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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^{-4}.

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:

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

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

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TABLE 1

PREDICTED INCIDENCE OF ANGIOSARCOMA IN RATS EXPOSED TO VINYL CHLORIDE USING VARIOUS MODELS VERSUS DOSE (v, μg VC METABOLIZED PER DAY) COMPARED TO EXPERIMENTAL RESULTS

Exposure[a] (ppm)	Dose[b] (v, μg/day)	Experimental[a] (%)	Predicted percentage (Models)[c]			
			A	B	C	D
10,000	5521	14.8 (9/61)	19.8	20.0	19.7	18.9
6,000	5403	21.7 (13/60)	19.3	20.5	19.3	18.6
2,500	5030	22.0 (13/59)	17.9	18.1	17.9	17.4
500	3413	11.9 (7/59)	12.1	11.8	12.2	12.2
250	2435	6.8 (4/59)	8.1	8.0	8.7	8.8
50	739	1.7 (1/59)	1.4	1.4	2.6	2.8

[a] From Maltoni and Lefemine (1975).

[b] Calculated from $v = [5706\ (\mu g\ VC/4\ hr) \cdot S(\mu g/liter)]/[860\ (\mu g/liter) + S(\mu g/liter)]$, where $S = 2.56\ (\mu g/ppm/liter) \times$ exposure (ppm) (Gehring *et al.*, 1978).

[c] Model A, Probit $\% = -1.625 + 1.543$ Log (dose); Model B, $\% = -1.48 + 0.389 \times 10^{-2}$ (dose); Model C, $\% = 0.3565 \times 10^{-2}$ (dose); Model D, $\% = [1 - e^{-\beta(dose)}]\ 100$, where $\beta = 0.38 \times 10^{-4}$.

RESULTS AND DISCUSSION

The incidence of hepatic angiosarcoma in subgroups of 9677 workmen with respect to their duration of exposure are given in Table 2. These workers include 95.1% of the 10,173 in the cohort study; the remainder could not be traced.

The atmospheric concentrations of vinyl chloride to which these workers had been exposed were not quantitated, except subjectively into high, medium, and low categories. Since the time-weighted-average (TWA) exposure recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) prior to 1972 was 500 ppm and subsequently 200 ppm until adoption of the Occupational Safety and Health Act standard of less than 1 ppm in 1974, it is assumed that even those exposures subjectively deemed low were high. Indeed, it is reasonable to expect the TWA exposures of 200 ppm and greater for 8 hr were common rather than the exceptions.

Table 3 depicts the average theoretical rat equivalent daily doses of biotransformation products of VC received by workers exposed to 200 or 500 ppm for 8 hr daily, 5 days/week adjusted for the fraction of their working life during which exposure occurred. The doses, v, are expressed as micrograms per 8 hr and were calculated from Eq. 3 (given under Introduction) multiplied by the fraction of an assumed 35-year working life during which exposure occurred.

Having estimated the rat equivalent daily doses of biotransformation products of VC received by the various subgroups of 9677 workmen exposed to a TWA of 200 or 500 ppm VC, the predicted incidence of hepatic angiosarcoma for each subgroup was calculated (Table 4). Examination of the data in this table indicates that Models C and D overestimate the incidence of hepatic angiosarcoma experienced by these workers while Model B underestimates the incidences. Models C and D may overpredict because they do not address either the enzymatic biotransformation of VC or repair of the lesion leading to development of angiosarcoma, both of which are likely to be distributed normally in human or animal populations.

It may be argued that Models C and D overpredict because the recommended TWA exposure values of 200 or 500 ppm VC are

TABLE 4

PREDICTED NUMBER OF ANGIOSARCOMAS IN WORKERS EXPOSED TO 500 OR 200 PPM VINYL CHLORIDE 8 HR/DAY, 5 DAYS/WEEK FOR VARIOUS FRACTIONS OF A 35-YEAR WORKING LIFE VERSUS THE NUMBERS OBSERVED USING BIOTRANSFORMATION AND ANGIOSARCOMA INCIDENCE DATA FROM RATS AND FOUR MODELS FOR EXTRAPOLATION[a]

Population	Angiosarcomas observed	Angiosarcomas predicted (Models)[b]							
		A		B		C		D	
		500[c]	200	500	200	500	200	500	200
4384	1	0.2	0.0	0	0	9.4	5.9	10.0	6.3
2339	0	2.4	0.8	0	0	16.7	10.4	17.7	11.1
946	2	3.0	1.1	0	0	11.5	7.2	12.1	7.6
1007	2	6.8	2.7	4.0	0	17.6	11.0	18.6	11.7
677	0	7.3	3.0	6.6	0.3	15.2	9.5	16.0	10.1
324	0	4.9	2.1	4.9	1.3	8.9	5.6	9.4	5.9
Total									
9677	5	25	10	16	2	79	50	84	53

[a] Observed number of angiosarcomas from "Epidemiological Study of Vinyl Chloride Workers," Final Report January 1978, prepared by Equitable Environmental Health Inc., Rockville, Md., for Manufacturing Chemists Association, Washington, D.C.

[b] Model A, Probit $\% = -1.625 + 1.543$ Log (dose); Model B, $\% = -1.48 + 0.389 \times 10^{-2}$ (dose); Model C, $\% = 0.3565 \times 10^{-2}$ (dose); Model D, $\% = [1 - e^{-\beta(\text{dose})^3}]\ 100$ where $\beta = 0.38 \times 10^{-4}$. The constants in these models were obtained using the biotransformation and angiosarcoma incidence data for rats exposed to vinyl chloride (Gehring *et al.*, 1978).

[c] Parts per million.

anticipated that a few additional cases of hepatic angiosarcoma will occur in this population. It is comforting that an epidemic of cases, as has been envisioned by some, is not to be anticipated.

As indicated in the beginning of the paper, the previous attempt to extrapolate data from experiments in rats to predict the occurrence of hepatic angiosarcoma in vinyl chloride workers appeared to overpredict the observed incidence even when differences in the biotransformation of VC to active products by humans and rats were incorporated in the extrapolation.

The foregoing analysis using a probit percentage incidence model (Model A) has revealed that data collected in experiments on rats may be used to predict the incidence of hepatic angiosarcoma in humans with reasonable accuracy. Further verification of this model will be assisted greatly by determination of the rate of biotransformation of VC by humans exposed to sufficient concentrations of VC to allow such measurement. Currently, this must be estimated by the rate of biotransformation in rats and its assumed relationship to body surface area (Gehring *et al.*, 1978). Nonetheless, the correlation between predicted and observed incidence of hepatic angiosarcoma in vinyl chloride workers seems to justify both the assumptions and the model (Model A, Probit %) used to make the predictions.

Since the predicted incidence of hepatic angiosarcoma in humans using results from studies in rats appears justifiable, it is of interest to use the same procedures to estimate the incidence in workers exposed to 1 ppm 8 hr/day for a 35-year working life, the upper limit of the current Occupational Safety and Health Act standard. These predictions are shown in Table 5 for all four models.

Models C and D predict an incidence

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