

Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on I-Compounds in Hepatic DNA of Sprague–Dawley Rats: Sex-Specific Effects and Structure–Activity Relationships

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Effects of 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin on I-Compounds in Hepatic DNA of Sprague–Dawley Rats: Sex-Specific Effects and Structure–Activity Relationships. RANDEATH, K., PUTMAN, K. L., RANDEATH, E., ZACHAREWSKI, T., HARRIS, M., AND SAFE, S. (1990). *Toxicol. Appl. Pharmacol.* **103**, 271–280. The effects of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related compounds on the specific patterns of age-dependent I-compound DNA adducts in the liver of male and female Sprague–Dawley rats were determined by the <sup>32</sup>P-postlabeling assay. In female rats, TCDD causes a dose-dependent decrease of several individual and total hepatic I-compound levels after administration of 1 and 5 μg/kg per week for 4 weeks. In contrast, no such effects were observed in male Sprague–Dawley rats treated with the 5 μg/kg dose level of TCDD. The relative effects of TCDD, 1,2,3,7,8-pentachlorodibenzo-*p*-dioxin (PCDD) and 1,2,4,7,8-PCDD on hepatic I-compound levels in the susceptible female Sprague–Dawley rats were determined using a dose of 5 μg/kg per week for 4 weeks. The two compounds which are substituted in all four lateral positions, namely TCDD and 1,2,3,7,8-PCDD, caused a significant decrease in hepatic I-compound levels, whereas 1,2,4,7,8-PCDD which is substituted in only three lateral positions was inactive. The structure–activity relationships observed for the effects of these compounds on hepatic I-compounds correlated with their corresponding structure-Ah receptor binding and structure–toxicity relationships. The results are therefore consistent with a role for the Ah receptor in the TCDD-mediated reduction in hepatic I-compound levels in female Sprague–Dawley rats. These results and data from previous studies demonstrate a correlation between the susceptibility of an organ/species to the carcinogenic effects of TCDD and the reduction of I-compound levels. The significance of this correlation in the development of TCDD-induced carcinogenesis has not been delineated.