

## Pharmacokinetics of [<sup>125</sup>I]-2-Iodo-3,7,8-trichlorodibenzo-*p*-dioxin in Mice: Analysis with a Physiological Modeling Approach

HON-WING LEUNG,\* ALAN POLAND,† DENNIS J. PAUSTENBACH,‡  
F. JAY MURRAY,\* AND MELVIN E. ANDERSEN§

\*Syntex Corporation, 3401 Hillview Avenue, Palo Alto, California 94304; †McArdle Laboratory for Cancer Research, University of Wisconsin, 450 North Randall Street, Madison, Wisconsin 53706; ‡ChemRisk, McLaren Environmental Engineering, 980 Atlantic Avenue, Alameda, California 94501; and §Chemical Industry Institute of Toxicology, 6 Davis Drive, Research Triangle Park, North Carolina 27709

Received April 21, 1989; accepted January 16, 1990

Pharmacokinetics of [<sup>125</sup>I]-2-Iodo-3,7,8-trichlorodibenzo-*p*-dioxin in Mice: Analysis with a Physiological Modeling Approach. LEUNG, H.-W., POLAND, A., PAUSTENBACH, D. J., MURRAY, F. J., AND ANDERSEN, M. E. (1990). *Toxicol. Appl. Pharmacol.* 103, 411-419. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD) is a potent inducer of hepatic microsomal enzymes. The influence of an inducing dose of TCDD on tissue distribution and other pharmacokinetic behavior of a TCDD analog in the mice was examined by employing a high specific activity radioligand, [<sup>125</sup>I]-2-iodo-3,7,8-trichlorodibenzo-*p*-dioxin (ITCDD). Female C57BL/6J mice were pretreated with 0.1 μmol/kg of TCDD or the vehicle only, followed by 0.1 nmol ITCDD/kg 3 days later. The control animals had the highest concentration of ITCDD-derived radioactivity in the fat, but the TCDD-pretreated animals had the highest concentration in their livers. Whole-body elimination of ITCDD approximated first-order behavior, and induction by pretreatment with the inducing dose of TCDD almost doubled the rate of excretion (control mice,  $t_{1/2}$  = 14.2 days; pretreated mice,  $t_{1/2}$  = 8.0 days). All disposition results in naive and pretreated mice were satisfactorily described by a consistent physiologically based pharmacokinetic model (Leung *et al.*, 1988a) in which induction increased the amount of microsomal ITCDD-binding protein from 1.75 to 20 nmol/liver and increased the rate constant for metabolism of free ITCDD from 1 to 3/hr/kg liver. The binding affinity of the microsomal ITCDD-binding protein was the same (20 nM) in both induced and noninduced mice. Model simulations indicated a time delay in the elimination of nonparent ITCDD metabolites from the body and a more rapid absorption of the parent ligand in the pretreated mice. Consistent with previous physiological modeling with TCDD in different mouse strains, the primary factor influencing the liver/fat concentration ratio appears to be the affinity and capacity of the microsomal TCDD-binding proteins, which are altered by induction. These dose-dependent pharmacokinetic differences with ITCDD are important considerations for TCDD risk assessment in which data from high dose rodent experiments are extrapolated to predict behavior at much lower environmental concentrations in exposed humans.