

DP

# THE TOXICOLOGIST

An Official Publication of the  
Society of Toxicology

**Abstracts of the  
31st Annual Meeting  
Vol. 12, No. 1, February 1992**

- 684 A GENERIC PBPK MODELING TOOL FOR RAPIDLY DEVELOPING PBPK MODELS. L A Cox, Jr., and F B Thomas. Cox Associates, Denver, Colorado and ENSR Consulting and Engineering, Houston, TX

Internal dose modeling is useful in cancer risk assessment to adjust for effects of high vs. low administered doses and to correct for interspecies differences in metabolism, pharmacokinetics, and route of dosing. The popularity of physiologically-based pharmacokinetics (PBPK) models requires users to master continuous simulation computer languages or to develop special-purpose modeling tools to expedite the PBPK modeling process. This paper presents a generic PBPK modeling program that shortens the time needed to develop a new PBPK computer model from days to minutes. The tool uses "adaptive menus" to prompt for needed information; provides on-line access to data libraries and allometric equations for suggesting default parameter values; and offers commands for selecting animal models and dose routes, running exposure scenarios in animals or humans, and displaying the results in both tabular and graphical form. Interactive graphics are used to rapidly form new models and edit old ones, while built-in consistency and range checks help users to specify appropriate PBPK parameter values. This computer tools dramatically cuts the costs of developing and validating PBPK models, while promoting consistency and encouraging inexpensive exploration and comparison of alternative models and assumptions.

- 685 PHYSIOLOGICALLY-BASED MODELLING OF THE PHARMACOKINETICS AND ENZYME INDUCING PROPERTIES OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD). J Mills, J Murphy, M Gargas and M Andersen, Chemical Industry Institute of Toxicology, RTP, NC

Physiologically-based pharmacokinetic (PB-PK) modelling has been used to examine the disposition of TCDD in mice and Wistar rats. We have extended this model to study TCDD disposition and enzyme induction in female Sprague-Dawley rats, the animals on which the current USEPA dioxin cancer risk assessment is based. Rats were injected ip with doses of  $^3\text{H}$ -TCDD between 1 and 10,000ng/kg bw ( $2\mu\text{Ci/kg}$ ) and killed after 7 days. Tissue TCDD concentrations were determined in 15 tissues and liver activities, protein levels, and mRNA levels estimated for both cytochrome P-450IA1 and P-450IA2. The liver/fat concentration ratio was dose dependent varying from 0.3 at 1ng/kg and 3 at 10,000ng/kg. P-450IA1, measured as ethoxyresorufin *O*-deethylase activity, increased in a dose dependent fashion from 10ng/kg to the highest dose used. The data on tissue concentrations and enzyme induction for both IA1 and IA2 have been used to create a combined model for TCDD pharmacokinetics and pharmacodynamics based on receptor TCDD concentrations, instead of receptor occupancy as previously used. These models will be critical in the development of biologically-based cancer risk assessments for this ubiquitous environmental contaminant.

This work was co-sponsored at CIIT by the American Paper Industry

- 686 DEVELOPMENT OF RISK-BASED RE-ENTRY LEVELS FOR PCBs, PCDDs, AND PCDFs FOLLOWING PCB FIRES. J Michaud, D Paustenbach. ChemRisk® - A Division of McLaren/Hart, Portland, ME.

A number of fires involving polychlorinated biphenyl (PCB)-containing transformers and capacitors have occurred in the U.S. PCB fires generate by-products such as polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzodioxins (PCDDs) and result in the contamination of the interior of building structures. Considerable concern exists over the potential human health effects associated with exposure by inhabitants to residual levels of PCBs, PCDFs and PCDDs. Indoor workers may be exposed to these chlorinated compounds via inhalation of contaminated particulates and vapors, dermal contact with contaminated surfaces, and incidental ingestion of dusts. A wide range of acceptable re-entry, or cleanup, levels have been developed for PCDDs to protect workers who re-occupy a building following a PCB fire. For example, surface contamination re-entry levels ranging from 1.0 to 28 ng/m<sup>2</sup> have been considered acceptable by various agencies (Kim and Hawley, 1985; Wade, 1987; NIOSH, 1986). Re-entry levels have been used by property owners and regulatory agencies as criteria for determining whether the building is safe to re-occupy or to determine the extent of needed remediation. In general, three risk-based approaches to setting such acceptable re-entry levels have been used. In this paper, the range of cleanup levels (as determined by air sampling and wipe sampling) used at PCB fire sites and the appropriateness of the approaches used to develop the levels are examined. Alternative PCDD, PCDF (using toxicity equivalent methods), and PCB acceptable re-entry levels or wipe sample criteria which are based on current information and risk assessment methods will be presented.

- 687 RISK ASSESSMENT AND MANAGEMENT DUE TO CONSUMPTION OF FISHERY PRODUCTS CONTAMINATED WITH CHEMICALS. F E Ahmed. Institute of Medicine, National Academy of Sciences, Washington, DC.

A small portion of fishery products contaminated with appreciable amounts of potentially hazardous inorganic and organic contaminants from natural and environmental sources seems to pose the greatest potential for toxicity to consumers. Risks are not generally of high magnitude; nevertheless, their control will improve public health. Inorganic contaminants with greatest potential for toxicity appear to be antimony, arsenic, cadmium, lead, mercury, selenium and sulfites. Among organic compounds, polychlorinated biphenyls, dioxins, several chlorinated hydrocarbon insecticides, certain processing-related and aquaculture-related contaminants pose sufficient potential risks for consumers. In general, lognormal distributions appear to provide good descriptions of the pattern of variation of contaminant concentrations among different geographic areas, and some contaminants appear to be much more variable than others; this variability offers a solution for reduction of exposure through restricting harvest of aquatic organisms from specific sites, and by excluding certain species. It is recommended that: existing state and federal regulations, and environmental monitoring be strengthened and enforced; a program of shared responsibility between federal and state agencies be developed; research and public education by government agencies and health professionals be expanded; and mandatory labeling be considered for some chemicals.