

Induction of Cytochrome P450-Dependent Monooxygenase Activities in
Rat Hepatoma H-4-IIE Cells in Culture by 2,3,7,8-Tetrachlorodibenzo-
p-Dioxin and Related Compounds: Mechanistic Studies
Using Radiolabeled Congeners¹

T. ZACHAREWSKI, M. HARRIS, AND S. SAFE²

*Department of Veterinary Physiology and Pharmacology, College of Veterinary Medicine,
Texas A&M University, College Station, Texas 77843-4466*

Treatment of rat hepatoma H-4-IIE cells in culture with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), 2,3,7,8-tetrachlorodibenzofuran (TCDF), 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PeCDD), 1,2,3,7,8-pentachlorodibenzofuran (PeCDF), 1,2,7,8-TCDF, and 2,3,7-trichlorodibenzo-*p*-dioxin (TrCDD) resulted in the structure-dependent induction of aryl hydrocarbon hydroxylase and ethoxyresorufin *O*-deethylase activities. The induction potencies followed the order 2,3,7,8-TCDD > 2,3,7,8-TCDF > 1,2,3,7,8-PeCDD ~ 1,2,3,7,8-PeCDF > 1,2,7,8-TCDF > 2,3,7-TrCDD and were comparable to structure-toxicity relationships which have previously been reported. In contrast, many of the properties of these compounds were structure-independent. For example, using tritiated congeners of high specific activity (>30 Ci/mmol) the sedimentation coefficients (S) for the nuclear and cytosolic aryl hydrocarbon (Ah) receptor complexes were 5-6 and 9-10 S, respectively, for all the radioligands. Moreover, examination of the processing of nuclear Ah receptor complexes for the radiolabeled congeners showed that after 6 h, the rates of nuclear processing were very low and varied between 0.006 and 0.0385 fmol degraded/mg protein/mg total DNA. These results were consistent with the reported stability and persistence of the nuclear Ah receptor complexes and in addition, there were no apparent structure-dependent differences in the processing rates. Inspection of the nuclear receptor levels and the corresponding induced enzyme activities for the congeners showed that there was a linear correlation between average nuclear receptor complex levels (18-42 h) and induced enzyme activities (32-42 h) for all six radioligands; these data indicated that the rates of cytochrome P450-dependent gene expression correlated with the levels of nuclear Ah receptor complex. In contrast, the accumulation of occupied nuclear receptor complexes in rat hepatoma H-4-IIE cells was structure-dependent and appeared to be one of the factors which governed the observed structure-induction and the previously reported structure-toxicity relationships for 2,3,7,8-TCDD and related halogenated aryl hydrocarbons.