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- 133 STRUCTURE-DEPENDENT INDUCTION OF ARYL HYDRO-CARBON HYDROXYLASE BY TCDD AND RELATED COM-POUNDS: MECHANISTIC STUDIES. T Zacharewski, M Harris and S Safe. Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX.

The structure-induction relationships observed for 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-trichlorodi-benzo-p-dioxin (TrCDD) in rat hepatoma H-4-II E cells confirmed that 2,3,7,8-substituted congeners were more active as inducers of aryl hydrocarbon hydroxylase (AHH) than compounds containing only three lateral chlorosubstituents (1,2,7,8-TCDF and 2,3,7-TrCDD). However, using [<sup>3</sup>H]-analogs (sp. activity 30-50 Ci/nmol) of these congeners, it was shown that the sedimentation coefficients of their respective cytosolic and nuclear receptor complexes were comparable; moreover, the rates of degradation of their respective occupied nuclear receptors were also not structure-dependent. However, the following structure-dependent effects correlated with the structure-induction relationships; namely, (i) higher levels of nuclear receptor complexes were observed for the 2,3,7,8-substituted compounds and (ii) at comparable levels of nuclear receptor, the induction responses were higher for the 2,3,7,8-substituted congeners (ES-03554).

- 134 2,2',4,4',5,5'-HEXACHLOROBIPHENYL (HCBP) AS A 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) ANTAGONIST IN C57BL/6 MICE: L Biegel, D Davis, M Harris, L Safe and S Safe. Department of Veterinary Physiology and Pharmacology, Texas A&M University, College Station, TX.

At dose levels as high as 750 to 1000 umol/kg, HCBP did not cause fetal cleft palate, suppress the splenic plaque-forming cell response to sheep red blood cells or induce hepatic microsomal ethoxyresorufin O-deethylase (EROD) in C57BL/6 mice. However, cotreatment with an effective dose of TCDD plus HCBP (400-1000 umol/kg) partially antagonized TCDD-mediated cleft palate, immunotoxicity (i.e., suppression of the splenic plaque-forming cell response to sheep red blood cells) and hepatic microsomal EROD induction. 4,4'-Diiodo-2,3',5,5'-tetrachlorobiphenyl [<sup>125</sup>I<sub>2</sub>-TCBP] exhibited comparable partial antagonist activity and [<sup>125</sup>I<sub>2</sub>]-TCBP (3,350 Ci/nmol) did not exhibit any specific binding activity to the cytosolic Ah receptor. These results contrasted with previous studies with Aroclor 1254 which suggested that this mixture acted as a competitive Ah receptor antagonist (ES-03843).

- 135 TRANSPORT, METABOLISM AND CONTROL OF THYROID HORMONES RATS TREATED WITH 2,3,7,8-TETRACHLORODI-BENZO-P-DIOXIN. W L Roth and S D Aust. Dept. of Biochem., Michigan State Univ., E. Lansing, MI.

Male Fischer rats treated with 10 nmol TCDD/Kg body weight (3.23 ug/Kg) were injected with tracer doses (iv) of either T4 or T3 3 days later. Blood, liver, kidney, bile and urine samples were collected and extracted at time points ranging from 2 min to 15 hr post-tracer. HPLC separation of these extracts yielded data for tissue uptake, excretion, deiodination, and glucuronidation of T4, T3, and major metabolites in each compartment sampled. Transport and metabolism rates for a five compartment model were estimated and then optimized via the CONSAM analysis and modeling program. As predicted from the induction curve for cytochrome P-450c and associated glucuronosyl transferases by TCDD, glucuronidation of T4 was maximal at this dose of TCDD. However, steady-state T4 levels decrease only 40 %, compared with a 75 % drop which occurs at 77 nmol TCDD/Kg (25 ug/Kg). Tissue uptake and metabolism of T3 were not significantly changed. Data for T3 production from T4 in the liver suggest that deiodination is controlled by the flux of T4 through the plasma membrane high affinity uptake system, rather than by the concentration of T4 in the cytoplasm of hepatocytes. (Supported by NIH Grant No. ES3585.)

- 136 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) ENHANCES ESTRADIOL HYDROXYLATION AND SUPPRESSES ESTROGEN-DEPENDENT GROWTH OF MCF-7 HUMAN BREAST CANCER CELLS IN CULTURE. J F Gierthy, D W Lincoln, S J Kampcik, H W Dickerman, L McKenna, H L Bradlow\*, T Niwa\*, and G E Swaneck\*, Wadsworth Center, NYS DOH, Albany, NY, \*The Rockefeller University, NY, NY. Sponsor: L S Kaminsky

TCDD suppresses spontaneous breast tumors in the rat, exhibits antiestrogenic activity *in vivo* and *in vitro*, and induces cytochromes P-450. The effect of TCDD on cell proliferation and induction of estrogen metabolism in MCF-7 cells was determined to establish an *in vitro* model of TCDD's action on estrogen-dependent human breast tumors. TCDD (10<sup>-9</sup>M) suppresses postconfluent MCF-7 estrogen-dependent cell proliferation, characteristic of cancer cell growth *in vitro*, and induces a persistent 8- and 2-fold increase in 2- and 16 $\alpha$ -hydroxylation of 17 $\beta$ -estradiol (E<sub>2</sub>), respectively. This was accompanied by a concomitant increase in aryl hydrocarbon hydroxylase activity indicative of cytochromes P-450 induction. These results suggest that increased E<sub>2</sub> hydroxylation may play a role in the antiestrogenic activity of TCDD in MCF-7 cells and that TCDD's activity may furnish a prototype for the study and management of estrogen-dependent breast tumors. Supported in part by NIEHS ES03561 and NIH HD 19825 and CA 39734.