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## IN VIVO METABOLISM OF 2-AMINO- $\alpha$ -CARBOLINE (A $\alpha$ C).

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2-Amino- $\alpha$ -carboline (A $\alpha$ C, 2-amino-9*H*-pyrido[2,3-*b*]indole) is one of the major heterocyclic amines present in fried or broiled fish, beef and chicken, in cigarette smoke condensate, and in diesel exhaust particles. A $\alpha$ C is carcinogenic in CDF<sub>1</sub> mice and has been shown to be genotoxic in several bacterial, insect, and mammalian systems. We have previously reported human and rodent phase I and phase II *in vitro* metabolism of A $\alpha$ C (Raza et al. 1996 *Drug Metab. Dispos.* 24:395-400; King et al. 1999 *Cancer Letters* 143:167-171; King et al. 2000 *Carcinogenesis* 21:1347-1354). Hydroxylation on the aromatic ring resulted in non-reactive, stable phenolic metabolites (3-OH-A $\alpha$ C, 6-OH-A $\alpha$ C). In contrast, exocyclic amine *N*-hydroxylation and subsequent *N*-*O*-sulfonation or *N*-*O*-acetylation formed products that bound covalently to DNA. We also observed reduction of the *N*-hydroxy-A $\alpha$ C (N-OH-A $\alpha$ C) back to the parent amine by human and rat liver microsomes, rat primary hepatocytes, and human hepG2 cells. We are now using adult male SD rats as an *in vivo* model for human metabolism of A $\alpha$ C, and the *in vivo* metabolism is expected to be a complex balance between all of the detoxification and bioactivation reactions. We chose use a rat model because of our previously reported comparisons of *in vitro* metabolism between rat and human samples. We chose to use the male SD rat because of our previous experience with the major sulfotransferase isoform in this strain, and its similarity to the major human isoform responsible for the bioactivation of N-OH-A $\alpha$ C.

This study aims to (1) characterize and quantify the major metabolites of A $\alpha$ C in bile, urine and plasma of rats after i.v. administration of <sup>3</sup>H-A $\alpha$ C or N-OH-A $\alpha$ C, and (2) to assess the stability of N-OH-A $\alpha$ C towards systemic transport to target tissues. To test the hypothesis that N-OH-A $\alpha$ C is stable enough to be transported systemically, animals will be injected directly with N-OH-A $\alpha$ C and the profile of metabolites and adducts determined. To test the hypothesis that bile removal will preclude transport directly to the intestine and enterohepatic recirculation, the profile of metabolites and adducts of bile-duct-cannulated and non-cannulated rats will be compared.

<sup>3</sup>H-A $\alpha$ C (17.5  $\mu$ Ci) or N-OH-A $\alpha$ C has been administered *via* the jugular vein to adult male SD rats and the bile, blood, and urine collected or sampled over a period of 3-7 hours after injection. Metabolites in each fluid were partially purified by solid-phase extraction and analyzed by HPLC with photodiode array and radioactive flow detection. This poster presents methods and current progress in identification/characterization of the major metabolites, and compares relative metabolite formation amongst each treatment group and fluid (bile, urine, plasma). Tissues have also been collected, frozen in liquid N<sub>2</sub>, and stored at -80°C to await DNA adduct analysis.