238 ESTIMATING PREVIOUS SERUM TCDD CONCENTRATIONS IN AN OCCUPATIONALLY EXPOSED COHORT USING A PBPK MODEL.

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This study estimated previous serum concentrations of 2, 3, 7, 8-tetrachlorodibenzo-*p*-dioxin (TCDD) in 134 male workers involved in producing sodium trichlorophenol or a derivative. These workers conceived children either during or after this employment. The estimated TCDD concentrations at the time of conception of children were used in a male reproductive health study (in press). Serum TCDD concentrations were estimated with a PBPK model. Available data were serum TCDD level at the end of the study, dates of employment in dioxin-related processes, and body mass index (BMI) at the end of the study and an earlier time point. A linear regression model estimated missing BMI values for 23 workers who had only one measured BMI. Each worker was assumed to have constant "background" exposure to TCDD, estimated from measured serum TCDD values in 79 controls. Individual occupational TCDD exposure rates were estimated for each worker based on final measured serum TCDD concentration and dates of exposure in TCDD-related processes. TCDD elimination in the PBPK model is proportional to hepatic TCDD concentration; the major site of storage is the fat compartment. The hepatic elimination rate constant for TCDD in this model was previously estimated from the Air Force Ranch Hand study. Although the instantaneous elimination rate of TCDD in the model is first-order, changes in body fat composition over time lead to non-linear kinetics. Unlike other simple first-order models, the volume of distribution of TCDD varies as BMI changes over time. The major conclusions are: (1) the retrospective serum TCDD concentrations are highly dependent on changes in body fat; and (2) data on individual body weight changes, as well as on TCDD exposures, should be gathered when modeling the long-term pharmacokinetic behavior of TCDD in humans. Use of this BMI-linked PBPK model for TCDD permits the investigator to distinguish between plasma kinetics and the whole-body kinetics of TCDD.

239 TISSUE DOSIMETRY BASED ANALYSIS OF SPECIES-SPECIFIC DIFFERENCES IN PULMONARY TOXICITY FROM STYRENE EXPOSURE: A PBPK MODEL-BASED APPROACH.

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Chronic rodent studies demonstrate species specificity in the pulmonary carcinogenic response to inhaled styrene (ST). Increased incidences of bronchioloalveolar tumors was observed in mice, but not in rats. Although the data are not definitive with regard to a target cell, ST-induced lung tumors in mice could be from Clara cells in the respiratory epithelium lining the terminal bronchiole. Clara cells metabolize ST to styrene-7, 8-oxide (SO), which is cytotoxic and weakly genotoxic. Rodent species show marked differences in density and distribution of Clara cells and their metabolic capacity. A physiologically based pharmacokinetic (PBPK) model was developed to predict the concentration of ST and SO in the respiratory tract tissues. The model incorporated a multi-compartment description of the respiratory tract, including species specific quantitative information on respiratory tract physiology and metabolic capacity. The model was validated against multiple data sets. The PBPK model predicts a 10 fold lower SO concentration in the terminal bronchioles in rats compared to mice, which is consistent with the observed species sensitivity to the development of respiratory tract neoplastic lesions. Furthermore, model-estimated SO concentration in the terminal bronchioles of mice show a close correlation to the incidence of neoplastic lesions. However, blood SO concentration do not correlate to the neoplastic lesions data, indicating that the carcinogenic response in rodent lung is controlled by local metabolism rather than systemic delivery.

240 ROUTE-SPECIFIC DIFFERENCES IN DISTRIBUTION CHARACTERISTICS OF OCTAMETHYLCYCLOTETRASILOXANE IN RATS: A PHYSIOLGICAL MODEL BASED ANALYSIS.

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Octamethylcyclotetrasiloxane (D4) has unusual pharmacokinetics resulting from its unique combination of low blood:air and high fat:blood partition coefficients. To understand the determinants of the pharmacokinetics of D4, a multi-route physiologically based pharmacokinetic (PBPK) model has been developed to characterize the retention, distribution, and elimination of D4 following inhalation, dermal, oral and intravenous (IV) exposures in the rat. Concentrations of D4 in plasma, D4 exhalation rates, and elimination rates of D4 metabolites in urine, measured following inhalation, dermal, oral or IV dosing, form the basis for the model. In addition to liver, lung, blood, richly and poorly perfused tissues; the PBPK model contains deep-compartments for the liver and lung, a blood-lipoprotein pool, and multiple fat compartments. The PBPK model only provided good fits to pharmacokinetic data from the multiple routes of exposure when the dose routes were treated as if the D4 entered the circulation in different pools for the different routes. The disposition of D4 following both inhalation and dermal exposure were similar and appear to be governed by direct delivery of free molecular D4 into the blood. In contrast, disposition of D4 following oral exposure appears to be governed by uptake into the blood-lipoproteins and subsequent sequestration in various lipid pools. Similarly, pharmacokinetics following IV administration was also best described by a model structure with delivery of D4 directly into the deep blood compartment, indicating that the microemulsion form of D4 never becomes readily available as a free form of the compound. Unexpectedly the physical form of D4 delivered varied among dose routes. These dose route-route differences in pharmacokinetics need to be considered in human exposure assessments and in Dose-Response modeling. Supported in part by Silicones Environmental, Health and Safety Council of North America.

241 HUMAN INHALATION PHARMACOKINETICS OF OCTAMETHYLCYCLOTETRASILOXANE (D4): EVALUATION WITH A PHYSIOLOGICAL MODEL.

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D4, a lipophilic, volatile liquid, is used as a reaction intermediate and is found in industrial and consumer products. Workers and consumers may be exposed to D4 by inhalation or dermal routes. A human inhalation pharmacokinetic (PK) study (Toxicology Sciences, 44:206-13, 1998) and a physiologically based pharmacokinetic (PBPK) model for D4 inhalation in rats (Toxicology Sciences, 60:214-31, 2001) were recently published. The rat PBPK model showed that D4 is eliminated rapidly from the body after exposure due to its low blood:air partition coefficient, Pb (~ 1), and its relatively high metabolic clearance. Some D4 was present in blood in a form that was not readily exhaled, presumably bound to lipids. From the human PK study, data from 12 subjects exposed by inhalation to 10 ppm D4 for 1 hour with alternating periods of rest and exercise were analyzed with the PBPK model. The human data required a Pb of about 0.9. Human metabolism and fat partitioning constants remain to be determined more accurately (i.e., they could not be estimated from the data). When values for these parameters were based on those of the rat study, the model matched observations in the human PK study very well. The PBPK model results were also consistent with the decreased retention with increased alveolar ventilation seen in humans. While the human data set is less extensive than the rat data set, similar PK behaviors were noted including rapid clearance by exhalation and longer persistence in plasma than expected based on the Pb and the rate of metabolism. Many of the conclusions reached in PBPK modeling of D4 inhalation kinetics in rats appear valid for human kinetics of D4. Thus, a similar model structure, with a key feature of D4 sequestration in blood lipids, is required in both species. Supported in part by Silicones Environmental, Health and Safety Council of North America and by NIEHS T32 ES07321 for M. Reddy.

242 ASSESSING THE METABOLISM OF HEXAMETHYLDISILOXANE USING GAS UPTAKE METHODS AND PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) MODELING.

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Gas uptake methods have been successfully used to assess the metabolism of a wide variety of volatile organic chemicals. The technique works best with compounds of moderate blood:air and relatively low fat:blood partitioning, and little propensity to adsorb onto chamber surfaces. We extended these techniques to evaluate the *in vivo* metabolism of hexamethyldisiloxane (HMDS), a low molecular weight volatile siloxane. The studies utilized a static atmosphere closed chamber system designed by Filser and colleagues (Arch. Toxicol. 42: 123-136, 1979). Soda lime, used to prevent accumulation of exhaled CO_2 in the system, adsorbed a substantial part of HMDS thus limiting the interpretation of the kinetic data. Soda lime was replaced

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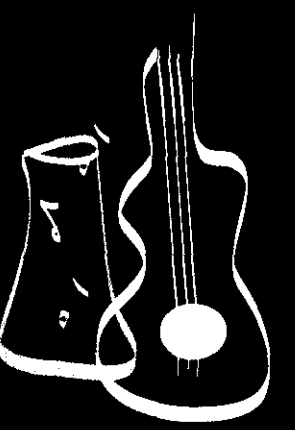

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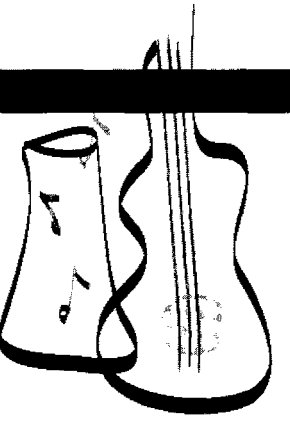

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Additional Late-Breaking Abstracts are issued in a supplement to this publication and are available at the 41st Annual Meeting and through the Society of Toxicology Headquarters office.

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