in the feces (55 percent) than the urine (48 percent). The opposite trend was seen in the low-dose females and repeated-dose rats of both sexes; these animals excreted approximately 58 to 64 percent of the ^{14}C dose in the urine and 42.5 to 46.5 percent in the feces within 7 days after dosing. High-dose animals excreted similar amounts (58 to 60 percent) of the radioactive dose in the urine and feces. Total recoveries of ^{14}C (urine, feces, and tissues) tended to be high and were between 105 and 122.5 percent.
870.7485	Metabolism and pharmacokinetics	In a rat metabolism study (MRID #431642-01), ^{14}C -Metolachlor was administered orally in PEG-200 HWI 6117-208 or corn oil ABR-94001 to groups (5 sex/dose) of male and female Sprague-Dawley rats at a low oral dose (1.5 mg/kg), repeated low oral dose (1.5 mg/kg x 14 days), and a single high dose (300 mg/kg). Control animals (1/sex) received blank formulation. Comparison of oral and intravenous data showed that of the administered dose, between 69.6% and 93.2% was absorbed. Distribution data showed that the only significant sites of residual radioactivity at 7 days post-dose were residual carcass (0.9 – 2.2% of the administered dose) and red blood cells (0.95 – 1.53 μg equivalents/gram in blood cells for all low dose male and female rats). Dosing regimen did not result in any apparent accumulation of residual radioactivity. Excretion data showed that urine and feces were both significant routes for elimination of metolachlor derived radioactivity. In the low dose groups, the urine appeared more of a predominant route for excretion in female rats than in males, whereas fecal excretion was slightly higher in males. However, at the high oral dose, there were no apparent sex-related differences in the pattern of urinary excretion. Examination of urinary excretion data as presented in graphical format indicated that at the 300 mg/kg dose, excretion was delayed vs the low oral dose, suggesting saturation of elimination.

The nature of the toxic effects caused by *S*-metolachlor are discussed in Table 1b below as well as the NOAEL and the LOAEL from the toxicity studies reviewed.

TABLE 1B.—SUBCHRONIC, CHRONIC, AND OTHER TOXICITY FOR S-METOLACHLOR (PC CODE 108800)

Guideline No.	Study Type	Results
870.3100	90-Day oral toxicity rodents	NOAEL = 15 milligram/kilogram/day (mg/kg/day) LOAEL = 150 mg/kg/day based on lower body weights/body weight gains, reduced food consumption and food efficiency and increased kidney weights in males
870.3100	90-Day oral toxicity rodents	NOAEL = 208 mg/kg/day in males and 236 mg/kg/day in females LOAEL was not defined.
870.3150	90-Day oral toxicity in nonrodents	NOAEL = 62 mg/kg/day in males and 74 mg/kg/day in females LOAEL = was not established
870.3700	Prenatal developmental in rodents	Maternal NOAEL = 50 mg/kg/day LOAEL = 500 mg/kg/day based on increased clinical signs of toxicity, decreased body weights/body weight gains, food consumption and food efficiency. Developmental NOAEL = 1,000 mg/kg/day LOAEL was not established
870.3700	Prenatal developmental in nonrodents	Maternal NOAEL = 20 mg/kg/day LOAEL = 100 mg/kg/day based on clinical signs of toxicity Developmental NOAEL = 500 mg/kg/day LOAEL was not established