

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

Guideline No.	Study Type	Results
870.7485	Metabolism and pharmacokinetics (rat)	<p>Quinoline-labeled and phenyl-labeled quinoxifen were rapidly absorbed with approximately 68-85% of the administered dose being eliminated within 24 hours. Overall recovery of the dosed radioactivity ranged from 83.5-96.2%. Sex, dose, and multiple dosing had little or no effect on the excretion profile at 48 hours post-dosing. Changing the position of the ¹⁴C-label altered the pattern of excretion. The major route of elimination was through the urine in the phenyl-labeled test substance (44.9-48.7% of dose in urine and 38.2-39.8% of dose in feces) and through the feces in the quinoline-labeled test substance (65.8-78.3% of dose in feces and 13.4-19.7% of dose in urine). Biliary excretion increased its contribution to fecal radioactivity as the dose increased. Concentrations of radioactivity in the tissues were generally slightly lower in the males than females and in the low-dose compared to the high-dose group. The highest concentrations of radioactivity were found in the kidney, liver, ovaries, perirenal fat, GI tract and carcass. Maximum plasma concentration occurred between 0.5 and 1.5 hours, and elimination half-lives were ≤ 1 hour and 15-19 hours (10 mg/kg group) and 2-3 hours and 18-22 hours (500 mg/kg group).</p> <p>The presence of several radioactive components was determined in the unhydrolyzed urine (up to 12), fecal extracts (up to 8), and bile (up to 6). No differences in the metabolite profile were observed that were related to sex or multiple dosing. Increasing amounts of the parent compound were found in the feces with increasing dose. No other dose-related differences were observed. Identified metabolites accounted for 41.0-42.8% dose in the [Phenyl-U-¹⁴C] XDE-795 treated group, and only 17.0-31.7% dose in the other treated groups. The [Phenyl-U-¹⁴C] XDE-795 treated group had no urinary metabolites in common with the [2-Quinoline-¹⁴C] XDE-795 treated groups suggesting cleavage of the parent molecule. An acid-labile conjugate of 4-fluorophenol was found in the urine of the [Phenyl-U-¹⁴C] XDE-795 treated group (28.7-32.8% dose). 5,7-Dichloro-4-hydroxyquinoline was observed in the urine of the [2-Quinoline-¹⁴C] XDE-795 treated groups in small quantities (0.7-1.7% dose). Thus, the identified metabolites in the urine followed diaryl-ether cleavage of the parent compound. Fluorophenyl-ring-OH-XDE-795 (two isomers) were found in the feces of all treated groups (5.4-10.6% dose). In the bile of the treated groups, two major metabolites were identified, a glucuronide and/or sulfate conjugate(s) of the two isomers of fluorophenyl ring-hydroxy-XDE-795 (9-19% dose) and an unidentified metabolite (13-21% dose).</p>

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 factor (SF) is retained due to concerns unique