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Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats

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Risk of Angiosarcoma in Workers Exposed to Vinyl Chloride as Predicted from Studies in Rats. GEHRING, P. J., WATANABE, P. G., AND PARK, C. N. (1979). *Toxicol. Appl. Pharmacol.* 49, 15-21. Dose-response data for the induction of angiosarcoma in rats exposed to various levels of vinyl chloride (VC) together with attendant biotransformation data were used to estimate the risk of developing angiosarcoma in persons exposed to VC. Since a biotransformation product of VC, not VC *per se*, is responsible for the induction of angiosarcoma, the body surface area of people relative to rats was used to estimate the dose of the carcinogen biotransformed from VC by the former. Four models were used to extrapolate the data. Using a probit model, 10 hepatic angiosarcomas were predicted to occur in a recently reported epidemiological cohort of 9677 workers whereas five have occurred. Linear models and that based on the equation, Risk $= 1-e^{-\beta x}$, where x = dose, do not appear as reliable. For an 8-hr day, 5 days/week, 35-year time-weighted-average exposure of 1 ppm, the predicted incidence of hepatic angiosarcoma using the probit model is 1.5×10^{-6}.

Exposure of rats (Maltoni and Lefemine, 1975) and humans (Creech and Johnson, 1974; Tabershaw and Gaffey, 1974; Makk *et al.*, 1976; Fox and Collier, 1977) to vinyl chloride (VC) has been associated with the development of hepatic angiosarcoma. Numerous studies in rats indicate that it is not VC *per se* which is responsible for production of angiosarcoma but rather a reactive metabolite formed from it in the body (Bartsch *et al.*, 1975; Barbin *et al.*, 1975; Kappus *et al.*, 1976; Malavielle *et al.*, 1975; Bolt *et al.*, 1975; Watanabe *et al.*, 1978). Biotransformation of VC in rats is a nonlinear process occurring in accordance with Michaelis-Menten kinetics:

$$v = V_m S/(K_m + S) \qquad (1)$$

(Watanabe *et al.*, 1976a,b,c; Bolt *et al.*, 1976). In this equation, v and V_m are velocity and maximum velocity, respectively, for the biotransformation of VC expressed as microgram equivalents VC metabolized daily. S and K_m are the concentration of VC being inhaled and the Michaelis constant expressed as micrograms of VC per liter of air, respectively.

Utilizing the foregoing information, Gehring *et al.* (1978) revealed a good correlation between the probit percentage incidence of angiosarcoma in rats exposed to varying concentrations of VC, 4 hr daily, and the amount of vinyl chloride biotransformed, v, microgram equivalents VC metabolized per day. The probit equation is:

$$\text{Probit percentage incidence} = -1.625 + 1.543 \log v. \qquad (2)$$

Hypothesizing that the biotransformation of VC is related directly to body surface area,

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