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IN VIVO METABOLISM OF 2-AMINO- α -CARBOLINE

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Cancer is currently one of the major health problems and over 30% of people in developed countries present with some form of cancer in their lifetime. Thirty percent of all cancers have been associated with food. Based on epidemiological data, two groups of highly mutagenic compounds present in cooked food have been identified: heterocyclic amines (HCA) and polyaromatic hydrocarbons (PAH). 2-Amino- α -carboline (A α C) is one of the major HCA's and is predominantly formed at higher temperatures with estimated levels of 1.6-5 ng/kg/day in an average American daily diet. Extensive studies indicate that A α C acts as a promutagen and pro-carcinogen. It is believed to be formed by the pyrolysis of tryptophan and other unidentified amino acids. *In vitro* studies using human and rat liver microsomes have established that A α C undergoes biotransformation through several enzymatic pathways of the phase I and phase II metabolism. The N-hydroxylation and subsequent N-O-sulfonation or N-O-acetylation form products that bind covalently to DNA, forming adducts. In contrast, hydroxylation on the aromatic ring results in non-reactive, stable phenolic metabolites. Thus, the overall balance of activation reactions (via N-hydroxylation) and detoxification reactions (via ring hydroxylation) is important. *In vivo* studies for A α C metabolism have not been done in humans or animal models.

The study aims to characterize and quantify major metabolites of A α C in bile, urine and plasma of rats after IV administration of ^3H -A α C (group I). Bile removal precludes enterohepatic circulation and the profile of metabolites in blood and urine of cannulated (group I) and non-cannulated rats (group II) will be compared. To test the hypothesis that N-OH-A α C is formed in the liver and is stable to be transported systemically (to target tissues) two groups of animals (bile cannulated – group III, bile not cannulated – group IV) will be injected directly with phase I metabolite N-OH-A α C.

^3H -A α C (17.5 μCuries) or N-OH-A α C has been administered to adult male SD rats and the bile, blood, urine collected. The bile, blood and urine have been purified using solid phase extraction, HPLC (simultaneous UV and flow scintillation analysis), and other techniques as required. The metabolites will be characterized by UV, NMR and LC/MS. Various tissues/organs would be analyzed by ^{32}P -DNA postlabelling for DNA adducts. Representative flow scintillation analysis and UV chromatograms will be presented.