

at later times, suggesting that the placenta delayed absorption. Fetal maximal concentrations were generally lower than in dam plasma. Ratios of AZT exposure between fetus and dam plasma suggest that at doses of 50 mg/kg/day or higher fetal exposures were similar to that of dams. Overall the data suggests that in the mouse fetal AZT exposure mirrors that of the dam, though the profile differs.

1253 DISPOSITION OF BDE 99 AND BDE 153 IN FEMALE MICE. D. Bauer¹, D. F. Staskal¹, J. J. Dileberto² and L. S. Birnbaum². ¹Curriculum in Toxicology, University of North Carolina - Chapel Hill, Chapel Hill, NC and ²Experimental Toxicology Division, USEPA, Research Triangle Park, NC.

Polybrominated diphenylethers (PBDEs) represent a novel class of compounds typically used as flame retardants in electrical and household consumer goods. Recently, increased bioaccumulation of PBDE congeners has raised concern over the potential toxicity of these compounds in humans. Of particular interest are the congener profiles found in biota as they do not parallel profiles of commercial mixtures; a phenomenon that may be due to differential exposure and/or differences in metabolic capacity. Previous studies in our laboratory have shown major differences in excretion patterns of BDE 47 in rats and mice. In this study, the distribution and excretion of two other prominent BDE congeners were examined. Female C57/BL6 mice were given [¹⁴C] 2, 2', 4, 4'-pentaBDE (BDE 99) or [¹⁴C] 2, 4, 4', 5, 5'-hexaBDE (BDE 153) via intravenous administration (1mg/kg). The results indicate that BDEs 99 and 153 are not as rapidly excreted in the urine of mice as BDE 47. 21% of BDE 47 was excreted in the urine 24 hours following exposure, in contrast to 6% of BDE99 and <1% of BDE 153. A total of 42% BDE 47 was excreted in the urine over a five day period, versus 11% of BDE 99. Preliminary metabolite analyses reveal a majority of parent compound in the urine, a result analogous to BDE 47. Remaining BDE 99 and 153 were found primarily in adipose and other lipophilic tissues. Excretion and retention of PBDEs in mice appears to be dependent on the degree of bromination; the dominance of lower brominated congeners in biota despite the rapid excretion patterns demonstrated in mice raise questions as to the animal model that should be used in human health risk assessment. (This abstract does not reflect EPA policy. This work was partially funded by EPA NHEERL-DESE CT826513 and T32 ES07126).

1254 DEVELOPMENT OF AN *IN VITRO* BLOOD-BRAIN BARRIER MODEL FOR BRAIN DISPOSITION SCREENING OF PHARMACEUTICALS.

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Solute distribution between blood and brain is strictly regulated by the blood-brain barrier (BBB). While the BBB performs an important function in keeping unnecessary or harmful molecules from the brain, it poses a challenging problem in delivering therapeutics, including anticancer, antibiotic or antipsychotic drugs into the brain. Conversely, preventing potentially damaging molecules from overcoming the BBB is also an increasing problem, especially when combinations of therapeutics are encountered. Medical and pharmaceutical scientists therefore have a growing need for rapid, reliable *in vitro* models of the BBB for preclinical screening of pharmaceutical BBB transport properties. The current presentation describes initial results in development of an *in vitro* BBB model derived from bovine brain capillary endothelial cells (BCEC). Capillary vessels were first isolated from bovine brains. Individual BCECs were then released by further enzymatic digestion of the capillaries. BCEC thus obtained were cryopreserved. The isolation procedure produced a highly pure population of BCECs, as demonstrated by immunocytochemical staining for the endothelial cell marker von Willebrand factor. After recovery from cryopreservation, BCECs were cultured on microporous membrane culture inserts to produce the BBB model. Transmission electron microscopy and H&E stained light microscopy of the cultures show uniform endothelial cell monolayers with evidence of tight junction formation. Immunocytochemical staining also demonstrated uniform expression of the tight junction protein ZO-1 localized along the BCEC borders. Permeation of Lucifer yellow across the BBB culture was low, further demonstrating development of barrier function. Finally, Western blotting experiments were conducted to reveal the presence of the important BBB efflux transporter p-glycoprotein. These results show significant progress in development of a reliable *in vitro* BBB model that will be useful for preclinical screening of candidate pharmaceutical compounds. This work was supported by NCI Grant # R43 CA101703-02.

1255 PHARMACOKINETICS OF TAF93, A NOVEL PRO-DRUG OF THE MTOR INHIBITOR RAPAMYCIN.

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Introduction: TAF93, a novel mTOR inhibitor, is intended for use in the prevention of organ graft rejection and the treatment of autoimmune diseases. It was developed as an orally administered pro-drug of rapamycin that will maintain efficacy

while altering the pharmacokinetics (PK) in such a way as to decrease clinical adverse effects. It has been proposed that some drug related adverse effects are due to the rapid rise in whole blood rapamycin levels after dosing. TAF93, upon hydrolysis to rapamycin, attenuates the rapid rise in rapamycin concentrations thereby potentially improving the safety profile. **Methods:** Pharmacokinetics were investigated in rats, dogs and primates. Hyperlipidemia was studied in a rat model. Efficacy was investigated in a rat heterotopic heart transplant model. **Results:** PK studies demonstrated that TAF93 displayed a significantly different PK profile than rapamycin. Specifically, C_{max} was blunted and T_{max} was significantly increased. In the rat TAF93 shifted the T_{max} for rapamycin from approximately 0.5 hours to approximately 3 hours and reduced the C_{max} for rapamycin by approximately 70% with only a 30% reduction in AUC. The altered PK in TAF93 treated rats was associated with cholesterol levels that were significantly lower (p < 0.01) than the levels measured in rapamycin treated animals. In addition, transplant data indicated that TAF93 prolonged graft survival, compared to control at doses of 2.5 and 10 mg/kg/day, and was equally efficacious to rapamycin at 2.5 mg/kg/day despite a 1/3 decrease in AUC. Graft survival times of 41±4 and 39±4 days were obtained for TAF93 and rapamycin respectively. **Conclusions:** TAF93 is a novel pro-drug of rapamycin which in preclinical trials alters the PK of rapamycin in such a way as to decrease some of the known side effects while maintaining efficacy.

1256 RAT STRAIN DIFFERENCES IN ETHYLENE GLYCOL RENAL TOXICITY IS DRIVEN BY THE RENAL CLEARANCE OF OXALIC ACID.

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The kidney has been identified as a primary target organ in toxicity studies with ethylene glycol (EG), with rats being more sensitive than mice and males more sensitive than females. The male Wistar rat also appears to be more sensitive than male rats from other strains. Kidney toxicity results from a build up of the terminal metabolite, oxalic acid (OX), which can precipitate with calcium to form crystals. In this study, the renal clearance of OX as well as inulin (IN), a marker for glomerular filtration, was evaluated in young and old male Wistar rats and in rats that have been exposed for one year to 0, 50, 150 or 300 mg/kg/day EG via the diet. Age had a slight affect on the ability of male Wistar rats to clear OX, as the ratio of OX to IN clearance increased from -0.6 to -0.9. No effects were observed following chronic dietary exposures to ethylene glycol as the ratio of OX to IN clearance remained -0.9. In all other rat strains and species studied (F344 rats, SD rats, dogs, sheep and humans), the clearance of OX was shown to be slightly higher than inulin (1.2-2.1), indicating the presence of an active transport process. In male Wistar rats, the net clearance of OX suggests that reabsorption processes are more important than active secretion, which likely contributes to the enhanced sensitivity of male Wistar rats. When OX and IN clearances are related to body weight, all species, with the exception of the male Wistar rat, have glomerular filtration and OX clearance rates that can be scaled allometrically. Since human risk assessments for renal toxicity may be driven by results from chronic studies in male Wistar rats, this quantitative assessment will be critical to determinations of human equivalent exposures and internal dose-response assessments. (Sponsored by the Ethylene Glycol Panel of the American Chemistry Council).

1257 DBDPO METABOLISM IN FISH AND MAMMALS: CONTRIBUTION TO LOWER BROMINATED DIPHENYL ETHERS.

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The flame retardant decabromodiphenyl oxide/ether (DBDPO) represents >80% of global polybrominated diphenyl ether (PBDE) use. PBDE typically detected in biota, tetra (BDE47), penta (BDE99, 100) and hexa (BDE153, 154), appear to originate from use of PentaBDE product. DBDPO metabolism has been questioned as a contributor; the evidence is reviewed. DBDPO is poorly absorbed. Its fish BCF_{water} was < 50.^{1,2} Trout absorbed 0.005% of 7.5 or 10 mg DBDPO/kg/d administered in food over 120 d.³ DBDPO was not detected in carp fed treated food for 90 d (940 ng/fish/d); 0.4% uptake was estimated based on presumed metabolites.⁴ PBDE typically reported in wild-caught fish were not detected. The test article purity was not stated by either, but one³ used a former product whose only known composition was 77% DBDPO, ~23% nona- and octa-BDE, and concluded "no evidence of debromination to these congeners [e.g. BDE-47, 99 and 100] was found". Rats absorbed DBDPO to a limited extent (0.28–2%, oral dose) with 98% eliminated in feces as parent.^{5,6} Production of metabolites was limited (2% @ 277ppm, diet) and thought to occur in the gut, not systemically. A rat study using a DBDPO formulation to enhance/maximize absorption/metabolite production reported trace amounts of 3 nonaBDE and perhaps OH-BDE.⁷ The test article was 98% DBDPO; nonaBDE are typical impurities. Similar results were found