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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 $= 1-e^{-Ax}$, 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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Gehring *et al.* (1978) determined that the amount of VC transformed to a reactive form by man on a mass equivalent basis to rat is:

$$V\,\mu g/8\text{ hr} = \frac{1675\,\mu g/hr \cdot S\,\mu g/liter}{860\,\mu g/liter + S\,\mu g/liter}. \quad (3)$$

Utilizing this relationship together with the foregoing probit equation, it was determined that incidence of hepatic angiosarcoma in workers exposed to 200 ppm should be approximately 1%. This incidence is 50-fold higher than that experienced (Fox and Collier, 1977). Various plausible explanations were put forth to explain this difference including greater sensitivity of rats and increasing latency for development as v decreases.

One plausible explanation not mentioned was that in worker populations studied to-date, many were exposed for only fractions of their working life. Furthermore, for some, the duration since initial exposure was likely insufficient for development of clinically detectable disease.

Recently available is a comprehensive epidemiological study[1] entitled, "Epidemiological Study of Vinyl Chloride Workers, Final Report." In this study, reasonably detailed information on 10,173 workers has been obtained for duration of exposure and lapsed time since first exposure.

Thus, much better information is available now to assess the reliability of the model proposed by Gehring *et al.* (1978) for predicting the incidence of hepatic angiosarcoma in humans utilizing data collected in rats. This assessment is reported here. In addition, three other models for estimating the incidence have been used for comparison of their reliability for predicting the incidence being experienced by workers exposed to vinyl chloride.

[1] Prepared for Manufacturing Chemists Association, 1825 Connecticut Avenue, N.W., Washington, D.C. 20009; prepared by Equitable Environmental Health, Inc., 6000 Executive Blvd, Suite 308, Rockville, Md. 20852, January, 1978.

METHODS

Four mathematical models were selected to analyze their reliability for calculating the incidence of hepatic angiosarcoma in rats as function of microgram equivalents of VC metabolized daily by rats exposed 4 hr/day, 5 days/week for 1 year. These models were as follows:

(A) Probit %

$$\text{Probit }\% = a + b(\text{Log } v)$$
$$= -1.625 + 1.543(\text{Log } v).$$

(B) Linear

$$\% = a + b(v)$$
$$= -1.48 + 0.389 \times 10^{-2}(v).$$

(C) Linear forced through origin

$$\% = bv$$
$$= 0.3565 \times 10^{-2}(v).$$

(D) One-hit model (Cancer Assessment Group, National Cancer Institute)

$$\% = 1 - e^{-\beta(v)}$$
$$= [1 - \exp(-0.38 \times 10^{-4} \times v)]100.$$

The constants given for the preceding models were determined by linear regression analysis and represent the best fit of the data for the incidence of hepatic angiosarcoma versus the amount of VC metabolized daily in rats exposed to different concentrations of VC (Gehring *et al.*, 1978).

The data used to derive the constants are given in Table 1. Using the equations derived for the models, the predicted incidence of angiosarcoma for the groups of rats exposed to different concentrations of VC were calculated. These results are shown also in Table 1.

All four models overpredict the incidence of hepatic angiosarcoma in rats exposed to 10,000 ppm VC. This is as expected because this exposure resulted in excessive mortality unrelated to development of angiosarcoma.

With respect to the predicted versus experimental incidence of hepatic angiosarcoma experienced by groups of rats exposed to the remaining concentrations of VC, none of the four models is unequivocally more reliable than any other. Thus, any one of the four models represents adequately the experimental data. Since no clear preference is discernible, all four models will be used to predict the incidence of hepatic angiosarcoma experienced or to be experienced by workers exposed to VC.

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, $\% = [1 - e^{-\beta(\text{dose})}]\ 100$, 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 2

INCIDENCE OF ANGIOSARCOMA IN 9677 WORKMEN EXPOSED TO VINYL CHLORIDE[a]

Population	Duration of exposure (years)	Mean exposure duration (years)[b]	Fraction of working life[c]	Observed angiosarcomas
4384 (0.31)[d]	<4	2	0.06	1 (18 years)[e]
2339 (0.27)	5–9	7	0.20	0
946 (0.58)	10–14	12	0.34	2 (15 and 23 years)
1007 (1.0)	15–19	17	0.49	2 (18 and 19 years)
677 (1.0)	20–24	22	0.63	0
324 (1.0	25+	27	0.77	0
Total 9677				

[a] 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] Assumed mean duration of exposure.
[c] Mean duration of exposure divided by 35 years.
[d] Fraction of population incurring first exposure 15 or more years prior to study.
[e] Duration between first exposure and diagnosis.

higher than those actually incurred by workers included in the epidemiological study. Undoubtedly, some were exposed to smaller levels. Many were reported exposed to much higher levels; in some cases at or above the odor threshold of approximately 3500 ppm. Unfortunately, in the absence of analytically determined exposure levels, approximations of the actual TWA values must be used. For a TWA exposure of 100 ppm VC, the predicted number of workers developing angiosarcoma in this epidemiological cohort are 4, 0, 30, and 32 for mathematical Models A, B, C, and D, respectively. For a 50-ppm TWA, the corresponding numbers are 1, 0, 17, and 18. Thus, utilizing values for TWA exposures which are thought to underestimate the actual exposures appear to overpredict still the number of workers developing angiosarcoma of the liver when mathematical Models C and D are used, albeit Model A apparently underpredicts when a TWA exposure of 50 ppm is used.

When a TWA of 200 ppm is utilized to represent the atmospheric concentration to which these workers were exposed, the predicted incidence of angiosarcoma of 10 cases using Model A compares favorably with that experienced, five cases. For a significant number of workers, the time elapsed since initial exposure has yet to reach 15 years, the shortest time needed for development of angiosarcoma in 1 of 5 of the afflicted workers (Table 2). Thus, it may be

TABLE 3

AVERAGE THEORETICAL RAT EQUIVALENT DAILY DOSES OF BIOTRANSFORMATION PRODUCTS RECEIVED BY A 70-kg HUMAN EXPOSED TO 200 OR 500 ppm VINYL CHLORIDE FOR VARIOUS FRACTIONS OF AN ASSUMED 35-YEAR WORKING LIFE

Mean exposure duration (years)	Fraction of working life	v, micrograms per 8 hr averaged over 35 hr[a]	
		500[b]	200
2	0.06	60	38
7	0.20	200	125
12	0.34	341	213
17	0.49	491	306
22	0.63	631	394
27	0.77	771	481

[a] v = [1675 μg/8 hr · S μg/liter]/[860 μg/liter + S μg/liter] × (fraction of working life).
[b] Parts per million.

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 500[c]	A 200	B 500	B 200	C 500	C 200	D 500	D 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, $\% = [1 - e^{-\beta(\text{dose})}]$ 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

TABLE 5

PREDICTED INCIDENCE OF ANGIOSARCOMA IN WORKERS EXPOSED TO 1 ppm VINYL CHLORIDE 8 HR/DAY, 5 DAYS/WEEK FOR 35 YEARS USING BIOTRANSFORMATION AND ANGIOSARCOMA INCIDENCE DATA FROM STUDIES IN RATS[a]

(A) Probit % or logarithm probability
1.5×10^{-6}% or 1.5/100,000,000

(B) Linear not forced through origin
None predicted below exposures of 98.7 ppm.

(C) Linear forced through origin
1.7×10^{-2}% or 1.7/10,000 or 177/1,000,000

(D) One-hit model (CAG)
1.89×10^{-2}% or 1.9/10,000 or 189/1,000,000

[a] Rat equivalent daily dose of biotransformation products received by workmen exposed for 8 hr to 1 ppm vinyl chloride is:
V = [1675 μg/hr·2.56 μg/liter]/[860 μg/liter + 2.56 μg/liter] = 4.97 μg/8 hr.

comparable to that experienced by workers exposed to much higher levels, again revealing their inadequacy because of overprediction. Model B, although a linear model, predicts zero response at 98.7 ppm VC. Thus, exposures to levels below this are not predicted to induce hepatic angiosarcoma. Using what appears to be the most reliable model (Model A, Probit %), the predicted incidence of hepatic angiosarcoma is 1.5×10^{-6}% or 1.5 cases in 100,000,000 workers. It is emphasized that use of Models A, C, and D to predict the incidence of hepatic angiosarcoma in workers exposed to 1 ppm VC assumes no threshold or even an inflection point in the dose–response curve (even though a threshold might occur).

In summary, the use of animal data for the assessment of risk in humans exposed to a chemical is not as mystical as frequently assumed. Dose–response data for the induction of angiosarcoma in rats exposed to various levels of VC together with attendant biotransformation data have been used to estimate, reliably, the risk of developing angiosarcoma in persons exposed to VC. There is every reason to believe that similar data can and should be used in the assessment of risk of exposure to specified levels of other substances.

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