

Structure-Dependent Induction of Aryl Hydrocarbon Hydroxylase Activity in C57BL/6 Mice by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Congeners: Mechanistic Studies

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Structure-Dependent Induction of Aryl Hydrocarbon Hydroxylase Activity in C57BL/6 Mice by 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin and Related Congeners: Mechanistic Studies. HARRIS, M., ZACHAREWSKI, T., PISKORSKA-PLISZCZYNSKA, J., ROSENGREN, R., AND SAFE, S. (1990). *Toxicol. Appl. Pharmacol.* **105**, 243–253. The time- and dose-dependent induction of murine hepatic microsomal aryl hydrocarbon hydroxylase (AHH) and ethoxyresorufin *O*-deethylase (EROD) activities by five polychlorinated dibenzo-*p*-dioxin and dibenzofuran congeners showed that the order of induction potency was 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) > 2,3,7,8-tetrachlorodibenzofuran (TCDF) > 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PCDD) > 1,2,3,7,8-pentachlorodibenzofuran (PCDF) > 2,3,7-trichlorodibenzo-*p*-dioxin (TrCDD). These structure-induction relationships were comparable to the structure-toxicity and competitive structure-receptor binding relationships previously reported for these compounds. However, using the corresponding radiolabeled congeners, the direct binding K_d values for dissociation of the cytosolic receptor-ligand complexes were 9.52, 7.96, 1.27, 3.10, and 8.31 nM for the 2,3,7,8-TCDD, 2,3,7,8-TCDF, 2,3,7-TrCDD, 1,2,3,7,8-PCDD, and 1,2,3,7,8-PCDF congeners and these data were clearly not structure dependent (i.e., similar to the structure-activity relationships). Some of the molecular properties for several radioligand-receptor complexes were similar; for example, the sedimentation coefficients for the cytosolic and nuclear receptor complexes varied from 8.8–10.4 S and 5.98–7.07 S, respectively, and the nuclear receptor complexes for all the radioligands eluted from a DNA-Sepharose column at salt concentrations of 0.27–0.29 M. Treatment of the mice with a maximum inducing dose of 2,3,7,8-³H]TCDD resulted in a time-dependent formation of the nuclear receptor complex which was maximized between 16–24 hr and subsequently decreased up to 72 hr after initial exposure. In parallel studies, the nuclear receptor complex levels were determined 16 hr after treatment of the mice with different doses (2.25, 4.5, and 45 μ g/kg) of all five radioligands. The results showed that at submaximal induction of the monooxygenase enzyme activities there was a linear correlation between the induced AHH or EROD activities (after 32 hr) and the corresponding nuclear receptor complex levels. It was also apparent from the data that the relative levels of nuclear receptor complex were structure dependent and this suggests that the transformation or activation of cytosolic receptor complexes may be a ligand structure-dependent process which correlates with the observed structure-activity relationships for 2,3,7,8-TCDD and related compounds.