periments exposed rat brain homogenates to binary mixtures of organophosphates, either simultaneously for a 15 minute incubation period or sequentially (second oxon added 15 minutes after the first, with a subsequent 15 minute incubation period). Levels of inhibition of individual oxons did not exceed 30%. The cholinesterase activity was then determined spectrophotometrically using acetylthiocholine as a substrate, and the cholinesterase inhibition was calculated. Mass action models were developed for the resultant inhibition in the binary mixture, with model calibration occurring from the inhibition of the individual compounds with a 15 minute exposure. Subsequently, the mass action models were adapted to partial order models (using guidance of existing reaction models present in the agronomy literature). The partial order models were more effective in prediction with the simultaneous exposures to the binary mixtures than were the mass action models. The partial order models were also more effective in prediction of the sequential exposures to binary mixtures within the calibration range (i.e., 15 minute exposures and lower levels of inhibition), but the mass action models are more robust for the longer time of incubation and the higher levels of inhibition. However, both types of models predict greater inhibition than the experimental data, indicating that there are factors influencing the levels of cholinesterase inhibition with binary mixtures that we have not yet identified for the mathematical models. (Supported by American Chemistry Council 0161).

1318 STOCHASTIC MATHEMATICAL MODELING OF TUMOR GROWTH AND DIFFERENTIATION IN HUMAN CARCINOGENESIS.

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Researchers generally agree that cancer is a multistage process where abnormal cells mutate to become cancerous cells. However, current research explores quantitative methods to describe the path and mechanisms that lead to the malignant state. As cancer is the unregulated growth of cells, there is a need for models that incorporate more biological realism while maintaining mathematical tractability. A stochastic multistage model with the expected number, variance and co-variance formulae expressed as ordinary differential equations is presented as a novel approach for characterizing possible carcinogenic mechanisms. The controlled growth and differentiation (CGD) model (Whitaker et al., 2003) was originally proposed to describe mechanisms in developmental toxicology. However, the model construct also allows for the implementation of a host of possibilities when modeling cancer. This model has a highly controlled birth and death process for cells at any stage of maturity. The formulation of the CGD model easily allows for the inclusion of an unspecified number of states in any biological process. The number of replications allowed in the progression of a cell colony is controllable and is able to more closely reflect the presence of a true stem cell population. The CGD model is able to provide a mathematical approximation to the number (and hence the size) of cells at each stage of the process. Expanding the model to calculate the size distribution of a cell colony can be incorporated and then compared to the observed size distribution. Here, we propose to fit the CGD model to the liver foci data set described in Kopp-Schneider et al. and compare the results of the CGD model, the existing one-stage clonal expansion model3, and the color-shift model (Kopp-Schneider et al., 1998).

1319 PHARMACOKINETIC (PK)/PHARMACODYNAMIC (PD) RELATIONSHIP OF PCB126 UNDER THE CONDITIONS OF MODIFIED ITO MEDIUM-TERM LIVER BIOASSAY.

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PCB126 is the most toxic congener of PCBs with carcinogenic potential. By using the modified Ito medium-term bioassay protocol, male F344 rats were given a single ip dose of 200 mg/kg of diethylnitrosamine (DEN) as an initiator. Daily oral PCB126 administration (3.3 and 9.8 μg/kg/day) was started at week 2 after DEN injection. One week after PCB126 dosing, a 2/3rd partial hepatectomy was conducted. Rats were sacrificed at 20, 24, 28, 47 and 56 days post-DEN injection. Tissue concentrations in the liver, fat, whole blood, kidney and muscle were measured by using GC/ECD following liquid extraction and clean up. Morphometric analysis of glutathione-S-transferase (GST)- P foci formation in the liver slices was performed as a PD endpoint to determine numbers and sizes of preneoplastic foci. Concentration-time courses of PCB126 in the liver, fat, kidney, muscle and whole blood were obtained. Despite high lipophilicity of PCB126, liver concentrations were the highest with the ratio between liver and fat concentrations of about 110-400 to 1. Assuming this is protein binding in the liver, our results revealed that PCB126 binds to liver about 11 to 40 times more strongly than TCDD. Proteomic analyses will shed further light on this interesting binding phenomenon. Dose- and time-dependence of GST-P foci formation were studied. Correlation analyses between area under the curve of PCB126 in the liver (AUC_{Liver}) as an internal dose and PD endpoints (foci numbers, area, and relative foci area) demonstrate linear relationship at low AUCs and nonlinear response at higher AUCs . The linkage of PBPK and clonal growth models will enable us to predict target tissue dosimetry as well as preneoplastic foci formation in F344 rats upon exposure to PCB126 in an Ito medium-term bioassay. (Supported by NIOSH/CDC grant 1 RO1 OH07556)

1320 REACTION NETWORK MODELING OF BENZO(A)PYRENE METABOLIC PATHWAYS: FURTHER DEVELOPMENT.

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We have been developing a modeling tool for predicting the complex biotransformation pathways of xenobiotics by using a chemical engineering approach, Reaction Network Modeling (RNM). RNM generates the reaction pathways automatically based on the chemical structures of the parent compounds and reaction rules. Graph theory is used to encode chemical structures and reaction rules at the molecular level. Benzo[a]pyrene (BaP) was used as the substrate for the first application of RNM to toxicology since it is a human carcinogen as well as a ubiquitous environmental pollutant. Despite thousands of papers in the literature on BaP, quantitative data on human enzyme kinetics useful for RNM are lacking. Thus, to obtain reaction rate constants for RNM, the time course profiles of BaP metabolic pathways were studied using recombinant human cytochrome P450 1A1 and epoxide hydrolase. In addition, considerable effort was devoted to developing HPLC methods for the analysis of 12 major BaP metabolites including dihydrodiols, phenols, tetrols, and quinones with detection limits in the nM range. The high detection sensitivities of BaP-quinones were achieved by an on-line post-column zinc reduction column, which converts the non-fluorescent quinones to their corresponding fluorescent hydroquinones. RNM provided good predictions of the time course profiles of these major BaP metabolites when compared with experimental data. The next phase is to link RNM with PBPK models. Ultimately, we will be able to simulate the entire reaction network of BaP from whole body pharmacokinetics down to the level of molecular interactions among enzymes, BaP, and its metabolites. Since RNM is encoded at the molecular structure level, it is a promising approach to handle the extremely complex biochemical reactions and reaction networks. (Supported by NIEHS Grant R01 ES09655).

1321 QUANTIFYING GENE EXPRESSION NETWORKS USING BAYESIAN METHODS: KNOWN NETWORK STRUCTURE.

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Gene expression arrays (gene chips) have enabled researchers to roughly quantify the level of mRNA expression for a large number of genes in a single sample. Several methods have been developed for the analysis of gene array data including clustering, outlier detection, correlation studies, etc. Most of these analyses are aimed at a qualitative identification of what is different between two samples and/or is there a relationship between two genes. Several researchers have also suggested the use of gene interaction mapping as a tool for the analysis of gene array data. Dynamic models, usually based on ordinary differential equations, have also been proposed and in some cases used for the analysis of microarray data; in most cases, these analyses have shown limited use of formal statistical methods. In this study, we propose a quantitative, statistically sound methodology for the analysis of gene regulatory networks using gene expression data sets. The model was developed based on Bayesian networks to formalize the direct quantification of gene-expression networks. Using this method, it is not only possible to determine the qualitative relationships between genes but the quantitative relationship and the probabilities associated with these quantitative connections. Using gene expression data from HPL1A lung airway epithelial cells after exposure to TCDD at levels of 0.1, 1.0 and 10.0 nM for 24 hours, a hypothetical gene expression network was assumed and the developed method applied to the data and the hypothetical network. Different from seeing gene by gene correlations, the method allows us to see the relationship between genes in terms of network. A new statistical approach to analyze microarray data is shown in this study.

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Preface

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