1274 INFLUENCE OF PARTICLES ON BENZO(A)PYRENE METABOLISM. D Warshawsky, R Reilman, J Cheu, and M Radike. University of Cincinnati Medical Center, Environmental Health, OH.

Epidemiological and experimental studies indicate that particles and chemical carcinogens are related to the development of respiratory disease. The long term objective is to investigate the role that pulmonary alveolar macrophages (AM) play in the particulate-dependent response of the lung to benzo(a)pyrene (BaP) via mechanisms involving BaP metabolism. An important biological response to inhaled particles is phagocytosis by AM and clearance from the lung. The comparative viability of the AM in the presence of ferric oxide, aluminum oxide, and crystalline and amorphous forms of silica was undertaken to determine the noncytotoxic doses during phagocytosis necessary for metabolic studies. AM from male-Syrian Golden hamsters, known to be susceptible to the formation of lung tumors by BaP-coated particles, were incubated with 0.0 To 0.5 mg of respirable size particles. After 48 hours the viability of AM for ferric oxide and aluminum oxide at 0.5 mg doses was similar to the controls. In the presence of crystalline and amorphous silica, the viability was similar to controls at 0.01 mg. At 0.05 mg silica the viability dropped to 40% and at 0.5 mg the viability was zero. These BaP-coated particles have a differential effect on the metabolism of BaP by the AM.

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1275 CYTOCHROME P450 (P450)-DEPENDENT METABOLISM OF ARACHIDONIC ACID (AA) IN GUINEA PIG LIVER: EFFECT OF ISOZYME SELECTIVE INHIBITORS. LC Knickle, CD Webb and JR Bend. Dept. of Pharmacology and Toxicology, University of Western Ontario, London, Canada.

Guinea pig hepatic microsomal P450 converts AA to two major classes of metabolites, epoxyeicosatrienoic acids (EETs; 45%) and ω/ω-1-hydroxy-AA (ω/ω-1-OH-AA; 30%). We examined the contributions of β-naphthoflavone (βNF)- and phenobarbital (PB)-inducible P450 isozymes to AA metabolism using αNF (inhibitor of P450IA) and N-benzyl-1-aminobenzotriazole (BBT, mechanism-based inhibitor selective for PB-inducible isozymes). Isozyme-selective monooxygenase activities, ethoxyresorufin O-deethylation (ERF) and pentoxyresorufin O-dealkylation (PRF) for βNF- and PB-inducible isozymes, respectively, were also determined. βNF treatment increased ω/ω-1-OH-AA and EETs production 4.1- and 1.2-fold, respectively. αNF (10^{-5} M *in vitro*) inhibited ω/ω-1-OH-AA and EETs production by 60% and 30% in βNF-treated, and 35% and <10% in untreated microsomes, respectively. PB treatment increased the production of EETs and ω/ω-1-OH-AA by 4.8- and 2-fold, respectively. In control animals treated *in vivo* with 7.5 μmol/kg BBT (iv, 4 hr), PRF was inactivated by 70%, ERF by 30%, but the AA metabolite profile was not altered significantly. In PB-induced animals treated with 0.75 μmol/kg BBT, which decreased PRF by 60% but had no effect on ERF, there was a 40% reduction in EETs and no effect on ω/ω-1-OH-AA production. These results show that βNF-inducible isozymes produce primarily ω/ω-1-OH-AA, whereas PB-inducible isozymes generate primarily EETs. (Supported by MRC of Canada)

1276 EFFECT OF CALORIC RESTRICTION ON THE METABOLISM OF 7-BROMO- AND 7-FLUOROBENZ[A]ANTHRACENE BY MALE B6C3F$_1$ MOUSE LIVER MICROSOMES: REDUCTION OF METABOLIC ACTIVATION PATHWAY. Y Xiao, L S Von Tungeln, M W Chou, R W Hart and P P Fu. National Center for Toxicological Research, Jefferson, AR. Sponsor: D W Roberts.

Caloric restriction has been shown to be an effective strategy to reduce the chemically induced tumor incidence in rats and mice, but it is not known if caloric restriction can alter the metabolic activation pathway of chemical carcinogens. We report here the metabolism of 7-bromobenz[a]anthracene (7-Br-BA) and 7-fluorobenz[a]anthracene (7-F-BA) by microsomes from 5-month old male B6C3F$_1$ mice fed ad libitum and mice, which starting at the age of 14 weeks, received 60% of the calories consumed by the control mice. After HPLC separation and spectral identification, ten metabolites were identified from the metabolism of 7-Br-BA: the trans-3,4-, 5,6-, 8,9- and 10,11-dihydrodiols, 5,6-epoxide and 4-, 5-, 6-, 8-, and 9-hydroxyl derivatives. Metabolites of 7-F-BA were similarly identified. Results from quantitation indicated that formation of the trans-3,4-dihydrodiols of 7-Br-BA and 7-F-BA, the proximate mutagens of 7-Br-BA and 7-F-BA, respectively, was reduced in the incubation with the microsomes from the caloric-restricted mice as compared to that from the mice fed ad libitum. These results suggest that caloric restriction can diminish the genotoxicity of polycyclic aromatic hydrocarbons by reduction of the metabolic activation pathway.

1277 DETERMINATION OF METABOLIC RATE CONSTANTS USING THE VIAL EQUILIBRATION TECHNIQUE: VEHICLE EFFECTS. C Kim, S Muralidhara, R Manning, R Brown*, and JV Bruckner. Department of Pharmacology & Toxicology, University of Georgia, Athens, GA and *Technical Resources, Inc., Rockville, MD.

A critical aspect of development of physiologic pharmacokinetic models for volatile organic chemicals (VOCs) is the choice of appropriate metabolic rate constants. The aims of this study were: to evaluate the merits of the vial equilibration technique of Sato and Nakajima (TAP 47:41, 1979); to determine optimum experimental conditions, and to assess vehicle effects in the system. A crude liver homogenate (20% w/v) was prepared from perfused livers of male S-D rats (275-325 g). The homogenate was centrifuged at 10,000 x g at 4°C for 30 min and the supernatant used. Trichloroethylene (TCE), either dissolved in isooctane or as an aqueous emulsion in 0.25% Emulphor®, was utilized for the study of vehicle effects. TCE was incubated with a mixture of 10,000 x g supernatant and cofactors in sealed headspace vials. Disappearance of TCE, as a measure of TCE metabolism, was monitored by headspace gas chromatography. Different trials were conducted to investigate time-activity, enzyme-activity, and enzyme-substrate relationships. The apparent K_m and V_{max} for TCE in isooctane were 0.4 μM and 0.23 nmole/mg/hr with substrate concentrations ranging from 19 to 76 nM. The apparent K_m and V_{max} for TCE in Emulphor® were 0.2 μM and 0.37 nmole/mg/hr with substrate concentrations ranging from 38 to 152 nM. Thus, the choice of vehicle is important, as isooctane inhibits TCE metabolism. The vial equilibration technique offers a rapid, reproducible means of determining *in vitro* metabolic rate constants for VOCs. (This paper has not been the subject of EPA review. Thus it does not necessarily reflect the views of the Agency, and no official endorsement should be inferred. Supported by EPA Contract #68-03-3479)

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