INFLUENCE OF PRECONSUMPTIVE METABOLISM UPON THE TOXICOKINETICS AND BIOAVAILABILITY OF A MODEL CARCINOGEN IN THE FLOUNDER (Pseudopleuronectes americanus)

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Polycyclic aromatic hydrocarbons (PAH) are important contaminants and procarcinogens in the aquatic environment (Richards and Jackson, EPA-600/9-82-013, 1982). Biotransformation is required to activate most PAHs to their carcinogenic forms. (Sims and Grover, P.L., Adv. Can. Res. 20:165-274, 1974). Recent work on in vivo PAH metabolism indicates that infaunal organisms such as Nereis virens have the ability to metabolize the PAHs to water soluble and bound metabolites, (McElroy, Mar. Environ. Res. 17:133-136, 1985). These organisms can serve as major food items for commercially important fish species. Concerns regarding food chain transfer of carcinogens to humans from aquatic species has highlighted interest in the production and transfer of activated PAHs from lower trophic levels to those species consumed by humans. The purpose of this study was to model the possible effects of preconsumptive metabolism upon the bioavailability and toxicokinetics of model PAHs in the flounder. Benzo[a]pyrene (BaP) and its metabolite BaP-7,8 diol were selected as model compounds for these comparisons.

Male and female flounder (Pseudopleuronectes americanus) maintained in flowing seawater at 13-16° C were anesthetized with MS 222 (40 mg/l) and cannulated via the caudal vein. Following a 24 h acclimation period four separate groups (N = 3-5) of cannulated fish received either a single intravenous (IV) or oral (PO by gavage) dose (77 mg/kg) of ^{14}C-BaP or ^{14}C-BaP-7,8 diol. Delivery was accomplished with compounds dissolved in DMSO for IV and homogenized in ground sandworm (Nereis) for oral administrations. Blood samples were collected via the indwelling cannula throughout a 48 hour time course. Samples of blood, urine, bile, intestine, liver and muscle were taken upon termination of the experiment. Total radioactivity was measured directly in plasma or after tissue digestion by liquid scintillation counting. All samples were corrected for quench and background.

Toxicokinetic analysis following line fitting was accomplished with compartmental and noncompartmental methodologies (Statistical Moment Theory). Oral bioavailability was calculated utilizing area under the curve (AUC) of iv and PO administrations.

The elimination of [^{14}C] from plasma following intravenous administration of (77 ug/kg) [^{14}C] BaP or [^{14}C] BaP - 7,8 diol is shown in figure 1. When examined compartmentally this data was described multiexponentially. The BaP-7,8 diol demonstrated a greater drop in [^{14}C] concentration during the redistribution phase when compared to BaP. The toxicokinetic parameters calculated from this data did not indicate significant differences in the alpha and beta half lives of compound equivalents in plasma. However, the volume of distribution (Vss) and whole body clearances (Cl_b) were both significantly greater for BaP-7,8 diol (Vss-1598 $\pm$ 83.3 ml/kg; Cl_b 89.4 $\pm$ 7.2 ml/h /kg) than for BaP (Vss - 1040.9 $\pm$ 223.0 ml/kg; Cl_b 51.4 $\pm$ 19.5 ml/h /kg). These data suggest that not only is the diol widely

distributed and sequestered it is more readily eliminated from those fluid spaces.

The oral bioavailability of BaP (7.2 ± 3.0%) and BaP 7,8 diol (10.3 ± 4.4%) were not significantly different as calculated from figures 1 and 2. These values when examined in conjunction with the distributional data (table 1) appear to be underestimates of the true bioavailabilty. This may be related to a significant first pass elimination from the plasma. The distributional data was consistent with the Vss and Cl_b values calculated for the two compounds. A lower percent of the BaP - 7,8 diol dose was retained in tissues at 48 hrs when compared to BaP. Both compounds were concentrated in the bile following administration. Distributional differences were evident between compounds, and treatments for the liver and bile.

These results suggest that preconsumptive metabolism of BaP to BaP-7,8 diol may appreciably alter select toxicokinetic parameters in the flounder without significantly altering bioavailability. Further studies are in progress to relate these parameters and compounds with the degree of covalent binding in the consumer. The combination of toxicokinetic and binding data will assist in determining the risk imparted to consumers by ingestion of preconsumptive metabolites of BaP.

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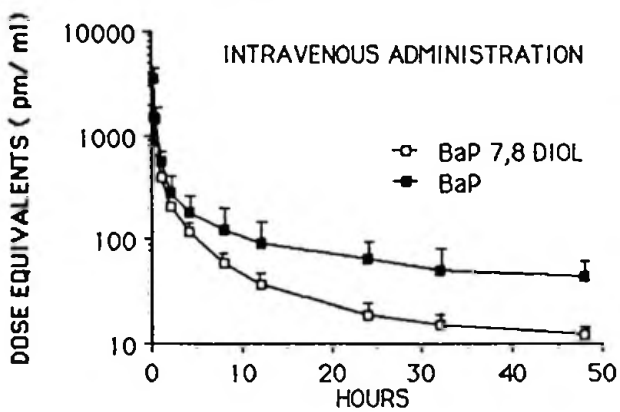

Figure 1. Plasma concentrations of of 14C] following intravenous administration of BaP or BaP 7,8 Diol.

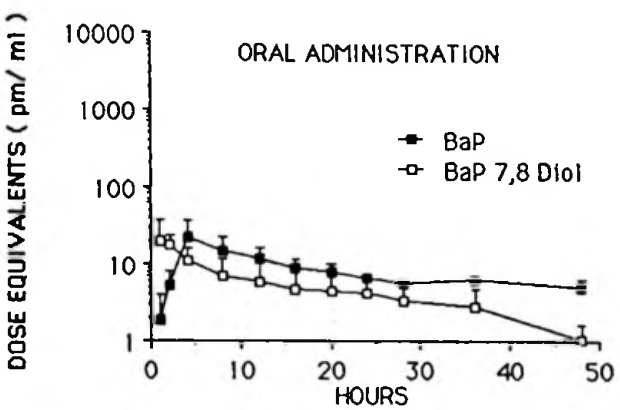

Figure 2. Plasma concentrations of [^{14}C] following oral administration of BaP or BaP 7,8 Diol.

Table 1: Distribution of ^{14}C in Winter Flounder 48 hours after a single dose % of dose.

	BaP		BaP 7,8-Diol	
	IV	PO	IV	PO
Blood	0.39 ± 0.28 (3)	0.03 ± 0.02 (5)	0.16 ± 0.05 (4)	0.02 ± 0.02 (4)
Bile	39.9 ± 7.90 (3)	4.71 ± 3.29 (5)	48.6 ± 21.2 (4)	12.5 ± 06.3 (4)
Liver	12.2 ± 9.30 (3)	1.64 ± 0.68 (5)	4.52 ± 3.34 (4)	1.18 ± 1.36 (4)
Intestine	1.74 ± 0.77 (3)	2.60 ± 1.42 (5)	0.58 ± 0.25 (4)	1.44 ± 0.76 (4)
Muscle	2.17 ± 1.73 (3)	2.18 ± 0.06 (5)	0.76 ± 0.52 (4)	0.11 ± 0.03 (4)
Terminal Urine	1.19 ± 0.31 (2)	0.14 ± 0.03 (3)	NC	0.10 ± 0.07 (3)

Mean ± SD (N)
NC = None collected