327 DIET-RELATED REDUCTION IN HEPATIC MICROSOMAL P450 AND RELATED CATALYTIC ACTIVITY IN HATCHERY-RAISED RED DRUM

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Specific hepatic microsomal parameters were investigated in redfish, a popular U.S. gulf coast aquaculture and gamefish species. Constitutive and induced levels of microsomal cytochrome P450 and P420, 7-ethoxyresorufin-O-deethylase and NADPH cytochrome C reductase catalytic activities, and the extent of membrane lipid peroxidation were compared in sexually-immature farm-raised and wild-caught animals. Our data indicate a diet-related reduction in active cytochrome P450 and an increase in cytochrome P420, the denatured form of cytochrome P450, in farm-raised redfish. Lipid peroxide formation was significantly higher and EROD catalytic activity was decreased in farm-raised redfish whereas wild-caught fish exhibited significantly higher levels of cytochrome P450 and EROD activity. No significant alterations in NADPH cytochrome C reductase activity were noted in farm-raised fish. The hepatopancreii from farm-raised redfish have increased levels of cellular lipid which correlate with increased levels of lipid peroxides and are apparently associated with the loss of active cytochrome P450. These data indicate that farm-raised fish fed a lipogenic diet have a reduced metabolizing capacity for endobiotics, drugs and hydrocarbon pollutants, and suggest that the existence of significantly increased hepatic lipid deposition may have potentially dangerous therapeutic and/or toxicological implications for these animals and their ultimate consumers.

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328 MECHANISM-BASED INHIBITION OF MOUSE P4502B AND 1A BY SELECTED ARYLALKYNES

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Suicide inhibitors of P450 families are excellent tools to predict which isoforms mediate the metabolism/activation of a variety of chemical agents. We compared the inhibitory effects of several arylalkynes on mouse P450 with published data in the rat model. The inhibition of P4502b specific dealkylation of benzyloxy-resorufin and 1a specific deethylation of ethoxyresorufin were measured in hepatic and pulmonary microsomes from male Swiss mice by 2-ethynylnapthalene (2-EN), 5-phenyl-1-pentyne (PPY), 4-phenyl-1-butyne (PBY) and 9-ethynylphenathrene (9-EPH). Mice were treated with 1,4-bis[2-(3,5-dichloropyridyloxl)]-benzene (TCPOBOP) to induce cytochrome P450 2b or 2,3,7,8-TCDD to induce P450 1a1 and 1a2. The IC50 was calculated for both liver and lung microsomes and compared to published values of K_i reported in the rat. PPY, PBY and 9-EPH were equally effective inhibitors of mouse 2b and the rat isoform. 2-EN was a 10-fold less potent inhibitor of mouse 2b, as compared to rat. By comparison, 2-EN was as effective an inhibitor of P450 1a2 in the mouse as reported for rat 1A2 in TCDD-induced liver microsomes. These data suggest that the active site of the mouse 2b enzyme is similar to the rat isoform 2B, with the exception of the disparity in IC50 for 2-EN. The potency of 2-EN for P450 1a2, however, was equivalent between mouse and rat hepatic microsomes.

329 STAPHYLOCOCCAL ENTEROTOXIN B (SEB) INHIBITS CYTO-CHROME P450-MEDIATED 2E1 ACTIVITY IN MICE

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It is well known that inflammatory stimuli can depress concentrations and activities of hepatic cytochromes P450. This phenomenon has been studied with gram-negative bacterial cell wall endotoxin, but has not yet been reported with gram-positive bacterial products. Because critically ill septic patients are more likely to have infections with gram positive organisms (often staph sp.) we decided to see if purified SEB (Toxin Tech, Inc. — 3 mg/kg) would affect P450s in male C3H/HeN mice (25 g) and compared it to endotoxin [lipopolysaccharide (LPS), *E. coli* 0111:B4–0.5 mg/kg]. Both agents were injected ip and microsomes prepared from mice killed 24h later. Total P450 concentrations were 0.95 ± 0.09 nmol/mg protein in saline controls, 0.62 ± 0.09 after LPS, and 0.66 ± 0.06 after SEB. Paranitro-phenol hydroxylase, a specific activity of P450 2E1, was 74 ± 19 pmol/mg/min in saline controls, 28 ± 12 after LPS, and 40 ± 9 after SEB. (Values are mean ± SD for 5 mice). We conclude that a gram-positive stimulus like SEB can also depress cytochrome P450 concentrations and at least the activity of the 2E1 isozyme in mice.

330 EFFECTS OF INDUCERS AND INHIBITORS OF STYRENE METABOLISM ON ITS TOXICITY IN MICE

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Styrene is metabolized by cytochromes P450 to the active metabolite styrene-7,8-oxide (SO) which is then detoxified primarily to the dihydrodiol by epoxide hydrolase. Non-Swiss albino mice were administered pyridine (PYR, 200 mg/kg, ip) to induce CYP2E1, phenobarbital (PB, 80 mg/kg/d × 4d, ip) to induce CYP2B, or β-naphthoflavone (β NF, 40 mg/kg/d × 3d, ip) to induce CYP1A. The hepatotoxicity of styrene (600 or 800 mg/kg, ip) was assessed by measurement of serum sorbitol dehydrogenase (SDH) and pulmonary toxicity by determination of lactate dehydrogenase and γ-glutamyl transpeptidase in bronchoalveolar lavage fluid (BALF). All 3 inducers increased the pulmonary toxicity of styrene. PYR and βNF increased the hepatotoxicity of styrene. PB caused a nonsignificant ($P > 0.05$) increase in SDH. The biochemical lesions were confirmed by histological analysis. The results suggest that induction of P450 isozymes enhances styrene toxicity. The epoxide hydrolase inhibitor trichloropropane oxide (161 mg/kg, ip) increased the hepatotoxicity of racemic SO and the R- and S-enantiomers as well as the pneumotoxicity of the enantiomers demonstrating potentiation of SO toxicity by inhibition of its detoxification. (Supported in part by NIH grant ES04362 and the Styrene Information and Research Center).

331 TIME COURSE STUDIES OF HEPATIC MICROSOMAL METABOLISM OF ORGANOPHOSPHORUS INSECTICIDES IN RATS TREATED WITH β-NAPHTHOFLAVONE

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The time dependent changes in parathion (P = S) and chlorpyrifos (C = S) metabolism were investigated after the administration of β-naphthoflavone (BNF) to female rats for 3 days. Ethoxyresorufin *O*-deethylase (EROD), pentoxyresorufin *O*-dealkylase (PROD) and aliesterases were also studied. Hepatic aliesterases from BNF-treated rats displayed lower activity than controls. EROD and PROD activities were induced by about 82 fold and 20 fold, respectively, after three days of BNF treatment. The BNF treatment significantly increased the rate of activation and detoxication of P = S by about 3.5 fold and 2 fold, respectively, and C = S by about 10 fold and 1.6 fold, respectively. All activities monitored had returned to control levels 7 days after the last BNF injection except EROD. With the activation reactions, 10 μM and 50 μM concentrations of C = S and P = S displayed similar profiles, with a peak of activity on day 3. However, there was a more rapid decrease in the activity of P = S activation than C = S. EROD activity, reflecting CYP1A1 levels, were substantially induced by BNF treatment. The induction of P = S and C = S metabolism, which followed the same time course as EROD, indicates that CYP1A1 can catalyze the activation and the detoxication of both compounds, although the patterns with the two compounds were different. The induction of phosphorothionate insecticide metabolism and the decrease in the protective aliesterases suggest that BNF treatment could alter the level of insecticide toxicity. (Supported by NIH RO1 ES04394).

332 EXPOSURE MODELING AND VALIDATION STUDIES FOR AEROSOLS: A CASE STUDY OF DIOXIN EXPOSURE DURING ROADSIDE WEED ABATEMENT WITH 2,4,5-T

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Aerosol exposure modeling creates unique challenges for exposure assessment due to the wide-ranging results that can be obtained by applying many assumptions to the modeling process. Our objective was to characterize the probable dioxin exposure that a roadside weed abatement worker would experience from blowback of aerosol while spraying 2,4,5-T solution from inside the cab of a truck. Our first step was to record worker observations regarding blowback exposure. Second, we determined upperbound and 'most-likely' estimates of exposure with an evaporative loss model based on exercise physiology principles. Third, we conducted a series of experiments measuring aerosol accumulation under varied wind speeds and spraying postures. The results of our analyses indicate that dioxin exposure from aerosol blowback is probably negligible for the roadside spraying routine simulated here. This is consistent with

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