

Development of a PB-PK Model for Vinyl Chloride

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Objectives: The objectives of this project were (1) to demonstrate the ability of modern techniques of pharmacokinetic analysis (based on mammalian physiology, PB-PK) to accurately describe the induction of liver tumors (angiosarcomas) in rats following exposure to vinyl chloride (VC) vapor, and (2) to show that extrapolations of risk from rats to humans based on PB-PK principles yield results which are consistent with data from the human tumor registry in populations occupationally exposed to VC.

PB-PK Model: For the purposes of this project, a four compartment PB-PK model similar to that developed by Ramsey and Andersen (1984) for styrene was employed. In this model, the body of mammalian species (rats, mice, and humans) was divided into four compartments: liver, fat, rapidly perfused organs, and slowly perfused organs. Volumes and blood flow rates of the compartments in each species for this model were obtained from Andersen *et al.* (1987). Partition coefficients for the tissue groups were obtained by one of us (Gargas) using experimental procedures described elsewhere (Gargas *et al.*, 1989). VC metabolism in the model consisted of a single, saturable metabolic pathway localized entirely in the liver compartment. Metabolic rate constants for rats were obtained from two data sets: (1) gas uptake studies conducted at WPAFB (Gargas, 1988), and (2) constant concentration inhalation exposures to ^{14}C -VC conducted at Dow Chemical Co. (Gehring *et al.*, 1978). Metabolic rate constants for humans were estimated by allometric scaling from rat parameters as described by Andersen *et al.* (1987) for dichloromethane, and were compared to data gathered with human volunteers exposed to VC in Germans (Butcher *et al.*, 1978).

The PB-PK model was used to describe the production of radioactive metabolites (non-volatile radioactivity) in male Sprague-Dawley rats following 6 hr exposures to ^{14}C -VC after exposure to 1.4, 9, 25, 51, 109, 250, 511, 1020, and 4600 ppm. Simulated and experimental data are plotted in Figure 1. The PB-PK model gave an excellent description of the metabolism of VC over this wide range of concentrations.

A very similar PB-PK model was used to describe data gathered in four independent gas uptake experiments with male, Sprague-Dawley rats at initial concentrations of 360, 600, 1500, and 3550 ppm VC. Simulated and experimental data are plotted in Figure 2. The PB-PK model gave an excellent description of the experimental data gathered from these four experiments.

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Risk Assessment (Rats): VC is metabolically activated to one or more mutagenic species in vivo, probably involving the generation of a reactive epoxide. In order to model the delivery of the mutagenic species to the target tissue (liver) the model was used to calculate the average daily rate of production of VC metabolites per unit volume of tissue as described by Andersen *et al.* (1987) for dichloromethane (dose surrogate = mg equivalents of metabolite/liter of liver/day).

Average model parameters were used in the calculation of this dose surrogate for exposure conditions corresponding to the results reported by Maltoni (1974) for experiments BT1, BT2, BT9, and BT15 (exposure concentrations of 0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2500, and 6000 ppm for 4 hr/day, 5 days/week). In these studies male and female Sprague Dawley rats were exposed for 1 year, so lifetime average daily doses (LADD) were calculated by multiplying the values obtained from the computer by 5/7 (to correct for less than daily exposure) and 1/2 (to correct for exposure for less than the normal lifetime). Results from male and female rats were combined and empirically fitted to a metabolic dose/tumorigenic response curve with the computer program GLOBAL83 (Howe and Crump, 1982; Howe, 1983).

Extrapolation from the fitted dose/response curve indicates that a LADD of 1.01×10^{-1} mg equivalents/day/liter of liver is associated with a lifetime increase of 1×10^{-4} in the cancer incidence of rats (MLE estimate).

Translated to humans, this means that a similar increase (1×10^{-4}) in the likelihood of developing liver angiosarcoma is produced when humans are continuously exposed (24 hr/day) to 0.0542 ppm of VC. For a 1/million increase in excess risk, the continuous human exposure level would be approximately 0.00054 ppm or 0.54 ppb.

For occupational exposure, it can be calculated that exposure to 1 ppm VC for 8 hr/day, 5 days/week, 50 weeks/year produces a LADD of 6.30×10^{-3} mg equivalents per day per liter of liver for each year of exposure. From the equation derived from rats, this corresponds to an incremental increase of 6×10^{-6} in lifetime risk per year of exposure to VC, or a projected increase in risk to 1×10^{-4} after about 17 years of occupational exposure.

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