viously shown that, in C57BL/6J mice, total BM cellularity decreased 2-fold following ip DMBA but not BP treatment. This investigation shows that the DMBA mediated decrease in BM cells targets early progenitor cells, and does not affect mature BM cell numbers. Wild type female C57BL/6 mice were injected ip with 10 or 50 mg/kg DMBA or BP, and the effect on BM lymphoid and myeloid progenitors determined over time. DMBA treated animals exhibited dose-dependent decreases in BM cells and disruption of marrow structure at 24 to 168 h post treatment. Flow cytometric analysis of BM cells revealed significant decreases in lymphoid and myeloid populations, consistent with the decrease in BM cells following DMBA treatment. BM cells showed significant dose-and time-dependent decreases in progenitor lymphoid (CFU-preB) and myeloid (CFU-GM) cells following DMBA treatment. In contrast, BP treated mice showed minimal effects. In addition, DMBA caused a greater decrease in spleen, thymus, and white blood cell counts. Changes in lung and liver weights were minimal, consistent with the IP administration that bypasses liver metabolism by Cyp1a1. Given that BP and DMBA are both metabolized by Cyp1b1 in the BM, the differential effects on BM cells may stem from differences in AhR-mediated removal of their reactive metabolites. Congenic mice with the low affinity AhR (AhRd), when treated with 50 mg/kg of BP or DMBA displayed similar toxicity for BM cells. This observation indicates AhR involvement in the selective effects of PAHs on BM haematopoiesis, in vivo, which slow the developmental program from haematopoietic stem cells through progenitor cells that subsequently mature and populate the spleen and lymphoid tissues.

611 ORGANIC CATION TRANSPORTERS 1 AND 2 MEDIATE PRALIDOXIME RENAL SECRETION.

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Objective: Pralidoxime (PRX) is an organic cation used as an antidote to treat organophosphate poisoning. The elimination of PRX is characterized by fast renal excretion considered the main determinant of PRX pharmacokinetics. In rodents, we studied the role of organic cation transporters (OCT) in the renal secretion of PRX using specific OCT substrates (TEA) and Knock-out mice (OCT1/2-/-; OCT3-/-). Methods: Male Sprague-Dawley rats received a loading dose of PRX (31 mg/Kg) followed by a continuous infusion to achieve a plasma PRX concentration of 10 mg/l during 180 min. Then, blood and urine were collected. In rats, the pharmacokinetics of PRX (50 mg/Kg, 30 min perfusion) was determined 15 min after TEA treatment (75 mg/kg, IM). Knock-out and wild type mice received a PRX injection (50 mg/Kg, IM), blood samples were taken at 45 and 90 min post-injection. Results are expressed as mean ± SEM. Statistical analysis used t-test and 2 way analysis of variance on log transformed data with $p< 0.05$. Results: Renal clearance of PRX (30.1±1.8 ml/min/kg) was significantly higher ($p< 0.001$) than t creatinine clearance (9.6±0.9 ml/min/kg) evidencing the renal secretion of PRX. Pretreatment by TEA significantly modifies the pharmacokinetics of PRX, increasing the beta half-life (224 vs 39 min-1) and decreasing the clearance of PRX(3.6 vs 2.2 l/h/kg) without modification of the volume of distribution. The defiency in organic cation transporters 1 and 2 in mice (OCT1/2-/-) resulted in a significant increase ($p< 0.001$) in plasma pralidoxime concentrations at 45 min (6.40±0.46 vs 2.37±0.13 mg/l) and 90 min (2.83±0.17 vs 1.47±0.07). Lack in OCT3 did not change the plasma PRX concentrations. Conclusion: Our data show that PRX is secreted in urine by an active process involving organic cation transporters 1 and 2 (but not 3).

612 PBPK MODELING OF DELTAMETHRIN IN RATS.

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The pyrethroid pesticide deltamethrin is cleared nearly twice as rapidly in human liver microsomes compared to rat liver microsomes. A species difference such as this could influence the toxic potency of deltamethrin between rats and humans. PBPK modeling is a tool that can be utilized to examine the impact that such a species difference may have on exposure-dose relationships. A previous PBPK model for deltamethrin in the rat by Mirfazaelian et al. (Toxicol Sci. 2006 Oct;93(2):432-42) suggests that absorption is dose dependent with little absorption of environmentally relevant exposures. In addition, the model employs both flow and diffusion-limited compartments and splits the blood compartment into plasma and red blood cells. Oral bioavailability studies were designed to examine the dose dependency in absorption. The results of theses studies indicate there was no significant difference in the fraction absorbed of oral doses of 0.3 and 3.0 mg deltamethrin/Kg. In contrast to the previous model which utilized both flow- and diffusion-limited tissue compartments the current model described all tissue compartments with diffusion-limited kinetics. The present model also describes the blood as a single compartment. These changes resulted in an improved ability of the deltamethrin PBPK model to describe the shape of the tissue concentration-time curves for both literature data and data from the present oral bioavailability studies. The description of the liver by diffusion- limited kinetics has the effect of reducing the impact of the species difference in metabolism since diffusion is the rate limiting step in the metabolic elimination of deltamethrin. (This abstract does not represent EPA policy; S.J.G. was supported by NHEERL-DESE, EPA CT826513 and, in part, by a NIEHS Training Grant T32-ES07126).

613 EFFECT OF NICOTINE EXPOSURE ON IN VITRO CYP450S-MEDIATED METABOLISM OF CHLORPYRIFOS (CPF) IN SPRAGUE-DAWLEY (S-D) RATS.

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Chlorpyrifos (CPF) is a common organophosphate (OP) insecticide which is metabolized by CYP450s to the neurotoxic metabolite chlorpyrifos-oxon (CPF-oxon) and a non-toxic metabolite 3,5,6-trichloro-2-pyridinol (TCP). The objective of this study was to quantify the *in vivo* effect of repeated nicotine exposure on *in vitro* metabolism of CPF and marker substrates in rats. Male S-D rats (~ 275 g bw) were divided into 6 groups (n = 4) and dosed s.c. with 1 mg nicotine/kg/day in saline, controls were given saline only. Animals showed signs of cholinergic crisis after the initial nicotine doses, but exhibited adaptation after a couple days of treatment. Rats were sacrificed after 4 hr, 24 hr, 7 days, 7 days + 4 hr, or 10 days of nicotine-treatment, and hepatic microsomes were prepared and stored at -80°C until analysis. While CYP450 reduced CO spectra were not different across the treatments, the 24 hr-group showed a 2-fold increase in CYP2E1 marker substrate (p-nitrophenol: PNP) activity over controls, whereas longer treatments resulted in no difference in PNP hydroxylase activity. The 7 day + 4 hr- and 10 day-groups showed decreased EROD/PROD marker substrate activity. Moreover, in 7 day- and 10 day-nicotine-treated groups, the estimated pesudo-1st order clearance rate constants (Vmax/Km) for TCP exhibited a 2-fold increase over that of controls, suggesting possible induction of CYP-mediated metabolism of CPF to TCP. The results of this *in vitro* study suggest that repeated nicotine exposure (i.e., from smoking) could alter the metabolism of OP pesticides. Future *in vivo* experiments based on these results will be conducted to ascertain the impact of *in vivo* nicotine exposures on CPF metabolism in rats. (This work was supported by NIOSH/CDC R01-OH003629-04)

614 DISPOSITION OF NOVEL NANOPARTICLE CONSTRUCTS IN JUVENILE SWINE.

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Gold and Palladium nanoparticles have many potential uses in medicine, including the enhancement of computed tomography (CT) imaging and targeted cancer therapy and detection. Several experiments have been conducted with the objective of determining the disposition of palladium and gold nanoparticles (NPs) in blood and tissues following intravenous and inhalation delivery to juvenile swine. Juvenile swine were anesthetized with isoflurane, and venous catheters were placed in the cranial vena cava. The nanoparticles were administered via the catheter at 2 mg Au or Pd/kg BW. Serial blood samples were collected at 15, 30, 60, 120, and 240 minutes post-dosing. A final blood sample was then collected at 24 hours and pigs were humanely sacrificed and tissues were collected for gold or palladium analysis using atomic absorption spectrophotometry or inductively coupled spectrometry. One of the gold nanoparticle compounds was delivered by the inhalation route via the anesthetic circuit to compare pharmacokinetic parameters to the same nanoparticle construct given intravenously. Nanoparticles were distributed according to a two-compartment model. There were measurable levels of gold in most tissues, however, the lung, liver, spleen, and kidney had the greatest concentrations. Retention of gold NPs administered by the IV route is long-lived with more than 90% of the dose retained in liver, lung, and spleen 90 days following an IV dose of 2 mg Au/kg body weight. Supported by the National Institutes of Health/National Cancer Institute, Cancer Nanotechnology Platform program (grant number: 1R01CA119412-01).

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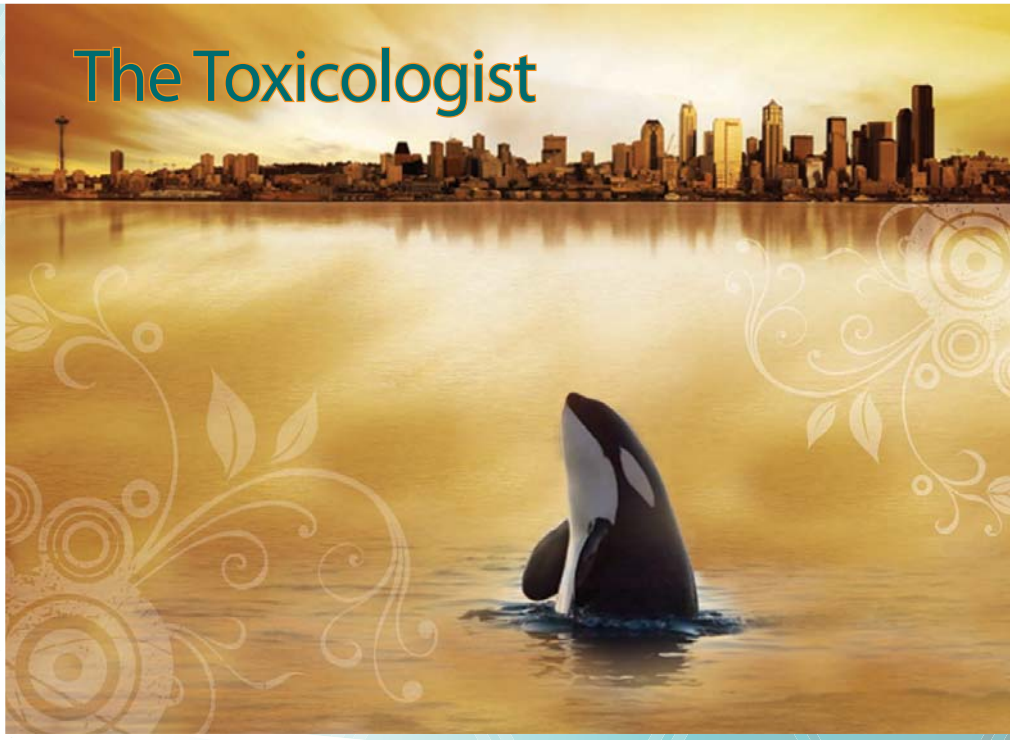

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