1758 CAPTURING AND MODELING HUMAN INTERINDIVIDUAL DIFFERENCES FOR HEALTH RISK ASSESSMENT: HEPATIC BIOACTIVATION OF CHLOROFORM.

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Chloroform (CF) is a volatile drinking water contaminant. Risks *via* the oral, but not inhalation route have been estimated. This study was conducted to adjust inhalation dosimetry between animals and humans and assess the impact of variability in some factors which may predispose humans to toxicity. CF partition coefficients were determined in tissues from young and mature rats, and in blood from adult and pediatric patients. CF metabolic rate constants and hepatic CYP2E1 protein concentrations were determined in liver tissue from adult rats and human adult and child organ donors. Vmax was extrapolated to intact tissue and scaled to body weight. The distribution of hepatic blood flow (HBF) as percent of cardiac output was determined from a total of 59 published individual values in human adults. These data were incorporated into physiologically based pharmacokinetic (PBPK) models constructed for mice; rats; and human adults, preadolescents and infants. Because of the relevance of the inhalation reference concentration to chronic, lifetime exposures, constant exposure to CF was simulated until steady state was reached rather than simulating intermittent exposure scenarios. Toxicity studies with mice demonstrate a duration-adjusted NOAEL (liver effects) of 0.9 ppm CF. Simulations indicated that the human equivalent exposure concentration, based on hepatic CF metabolism, was approximately 6 ppm. Among adults, increases in CYP2E1 content and activity, blood:air partitioning, and HBF produced approximately 1, 4 and 17% increases in CF metabolism, respectively. Children converted as much as 34% more CF to metabolites than equivalently exposed adults. These findings will be useful in determining the magnitude of PK variability in the risk relevant PK outcomes between species and among humans.

1759 THE CONTRIBUTION OF PHARMACOKINETIC VARIABILITY TO VARIABILITY IN HEPATIC LABELING INDEX DATA FROM B6C3F1 MICE EXPOSED TO CHLOROFORM.

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We have extended a PBPK model for chloroform to describe a plausible mechanism of hepatic cell killing and regenerative proliferation (Toxicol. Sciences. 75, 192-200, 2003). The resulting PBPK/PD model simulates labeling index (LI) data. A Monte Carlo implementation of the PBPK model (Regul. Toxicol. Pharmacology 2, 144-155, 2000) provides an opportunity to examine the role of PK variability in the LI data. We used this approach with a hepatic LI data set where female B6C3F1 mice inhaled chloroform for 7 consecutive days at various combinations of duration and concentration (Toxicol. Sciences. 66, 201-208, 2002). Our analysis is showed that variability in the parameters of the PBPK model accounted for most of the variability in the LI data. LI variability was slightly under predicted when the LI was close to its control level (e.g., measured: control, 0.55 ± 0.26, 30 ppm for 2 h/day, 1.5 ± 1.23; simulated: 1.10 ± 1.12). For exposures that led to larger increases in LI (e.g., LIs from 2.82 to 19.92), Monte Carlo-predicted PK variability accounted for all of the variability in measured LI. Under prediction of LI variability for small changes in LI may reflect the implementation of the Monte Carlo model or uncertainties associated with experimental measurement of LI. While contribution from variability in the PD cannot be ruled out, this result suggests that PK variability is a major determinant of variability in LI data from chloroform-exposed female B6C3F1 mice. We plan to extend these analyses to male mice and to male and female rats with the goal of better understanding the role of PK variability in variability of LI data. This understanding will guide the eventual scale-up of the PBPK/PD model to humans.

1760 A TRIAL OF TOXICOGENOMIC ANALYSIS OF HUMAN UMBILICAL CORDS FOR DEVELOPING A NEW RISK ASSESSMENT METHOD OF FETAL EXPOSURE TO MULTIPLE CHEMICALS.

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It has been shown that human fetuses are exposed to multiple chemicals including endocrine disruptors. Since there is anxiety that these multiple chemical exposures may cause delayed long-term effects, it is necessary to establish a new evaluation method of health risk derived from exposure to multiple chemicals during fetal period. We are attempting to apply toxicogenomic analysis of human umbilical cords to the future risk assessment. In this study, we analyzed relationship between concentrations of persistent chemicals and gene expression patterns in umbilical cords of 9 Japanese newborns. In the concentration of the chemicals, significant correlations were observed between total polychlorinated biphenyls and many of other chemicals. Gene expression in each umbilical cord was examined by cDNA microarrays, using cultured human umbilical vein endothelial cells as reference. Expression profiles of the umbilical cords were analyzed by principal components analysis and hierarchical cluster analysis, and compared with chemical concentration profiles. The expression profiles of highly exposed umbilical cords were different from those of umbilical cords with lower exposure levels. However, there was an exceptional case. In the exceptional umbilical cord, total concentration of the chemicals was lowest, but its gene expression profile was quite similar to those of the umbilical cords with higher total chemical concentration levels. These results suggest that gene expression profile of umbilical cord can be used for evaluation of exposure levels at fetal period. Moreover, it might be useful to detect potential high risk group, because both of actually higher exposure level and genetically higher susceptibility of an individual to multiple chemicals might be regarded as higher health risk to the individual.

1761 APPLICATION OF A PBPK MODEL TO AID IN UNDERSTANDING THE RELATIVE POTENCIES (REPS) OF DIOXIN-LIKE CHEMICALS.

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The TEF methodology is a relative potency scheme used in risk assessments for dioxin-like chemicals to derive the TCDD equivalents of a mixture. TEF values were assigned to chemicals by an expert panel based on a review of all available data. A criticism of this method is the large range, over 1000-fold, in the REPs for some dioxin-like congeners. One reason for this variability could be experimental design. The aim of this study is to apply a PBPK model to examine the impact of study designs used to estimate REPs. A PBPK model developed for TCDD in rats was used to simulate experimental studies of model dioxin-like chemicals. CYP1A2 induction is by described an Ah receptor-mediated mechanism. Model outputs for CYP1A2 induction were used to estimate REPs. Acute and subchronic exposure conditions were simulated. In the acute simulations, the model was run for up to 14 days post exposure. Subchronic exposures were simulated for 90 days. In order to simulate a variety of dioxin-like chemicals, the AhR affinity was varied (10-1 to 10-4 nmol/ml) and the elimination rate (Kel) was increased by 10 and 20 fold compared to the TCDD. Dose response simulations were run and ED50s for predicted CYP1A2 induction were estimated for each simulation. The REP was calculated as the ratio of the ED50s for model chemical vs. TCDD simulations. When only the AhR affinity is varied, study design had no impact on the estimate of the REP. Study design significantly affected the estimate of the REP when Kel was varied. The REP varied by 100 fold when Kel was increased 20-fold depending on the study design. The present study demonstrates the utility of PBPK models when applied to the TEF methodology. If sufficient data on AhR binding and pharmacokinetics in humans were available for a particular congener, it would be possible to use these models to estimate human TEF values. (This abstract does not represent USEPA policy. Funded by in part by a cooperative agreement with NRC and EPA (CR 828790)).

1762 DERIVATION OF A RANGE OF INTERIM INHALATION CANCER SLOPE FACTORS FOR TCE USING PHYSIOLOGICALLY BASED PHARMACOKINETIC MODELING.

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Widespread use of trichloroethene (TCE) as a solvent and its relative stability has resulted in it being one of the most frequently detected groundwater contaminants in the United States. Although extensively studied, derivation of a cancer slope factor (CSF) representative of potential human health risk remains controversial and the recent EPA re-assessment of TCE did not identify an inhalation CSF. Both animal and human data are suggestive of a threshold for cancer. However, the absence of a consensus on the mechanism(s) of action complicates implementation of a threshold approach. Animal models demonstrate high species, strain, sex, and route of exposure specificity, with carcinogenicity, if it occurs at all, typically seen following cellular damage. The epidemiological studies of TCE inhalation and carcinogenicity in workers are largely negative. For those few studies reporting significant increases in cancer, there are substantial study design problems and a lack of quan-

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