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1131 PARAMETER ESTIMATION TECHNIQUES FOR PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PB-PK) MODELS. H.J. Clewell III, D.W. Quinn,* and M.E. Andersen, AAMRL/THB, and *AFIT/ENC, Wright-Patterson AFB, OH.

PB-PK models offer significant advantages over conventional empirical models for interpreting and extrapolating data, but their increased power is obtained at the cost of an increased number of parameters. Although most parameters are based on physiology or derived from *in vitro* studies, there are often several which must be estimated by matching model predictions to kinetic data. We have compared numerical techniques for performing this process with a manual method in which an investigator interactively varies model parameters to obtain a visual match between model output and data. Both gradient and direct search techniques were used to minimize a weighted least squares objective function. The number of estimated parameters ranged from one to ten, and the PB-PK models and data sets represented a range of complexity. The performance of the numerical methods was often disappointing. When initial parameter estimates based on a manual fit were used, there was little improvement. When other initial estimates were used, they were generally unable to match important features of the data. In this paper we describe our attempts to improve parameter estimation by using objective functions incorporating analysis of data curvature and use of Bayesian priors.

1132 ALTERNATIVE APPROACHES TO MATHEMATICALLY ANALYZING THE BIOASSAY DATA FOR 2,3,7,8-TCDD. R.L. Sielken¹, F.W. Carlborg², D.J. Paustenbach³, H.P. Shu³, F.J. Murray³. ¹Professor of Statistics, Texas A&M Univ., College Station, TX. ²Statistical Consultant, St. Charles, IL. ³Syntex (U.S.A.), Inc., Palo Alto, CA.

This paper will critically evaluate the approaches currently used by regulatory agencies in assessing the cancer risk of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). These agencies use mathematical models when estimating cancer risk by extrapolating from high doses, where animal tumor data exist, to very low doses, where human exposure is likely to occur. These models are based on the hypothesis that cancer is an expression of a permanent, replicable change in cellular genetics, i.e., an initiator. These models typically assume a linear, non-threshold, irreversible response at very low doses for all chemical carcinogens. Due to the assumptions inherent in the various models, the virtually safe dose (VSD) estimated by these models may vary by 3-4 orders of magnitude. There is no convincing evidence that TCDD possesses initiating activity. The data from mutagenesis assays, DNA binding studies and tumor promotion studies strongly support a non-genotoxic mechanism for TCDD carcinogenesis. Specifically, this paper will discuss the VSDs predicted by various linear, non-threshold models and present arguments that the resulting VSDs are likely to be overly conservative, given what we know about the mechanism of action of TCDD. We will discuss alternative and more justifiable methods for analyzing the TCDD cancer data. These alternative methods will incorporate such data as time-to-tumor development, correction for early death, a threshold or a non-linear dose-response relationship, receptor-mediated mechanism, and limited low-dose linearity. We will demonstrate that as the histopathology of the lesion progresses to that of a tumor, the dose-response curve becomes more and more non-linear. This phenomenon has also been seen with other non-initiating carcinogens, including saccharin.

1133 AN EXAMINATION OF CRITICAL ASSUMPTIONS IN HEALTH RISK ASSESSMENTS OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN CONTAMINATED SOIL. D.J. Paustenbach, H.P. Shu, and F.J. Murray, Syntex (USA) Inc., Palo Alto, CA

Environmental limits for 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are currently being considered by regulatory agencies worldwide. Among these are limits for tap water, soil at industrial sites, residential soil, fish, and air and fly ash. Thus far, in the United States, standards have been promulgated but a few have been suggested. This presentation will review several critical assumptions used in proposed approaches to setting limits for TCDD in residential soil and soil within industrial sites. For example, it will be shown how the results of the risk assessment and, subsequently, the magnitude of recommended limits can be profoundly affected by unjustifiable assumptions regarding the quantities of soil typically consumed by children and adults, the nongenotoxicity, its degradation at the soil surface, and its bioavailability in soil. Two case studies will quantitatively illustrate the effect of these assumptions on the risk estimates will be presented. This assessment will indicate that a concentration of TCDD considerably in excess of 1 ppb should be acceptable for soils in residential and nonresidential areas. Western land management practices which consider TCDD's nongenotoxicity in estimating the virtually safe dose will be compared and contrasted with the approach used in the United States.

1134 TETRACHLOROETHYLENE: METABOLISM AND PHARMACOKINETICS IMPLICATION FOR RISK ASSESSMENT. J. Parker, C.W. Chen, and I.W.F. Davidson, Environmental Protection Agency, Washington, D.C. and Bowman Gray School of Medicine, Winston-Salem, N. C. Sponsor: R. P. Beliles.

Lifetime studies of mice and rats showing the carcinogenicity of tetrachloroethylene (perc) cancer-carcinogenicity serve as the basis for estimation of human carcinogenic risk. Experimental data on human pharmacokinetics and covalent binding studies were evaluated for incorporation into risk assessment. Evidence indicates liver and kidney are the primary and carcinogenicity potential of perc are dependent on its metabolic conversion to highly reactive intermediates. Reactive perc metabolites bind irreversibly to cellular macromolecules. *In vivo* binding is independent of route of exposure, proportional to amount metabolized. Indices of cellular toxicity and cellular damage have been shown to correlate linearly with metabolic rate. Comparative experimental evidence shows that metabolic pathways for perc qualitatively differ in rats, mice, and humans. Data for these species suggest metabolism of perc after oral or inhalation exposure is rate-limited and proceeds according to Michaelis-Menten kinetics. Methods for establishing metabolized dose-tumor relationships for the bioassays and for extrapolation to man are outlined. Where available human pharmacokinetic data are incorporated into the quantitative assessment, various approaches result in similar cancer risks.