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946 DOSE-DEPENDENT PHARMACOKINETICS OF [125I]-2-
IODO-3,7,8-TRICHLORODIBENZO-P-DIOXIN (ITCDD)
IN MICE. H W Leung, A P Poland*, F J Murray,
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2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) is a potent inducer of hepatic microsomal enzymes. The influence of induction on TCDD pharmacokinetics was studied with ITCDD, a radioiodinated TCDD analog. Female C57BL mice were treated with an inducing dose of TCDD (0.1 μ mol/kg) or vehicle, followed by a non-inducing dose (0.1 nmol/kg) of ITCDD 3 days later. In naive mice the peak ITCDD level was found in the fat (400 pmol/kg). In contrast, in induced mice the highest ITCDD level was in the liver (605 pmol/kg). Induced mice attained peak tissue ITCDD concentrations earlier than naive mice (1 day vs 4 days after dosing). Whole body excretion was also faster in the induced mice. These results were satisfactorily described by a physiological pharmacokinetic model in which induction increased the amount of microsomal TCDD-binding protein and the metabolic rate of free ITCDD. In agreement with results from earlier physiological modeling, the primary factor influencing the liver/fat concentration ratio is the affinity and capacity of the microsomal TCDD-binding protein. Risk assessments based on high-dose rodent experiments need to consider these dose dependencies of TCDD distribution.

947 EVALUATION OF IN VITRO ESTIMATIONS OF TISSUE/
BLOOD DISTRIBUTION COEFFICIENTS FOR ORGANOTHIOPHOSPHATE INSECTICIDES. B Kim, TM Soranno, L Woods, and L G Sultatos. Dept. Pharmacology, UMDNJ, Newark NJ.

Physiologically-based pharmacokinetic modeling is dependent on the accurate determination of tissue/blood distribution coefficients (K_p). The present study was undertaken to evaluate the validity of the in vitro estimation of K_p s of organothiophosphate insecticides. Single-pass perfusions of mouse livers in situ with parathion (PS) or methyl parathion (MPS) were performed in order to determine K_p from the following equation $t_{1/2} = 0.693 (VH)(K_p)/Q$ where $t_{1/2}$ is the half-life for approach to steady-state of the chemical, VH is the volume of the liver, Q is the rate of perfusate flow, and K_p is the liver/perfusate distribution ratio. Equilibrium dialysis of liver homogenate and perfusate was utilized to estimate K_p in vitro. K_p for MPS was found to be 16.4 ± 7.5 and 7.7 ± 2.3 (MEAN \pm SD) from perfused livers and equilibrium dialysis respectively. Estimations of K_p for PS gave 15.6 ± 6.3 and 9.5 ± 2.6 from perfused livers and equilibrium dialysis, respectively. These results suggest that equilibrium dialysis can be utilized to give a reasonably accurate estimation of tissue partitioning of these insecticides. (Supported by NSF/Industrial/Univ. Center for Res. in Hazardous and Toxic Substances, and NIEH Grant ES04335).

948 A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR CHLOROFORM. R A Corley¹, A L Mendrala¹, F A Smith¹, M L Gargas², R B Conolly³, M E Andersen² and R H Reitz¹. ¹Dow Chemical Company, Midland, MI; ²AAMRL/TH WPAFB, OH; ³NSIT, Dayton, OH.

A physiologically-based pharmacokinetic model was developed and validated to describe the disposition of chloroform and its metabolites in mice, rats and humans. Macromolecular binding, which has been associated with chloroform-induced cytotoxicity, was emphasized as a measure of "internal dose." Metabolic and macromolecular binding constants for rodents were derived from *in vivo* metabolism studies. Human metabolic constants were estimated from *in vitro* studies with human tissues. The model successfully described a wide variety of experimental data in several species, including humans, exposed to chloroform by different routes. Recurrent cytotoxicity followed by compensatory cellular regeneration is one important stage by which compounds such as chloroform are believed to influence the process of carcinogenesis in laboratory animals. The PB-PK model for chloroform represents the first stage in the development of a pharmacodynamic cancer model linking mechanistic and kinetic data with cytotoxicity and cellular regeneration.

949 A BIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR ORAL DOSING OF ETHYL ACRYLATE. C B Frederick, D W Potter, I M Chang-Mateu, M E Andersen*. Rohm and Haas Co., Spring House, PA and *AAMRL/TH, Wright-Patterson AFB, OH.

A biologically-based computer model has been developed to describe the metabolic fate of ethyl acrylate (EA) in rats following gavage dosing. The model is based on *in vitro* rates of ester hydrolysis, protein binding, glutathione conjugation, and blood:tissue partitioning and *in vivo* rates of glutathione synthesis for 14 tissues. The predictions of the model are consistent with a variety of *in vivo* metabolic results. For example, the predicted and observed metabolic profile of a high gavage dose of EA is concordant with a toxic response only at the site of dosing that follows severe glutathione depletion. Lower gavage doses are predicted to cause minimal changes in glutathione concentration and no subsequent local toxicity. Rapid systemic detoxification is predicted that is consistent with the lack of toxicity observed in tissues remote from the site of dosing. The model provides a valuable quantitative tool in understanding and predicting the toxic response (or lack thereof) of a tissue based on the rate of EA delivery and the metabolic characteristics of the tissue.