tissue is altered by exposure to the mixture compared to exposure to the single chemical. Physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models simulate target tissue dose based on exposure levels (PBPK models) and simulate tissue responses based on target tissue doses (PBPD models). The PK models are much better developed than the PD models. Nonetheless, these two types of model structures describe the quantitative interrelationships among critical biological and physiological determinants regulating toxic responses. These models can account for PK and PD interactions and account for the changing nature of apparent interactions as doses escalate, for instance, the change from no interactions and additive toxicity at low doses to less than additive responses at higher doses. Furthermore, interactions examined in vitro can be used to generate predictions of in vivo responses using these PK/PD models. This talk details the role these models should play in studying mixtures and the value of PD model predictions in defining interactions among groups of chemicals.

1324 DEVELOPMENT OF PHYSIOLOGICALLY BASED PHARMACOKINETIC AND PHARMACODYNAMIC (PBPK/PD) MODELS TO DETERMINE DOSIMETRY AND CHOLINESTERASE INHIBITION FOLLOWING EXPOSURE TO BINARY MIXTURES OF ORGANOPHOSPHORUS INSECTICIDES.

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PBPK/PD models have been developed for the organophosphorus (OP) insecticides chlorpyrifos (CPF) and diazinon (DZN). These insecticides share common metabolic activation/detoxification pathways and a common mechanism of neurotoxicity associated with excessive cholinergic stimulation. To develop a binary OP PBPK/PD model, rats were orally administered CPF, DZN or a CPF/DZN mixture (0, 15, 30 or 60 mg/kg) and blood (plasma and RBC), brain and urine were collected for analysis. Chlorpyrifos, DZN and their respective metabolites, trichloropyridinol and isopropy-methyl-hydroxypyrimidine were quantified in blood and/or urine and cholinesterase (ChE) inhibition was measured in brain, RBC, and plasma. Co-exposure to CPF/DZN at the low dose (15/15 mg/kg) did not alter the pharmacokinetics of CPF, DZN or their metabolites in blood. Whereas, a high binary dose (60/60 mg/kg) increased the Cmax and AUC and decreased the clearance for both parent compounds, likely due to competition between CPF and DZN for CYP450 metabolism. At lower doses the pharmacokinetics appeared linear. A dose-dependent inhibition of ChE was noted in tissues for both the single and co-exposures, and the extent of inhibition was plasma > RBC ≥ brain. The overall relative potency for ChE inhibition was CPF > CPF/DZN > DZN. A comparison of the ChE response at the low binary dose (15/15 mg/kg), where there were no apparent pharmacokinetic interactions, suggested that the overall ChE response was additive. Based on these pharmacokinetic results a binary OP PBPK/PD model has been developed. This model facilitates understanding the mixture interactions and the potential for additivity, synergism or antagonism from multi-OP exposures. It is envisioned that this binary model will be useful for accessing exposure and health risk to a wide range of exposed individuals. (Supported by CDC/NIOSH grant 5 R01 OH003629-03)

1325 PBPK MODELING OF METABOLIC INTERACTIONS: EXTRAPOLATING FROM BINARY TO MORE COMPLEX MIXTURES.

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One of the challenges in risk assessment relates to the inability to make use of binary interaction data. The nature and magnitude of an interaction between two chemicals may be further altered by other chemicals in a mixture. This presentation will focus on the novel application of physiologically-based pharmacokinetic (PBPK) models to predict the kinetics of chemicals in mixtures of increasing complexity, solely on the basis of binary interaction data. In this methodology, individual chemical PBPK models are developed and interconnected on the basis of binary-level interactions. As such, with a single set of physiological parameters and multiple sets of chemical-specific parameters, the simulations of the kinetics of mixture components can be obtained. Binary connections between mixture components, where feasible, are established within the model on the basis of interaction mechanisms. Studies conducted so far have focused on the modeling of competition among CYP2E1 substrates for hepatic metabolism. Data collected in rats exposed to binary, ternary, quaternary and pentameric mixtures of toluene, m-xylene, benzene, dichloromethane and ethyl benzene have been used to validate the predictions of the binary-based PBPK model. When all binary level metabolic interactions in a mixture can neither be identified nor characterized, the limits of metabolic interaction (0 – 100%) have been used to simulate the potential consequences of mixed exposures. Such an approach has been validated using several mixtures of volatile organic chemicals. The PBPK modeling approach has also been used to simulate the kinetics of mixtures of PCBs in rats, on the basis of metabolism constants that reflect the net effects of inhibition and induction. Overall, the PBPK modeling approach allows the prediction of the kinetics and internal dose of mixture components on the basis of binary level interactions as well as the net effect of processes affecting the rate of metabolism.

1326 DEVELOPMENT OF A PBPK MODEL FOR GASOLINE AND SEVERAL OF ITS COMPONENTS EXHIBITING METABOLIC INHIBITION.

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Gasoline contains benzene and hundreds of other chemicals that are carcinogenic, neurotoxic, or systemically toxic. Exposure to gasoline mixtures reduces metabolism of individual components through metabolic inhibition. We explored this issue by conducting gas uptake pharmacokinetic (PK) experiments in F344 rats. Total metabolism of components was reduced, for example, by 4% – 27% during a six-hour exposure to 300 ppm gasoline. To develop a better quantitative understanding of this issue, a PBPK model was developed for gasoline PKs in the rat. Rather than attempting to develop inhibitory constant estimates for each component, the majority of the mixture was incorporated into the model as a lumped chemical with single parameter estimates for biochemical and partitioning processes. In addition, five individual chemicals (benzene, toluene, ethylbenzene, xylene, and n-hexane) were treated as single chemicals. Competitive inhibition was inferred from PK data and treated as occurring between each binary combination of chemicals within the mixture. Estimates of the inhibitory constant (Ki) for each non-lumped chemical were developed from initial PK experiments where one chemical was provided at very high levels and other chemicals were at low levels, to improve sensitivity. These constants were then used in the PBPK model without further refinement, and a constant for the lumped chemical was estimated from the whole gasoline studies. Finally, experiments and models were developed for lighter fractions of gasoline that would evaporate during a gasoline spill. The model provides an excellent description of gasoline PKs in the rat, and demonstrates the utility of the chemical lumping approach within the context of PBPK modeling. A model such as the one described can be used in risk assessment to determine the extent of metabolism of carcinogenic metabolites under various exposure conditions, and in other applications. [Supported in part by a Cooperative Agreement from ATSDR (U61/ATU 881475) and the NIEHS Quantitative Toxicology Training Grant T32 ES07321].

1327 MODELING THE INTERACTION THRESHOLD: THE BREAK-POINT BETWEEN ADDITIVITY AND NON-ADDITIVITY.

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Dose-dependent changes in toxicity mechanisms of single chemicals can possibly take place along the full dose-response spectrum. At high doses, the possibility exists for some steps in the principle mechanism of toxicity to shift to other mechanisms. The possibility of mechanism shifts for single chemicals can also be observed for interaction mechanism of chemical mixtures. For instance, interactions (synergism or antagonism) taking place at high individual doses of a mixture, may not be significant at low levels. One of the early experiments indicating a change of the mechanism of interaction with dose was conducted using chloral hydrate and ethanol. The boundary that separates the dose space into regions of interaction and additivity is called the interaction threshold boundary. The interest in defining this region is important because it signifies the need to include or exclude interactive effects in the calculations of health risks of the mixtures, specifically at low environmentally relevant doses. The interaction threshold boundary may take a variety of different shapes, and the shape of this boundary is not likely to be known. Hamm et al. (2005) developed a general procedure to accommodate various potential shapes for this boundary. Predictive modeling (such as PBPK/PD models) along with mode-designed experiments provides an efficient methodology for the identification of interaction thresholds. Based on mechanistic consideration of enzyme inhibitions, prediction of the presence of an interaction threshold between binary chemicals was performed using PBPK models for two different set of chemicals; volatiles (TCE and 1,1-DCE), and pesticides (chlorpyrifos and parathion).

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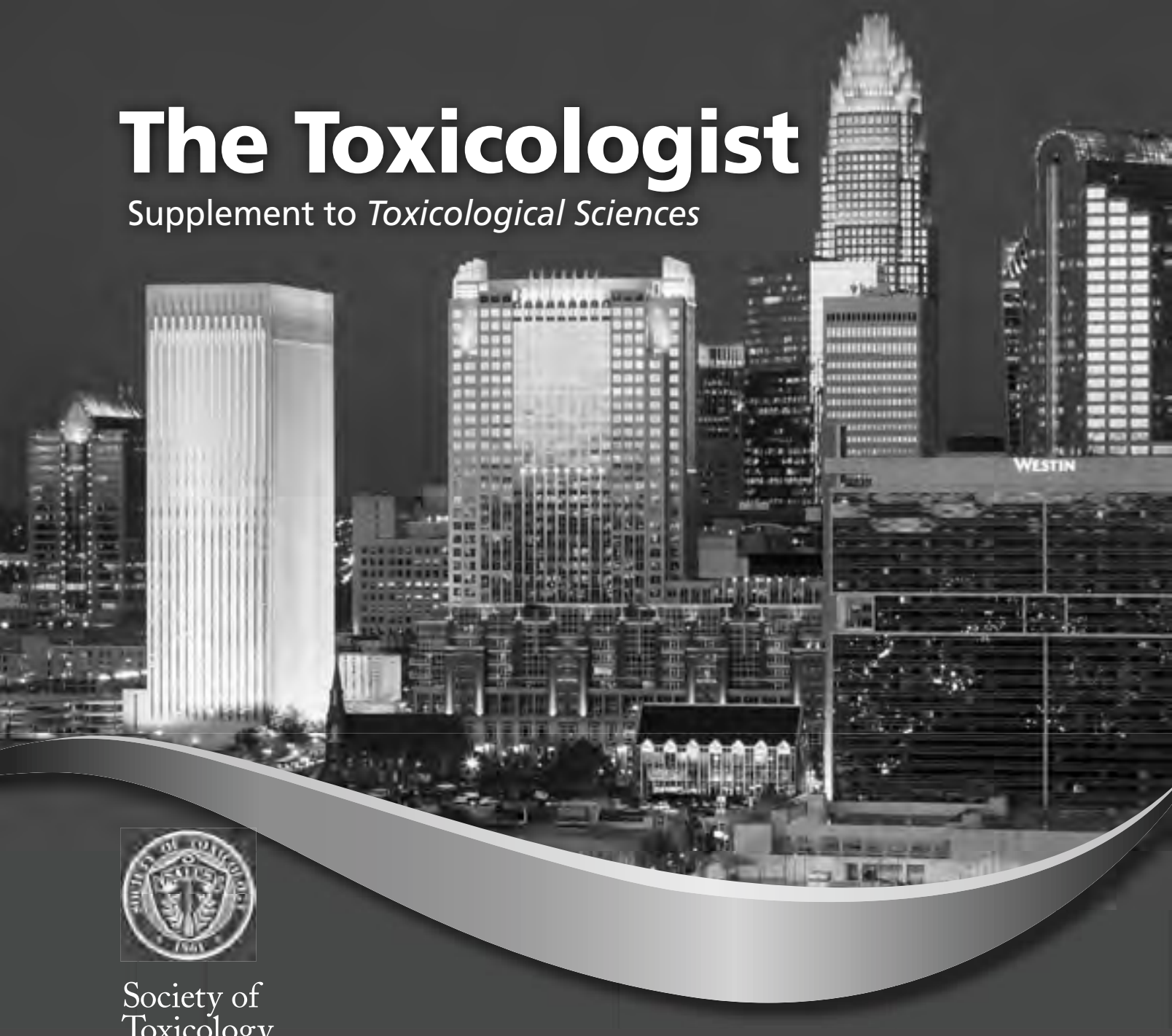

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Preface

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