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FACTORS INFLUENCING THE ESTIMATION OF HAZARD FROM AN ACCIDENTAL ARSINE RELEASE. G V Alexeeff, California Department of Health Services, Berkeley, CA

Arsine is an extremely hazardous substance that requires evaluation for the potential consequences of an accidental release. Reported rat LC50s indicate that arsine is of similar toxic potency as methyl isocyanate. Although over 470 human cases of arsine poisoning have been reported in the literature, quantitative dose-response data are lacking. Thus, available data reported for laboratory animals were evaluated to calculate concentrations that could produce fatal or severe toxic effects (hemolysis) in humans. Reported data for mice indicate that the toxic response to arsine varies as a function of concentration² x time. Calculations based on the administered concentrations indicate that the mouse (10-min LC50 ≈ 85 ppm, 10-min LOEL ≈ 12 ppm) is more sensitive than the rabbit (10-min LC50 ≈ 250 ppm, 10-min LOEL ≈ 16 ppm). However, calculations based on the estimated quantity of arsine absorbed per RBC, indicate that the rabbit may be 5 to 10 times more sensitive to the effects of arsine than the mouse. Based on evaluation of pharmacokinetic parameters, children would receive approximately twice the arsine dose per RBC compared to adults breathing the same concentration.

A BIOLOGICALLY-BASED COMPUTER SIMULATION MODEL FOR HEPATOCYTOTOXICITY. J M Gearhart¹, L J Goodpaster¹, M E Andersen² and R B Conolly¹. 1 Northrop Services Inc., Dayton, OH, 2 AAMRL/TH WPAFB, OH.

A number of cytotoxicants (C) are carcinogenic in rodent bioassays. Their carcinogenicity may be due to continual regenerative hyperplasia (RH) following repeated toxicity. Evaluation of this hypothesis requires, in part, quantitation of necrosis and RH after C exposure. We have developed a simulation model describing C pharmacokinetics and a biochemical mechanism leading to cell death. In this model a metabolite of C attacks a target macromolecule (T) and cells die when T falls below a threshold concentration. Soluble enzymes are released by viable, leaky cells while membrane-bound enzymes are only released when cells die. Computer simulations of hepatotoxicant inhalation and resultant cytotoxicity are presented. One aspect of model validation is the quantitation of hepatic enzyme activity *in situ* and of its clearance from blood. SGPT, a soluble hepatic enzyme, had *in situ* activity of 19,450 ± 3,700 SF units/g liver in male Osborne-Mendel rats and was cleared from the blood by a biphasic process with half-lives of 3.4 and 35 hr, respectively. Full validation of the model may enable activities of membrane-bound hepatic enzymes in blood to be used as quantitative indices of hepatocyte death.

617 BIOLOGICALLY-BASED COMPUTER SIMULATION OF DOSE-RESPONSE (D-R) CURVES FOR CYTOTOXIC CHEMICAL CARCINOGENS. R B Conolly¹, H J Clewell, III², R H Reitz³, and M E Andersen². 1 Northrop Services, Inc., Dayton, OH; 2 AAMRL/TH. WPAFB, OH; 3 Dow Chemical Co., Midland, MI

Predicting the shape of carcinogen D-R curves at low doses is a long-standing problem which can be addressed by computer simulation. We have developed a simulation model for a cytotoxicant (C), including its pharmacokinetic behavior, biochemical mechanism of toxicity, and for a linkage between toxicity and tumor formation. Target tissue cells have basal birth and death rates. Mutations occur during replication and cause transition of normal cells to intermediate and then malignant genotypes (0, 1 and 2 mutations, respectively). For cytotoxicity, a metabolite of C wrecks a target macromolecule (T) and cells die when T falls below a threshold concentration. Individual cell thresholds are normally distributed. Cell death is followed by regenerative hyperplasia which increases the transition rates. Six hr/day, 5 day/wk for 2 yr inhalation exposures were simulated. The threshold for cytotoxicity was varied and D-R curves obtained from 1 ppb through 100 ppm. As expected, shapes of carcinogen D-R curves were a function of cytotoxic threshold. This study illustrates the use of computer simulation to integrate information on carcinogen exposure, pharmacokinetics, mechanism of action, and tumor formation.

618 A PHYSIOLOGICAL PHARMACOKINETIC DESCRIPTION OF THE TISSUE DISTRIBUTION AND ENZYME INDUCTION OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN IN THE RAT. H W Leung, *M E Andersen, R H Ku, and D J Paustenbach. Syntex (USA) Inc., Palo Alto, CA, and *Consultant, Dayton, OH.

The disposition of TCDD in the mouse is primarily determined by high affinity hepatic binding to a cytosolic receptor and a microsomal binding domain. Distribution studies provided estimates of the binding constant for the latter, but not for the former. We developed and validated a physiological pharmacokinetic model for the mouse which included the 2 hepatic binding sites. We then modified the model to include enzyme induction, which was assumed to be related to the fractional occupancy of the cytosolic receptor. This model was scaled up for the rat to evaluate literature data for enzyme induction by TCDD. The cytosolic receptor binding affinity *in vivo* was estimated by simulation to be about 10 pM. This rat model also accurately predicted the tissue distribution following repeated dosing as described by Rose et al. (Toxicol. Appl. Pharmacol. 36 (1976) 209). In both instances, the behavior was extremely sensitive to binding affinities, but much less sensitive to binding capacities in the dose range studied. This physiological model for TCDD which accounts for hepatic binding and enzyme induction is useful for cancer risk assessments when it is coupled with biologically-based models for tumor promoters.