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possible to establish whether tissue-specific biomarker responses are related to the tissue-specific carcinogenic potency of these agents. (Supported in part by NIEHS ES09440, USEPA R825808)

831 ZEBRAFISH FIN REGENERATION AS A MODEL FOR DEVELOPMENTAL TOXICITY OF 2, 3, 7, 8-TETRACHLORODIBENZO-*P*-DIOXIN (TCDD).

J. M. Zodrow and R. L. Tanguay. *School of Pharmacy, University of Colorado Health Sciences Center, Denver, CO.*

Adult zebrafish completely regenerate their caudal fins following amputation. Fin regrowth can easily be followed *in vivo* and the new tissue can be used to study developmental processes. 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) is known to cause toxicity through the AhR pathway, binding to AhR allowing it to translocate to the nucleus and bind with ARNT, activating gene transcription of xenobiotic responsive genes. Hif-1α, a protein of the hypoxia responsive pathway, also requires ARNT dimerization for activation of the hypoxia responsive element and transcription of hypoxia genes. The expression of hypoxia regulated genes are essential for wound repair and neovasularization. Our laboratory has been using caudal fin regeneration in zebrafish to investigate molecular mechanisms of TCDD toxicity during development. When adult zebrafish were treated with 70 ppb TCDD (i.p.) and their fins were amputated, there was consistent inhibition of caudal fin regeneration. To determine the regeneration stage blocked by TCDD toxicity, zebrafish caudal fins were amputated and fish were injected at various time points during regeneration. We found that TCDD impaired fin regeneration at multiple stages of regeneration. Effects of TCDD on vasculature regrowth of the fin were studied using transgenic zebrafish that express green fluorescent protein driven by the blood cell specific GATA-1 promoter, allowing us to visualize the functional vasculature. TCDD significantly affects caudal fin vascular structure and function. We propose that TCDD activation of the AhR pathway squelches the Hif-1α pathway, resulting in decreased expression of hypoxia regulated genes, thereby decreasing neovascularization and fin regeneration.

832 INHIBITION OF HUMAN AND RAT CYP1A2 BY TCDD AND DIOXIN-LIKE CHEMICALS.

D. F. Staskal[1], L. S. Birnbaum[2] and M. J. DeVito[2]. [1]*Curriculum in Toxicology, University of North Carolina at Chapel Hill, Chapel Hill, NC and* [2]*ETD, NHEERL, ORD, USEPA, Research Triangle Park, NC.*

The tissue distribution of dioxins is dose-dependent due to hepatic sequestration by CYP1A2, which is an inducible binding protein. Thus the disposition of dioxins is dependent upon the ability to bind and induce CYP1A2. Current risk assessments assume that humans and rats sequester dioxins in a similar manner. The present study examines this assumption by comparing the ability of dioxins to inhibit human and rat CYP1A2 activity. Rat and human CYP1A2 + P450 reductase SUPERSOMES were obtained from GenTest Corporation (Woburn, MA). Methoxyresorufin-O-deethylase (MROD) activity, a prototype substrate, was monitored in human and rat CYP1A2 SUPERSOMES in the presence of varying concentrations of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), 1, 2, 3, 7, 8-pentachloro-*p*-dioxin (PCDD), 2, 3, 4, 7, 8-pentachlorodibenzofuran (4-PeCDF), 2, 3, 7, 8-tetrachlorodibenzofuran (TCDF), 3, 3', 4, 4', 5, 5'-hexachlorobiphenyl (PCB 169), 3, 3', 4, 4', 5-pentachlorobiphenyl (PCB 126), 2, 3, 3', 4, 4', 5-hexachlorobiphenyl (PCB 156), 2, 3', 4, 4', 5-pentachlorobiphenyl (PCB 118), and 2, 3, 3', 4, 4'-pentachlorobiphenyl (PCB 105). Both human and rat CYP1A2 metabolized methoxyresorufin, evidenced by similar K_M values between species (0.10nM human, 0.09nM rat). Rat SUPERSOMES had a slightly higher V_{max} than human SUPERSOMES, 3.5 and 2.4 pmol/min/mg CYP1A2 respectively. Our results demonstrate similar dose-dependent inhibition of human and rat CYP1A2 activity for all chemicals tested. TCDD, TCDF and 4-PeCDF were the most potent inhibitors. These chemicals appear to be mixed type inhibitors, with K_i values of approximately 1-100 μM. Inhibition of CYP1A2 activity by this series of chemicals *in vitro* may explain the lack of correlation between CYP1A2 activity and dioxin exposure in human epidemiology studies (This abstract does not reflect EPA policy.)

833 SUBCHRONIC TOXICITY OF 3, 3', 4, 4'-TETRACHLOROAZOBENZENE(TCAB) ADMINISTERED BY GAVAGE TO HARLAN SPRAGUE-DAWLEY RATS.

D. F. Gerken[1], M. J. Ryan[1], A. F. Fuciarelli[2], D. E. Hartter[1], M. R. Hejtmancik[1], S. W. Graves[1], M. J. Hooth[3], N. J. Walker[3], A. P. van Birgelen[4,3] and M. Vallant[3]. [1]*Battelle Columbus, Columbus, OH,* [2]*Battelle Toxicology Northwest, Richland, WA,* [3]*NIEHS, Research Triangle Park, NC and* [4]*Hoffmann-La Roche, Inc., Nutley, NJ.*

Tetrachloroazobenzene is a by-product formed during the manufacture or environmental degradation of 3, 4-dichloroaniline or its herbicidal derivatives. Because of the structural resemblance of TCAB to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD), this study was performed to obtain data for the determination of the potency of TCAB relative to TCDD for a variety of endpoints. Male and female Sprague-Dawley rats (10/sex/group) were administered TCAB (100% pure) in corn oil containing 1% acetone by gavage at dosages of 0(control), 0.1, 0.3, 1, 3, 10, 30 and 100 mg/kg, 5 days/week, for approximately 13 weeks. No treatment-related clinical signs were observed or early deaths occurred during the study. There was a statistically significant treatment-related decrease of less than 8% in mean body weight in all female treatment groups above 0.3 mg/kg at termination. Serum total and free T4 were decreased in all dosage groups with generally undetectable concentrations in the groups above 3 mg/kg; no effects were noted on serum T3 or TSH concentrations. TCAB-related decrease in hemoglobin and increases in alkaline phosphatase and cholesterol were noted in both sexes. Liver CYP1A1, CYP1A2, CYP2B and pulmonary CPY1A1 activities were increased at 0.1 mg/kg and higher in a dose-related manner. Significant effects on P450 activity and thyroid hormones were reported in the lowest dosage (0.1 mg/kg); therefore, a NOEL could not be determined. Dose-dependent induction by TCAB of the expression of cytochromes P450, CYP1A1 and CYP1A2 was compared to the induction by TCDD after 13 weeks of daily dosing under similar study conditions. The daily doses needed for similar levels of induction of these genes was 6 orders of magnitude higher than for TCDD indicating that TCAB is only a weak Ah receptor agonist *in vivo*. (Supported by N01-ES-65406.)

834 COMPARING MIXTURES OF DIOXIN-LIKE AND NON-DIOXIN-LIKE PCBs TO TCDD.

D. E. Burgin[1], J. J. Diliberto[2] and L. S. Birnbaum[3]. [1]*Toxicology, UNC, Research Triangle Park, NC,* [2]*ETD/PKB, USEPA/ORD/NHEERL, Research Triangle Park, NC and* [3]*HSD, USEPA/ORD/NHEERL, Chapel Hill, NC.*

Environmental exposures to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) always occur as part of a complex mixture. In order to assess the potential risk associated with these exposures, the Toxic Equivalency Factor (TEF) method was developed, and uses toxic equivalents (TEQ) to relate a chemical to TCDD. While this method adequately accounts for the effects of mixtures of TCDD or dioxin-like (DL) chemicals, there are almost always non-dioxin-like (NDL) chemicals present, in particular, the NDL polychlorinated biphenyls (PCBs). To further examine the interactions of dioxin with NDL PCBs, the present study compared the effects on multiple responses of different laboratory-defined mixtures, based on mass ratios found in food, of dioxin and NDL PCBs in both wild type C57BL/6J and CYP1A2 null male and female mice. These chemical groups are: 1) TCDD alone; 2) DL Mix A containing TCDD, 1, 2, 3, 7, 8 Pentachlorodibenzo-*p*-dioxin, 2, 3, 4, 7, 8 Pentachloro-dibenzofuran, PCB 126; 3) NDL Mix B containing PCB 118, PCB 138, PCB 153, PCB 180; and 4) Mix C - a combination of Mixes A and B. The dose levels used were 0.0, 0.001, 0.01, 0.1, 1.0, and 10.0 μg TEQ/kg body weight for Mix A, B and C, and the same plus 100.0 μg /kg for TCDD. No effects were seen in body weight or other tissues, in male or female wildtype or knockout mice. Although we expected an increase in liver weights in Mix B and Mix C, liver weight was increased only in Mix C in both male and female, wildtype and knockout. The effect appears to be synergistic, not additive. No effects were observed in levels of glutathione, a marker of oxidative stress, in either wildtype or knockout, although this is not surprising due to the large pools of glutathione in the body. Based on these findings, it appears that these mixtures have a synergistic effect greater than the sum of the individual congeners, or TCDD alone. (This abstract does not reflect EPA policy. This research was supported by EPA CT902908)

835 EFFECT OF CHLORINATED PHENOTHIAZINES ON OVULATION IN RATS.

K. W. Fried[1,2], X. Gao[4,5], B. K. Petroff[4,5], K. W. Schramm[2], P. F. Terranova[4,5,6] and K. K. Rozman[1,3]. [1]*Pharmacology, Toxicology & Therapeutics, University of Kansas Medical Center, Kansas City, KS,* [2]*Section of Ecotoxicology, GSF-Institut für Ökologische Chemie, Neuherberg, Germany,* [3]*Section of Environmental Toxicology, GSF-Institut für Toxikologie, Neuherberg, Germany,* [4]*Center for Reproductive Science, University of Kansas Medical Center, Kansas City, KS,* [5]*Molecular & Integrative Physiology, University of Kansas Medical Center, Kansas City, KS and* [6]*Obstetrics & Gynecology, University of Kansas Medical Center, Kansas City, KS.* Sponsor: K. Rozman.

Adult female Sprague-Dawley rats were administered 1mg/kg/day of tetrachlorophenothiazine (TCPT) or its sulfoxide (TCPT-O) in xylene (4ml/kg). Estrous cyclicity of the rats was determined by obtaining vaginal smears for three weeks prior to the beginning of dosing and for two weeks during daily dosing. Similar to 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) both phenothianzines had a profound effect on cycling with prolonged periods of diestrous and the loss of proestrous and estrous. The sulfoxide was more potent than the parent compound.