Cancer Induction Following Single a Multiple Exposures to a Constant Amount of Vinyl Chloride Monomer

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Vinyl chloride monomer (VCM), already identified as a human animal carcinogen, was selected as a model agent to explore an area of concern for single and intermittent low level exposure. In traditional cancer bioassay, animals are repeatedly exposed over their lifespan to a dose of suspected chemical.

In the current studies rats and mice were exposed in an inhalation chamber to single one-hour doses of VCM ranging from 50 to 50,000 ppm.

A second group was given 10 one-hour exposures to 500 ppm or 100 one-hour exposures to 50 ppm of the same chemical. All animals were then observed for the remainder of their lives, generally 18-24 months. Moribund animals were euthanized, and survivors were sacrificed on schedule and their tissues examined for pathological changes. Specifically, the oncogenic study demonstrated dose related effects for single one-hour exposure of VCM at high levels, i.e., 5,000 and 50,000 ppm. These concentrations increased the incidence of pulmonary adenomas and carcinomas in mice.

Repeated exposure of A/J mice to the same chemical at 500 ppm × 10 one-hour exposures also increased the incidence of pulmonary adenomas and carcinomas which are considered highly significant ($p = 0.001$) when compared to match controls. At the lower dose of 50 ppm × 100 one-hour exposure, no significant increase in tumors was observed. Rats exposed to identical concentrations of VCM failed to elicit a tumorigenic response.

Introduction

In the last decade there have been concerted efforts by industry and the Federal government to identify carcinogenic substances in the workplace. However, carcinogens are not limited to occupational exposures. Many of these same chemicals are also used in the formulation of household products. Therefore, consumers in all walks of life may be exposed to suspect chemicals in their homes without their knowledge. This type of consumer usually brief and at very low levels. T chemical may be modified in the proce facturing the consumer product, i.e., as of polymerization of vinyl chloride (VC nyl chloride) (PVC), or trace quanti unreacted monomer may be present in which may be leached out under norma of use. There are other situations wher cal like VC is used because it is chemical example as a propellant, and as an gaseous chemical it could become a pote problem.

While regulatory bodies try to est exposure levels and industry attempts exposures in the production facilitie control measures would be of practical

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cancer bioassays involve daily exposures to the test chemical over the animal's lifetime. There were no comparable studies on short-term exposure to a carcinogen like VC followed by a lifetime monitoring for toxicological symptoms with complete histopathological examination at death. Therefore, our approach was to explore what happens to laboratory animals following brief or intermittent exposure to a known carcinogen like VC. Vinyl chloride appeared to be the ideal chemical to use in these experiments because of its widespread use in industrial and consumer products. Furthermore, the relationship for inducing unique pathological lesions, i.e., angiosarcoma of the liver for high exposure levels in animal and man was already established by Viola et al. (*1*) Maltoni (*2*) and Creech et al. (*3*).

Quite apart from the need to establish a bench mark for acute short-term intermittent exposures to a carcinogen, such as vinyl chloride, was the question of "threshold effects" or "safety factor" for low level exposures. In setting up our experiments we were mindful of the many factors that could have an impact on the study design. Some of the more important factors are that (1) the substance may not reach a susceptible cell; (2) the substance may make noncarcinogenic biochemical combination with the cell; (3) the "initiated" lesion may not receive adequate "promotion"; (4) host factors may be unfavorable to carcinogenesis; (5) biochemical repair of the DNA lesion may occur; (6) morphological regression of tumorigenic proliferation may occur; (7) carcinogenic cells may be destroyed by the body's immune system. These items need to be addressed in any conventional cancer bioassay but are even more critical in searching for noncarcinogenic exposure levels.

Experimental Conditions

Two strains of rats, Fischer 344 (Charles River Laboratory, Wilmington, Mass.) and Sprague-Dawley/Wistar (Chemical Systems Lab, Edgewood, Md.), and two strains of mice, A/J (Jackson Lab, Bar Harbor, Maine) and ICR (Charles River Laboratory) were treated in single or multiple intermittent inhalation exposures to VC. The chambers were Rochester type, stainless steel, 1000 liter, constructed to provide laminar air flow and insure uniform exposures to VC to test animals.

Chamber concentrations were established by proportioning the amounts of VC being dispersed with the air flow through the chamber. Airflow in the chamber at all times when o
the exhaust gas completely filtere
particulate filter) before discharge t
ment. The concentration of gas in
chamber was monitored by usin
Packard 5830A gas chromatograph
flame ionization detector.

Exposure Procedures for VC Cancer Studies

Male and female rats and Fischer
mice were totally exposed for 1 hr t
and 50,000 ppm VC. Fischer rats
equally divided by sex received ten
to 500 ppm VC (1 hr/day, 5 days/wk
100 1-hr exposures to 50 ppm (1 hr/
for 20 weeks). Male and female par
Dawley/Wistar) rats (obtained from V
ical Division, Edgewood Arsenal,
reproduction study were also maint
served for 24 months post exposur
ppm VC 1 hr per day, 5 days per wee
(49 exposures).

Following exposure, all animals w
until the chamber concentration w
ppm VC. Animals of the same sex w
in stainless steel cages with a maxim
5 rats in each compartment and place
holding area. Mice were similarly treat
cages were used and the number of
partment was limited to two. The
observed twice daily for general healt
es, alertness, activity or mortalit
were weighed weekly for the first
exposure and monthly thereafter.
schedules for the studies described a
in Tables 1-3. No blood chemistries
studies were performed.

Pathology

Gross and Light Microscopy. A
and microscropic examination was
most control and exposed animals
were sacrificed. Autolysis precluded
tion in a few cases.

All rodents were to be serially sac
and 24 months post exposure. How
span of the mice forced some chang
times of sacrifice and termination of
ments. For single exposure the plan
month sacrifice were replaced by 18 m

Species	Sex	Dose, ppm	AM	PM	
Fischer 344 rat	M	50	3/4/75		90
		500	3/11/75		90
		5000	3/18/75		85
		50000	3/25/75		90
	F	50		3/4/75	90
		500		3/11/75	100
		5000		3/18/75	95
		50000		3/25/75	88
ICR mouse	M	50	3/4/75		90
		500	3/11/75		90
		5000	3/18/75		90
		50000	3/25/75		90
	F	50		3/4/75	90
		500		3/11/75	90
		5000		3/18/75	90
		50000		3/25/75	90
Rat	M	Neg/Cont.			92
	F	Neg/Cont.			79
Mouse	M	Neg/Cont.			82
	F	Neg/Cont.			88

Table 2. Exposure schedule for animals exposed repeatedly to VC.

Species	Sex	Dose, ppm	Exposure periods, days	Exposure dates		Exposure group size		
				From	To	Start	End	St
Fischer rat	M	50	100	8/27/75	1/26/76	90	86	2
		500	10	7/1/75	7/28/75	90	90	1
	F	50	100	8/27/75	1/26/76	90	87	2
		500	10	7/1/75	7/18/75	90	90	1
A/J mouse	M	50	100	7/1/75	7/18/75	90	87	1
		500	10	8/27/75	1/26/76	90	90	
	F	50	100	7/1/75	7/18/75	90	88	1
		500	10	8/27/75	1/26/76	90	90	
Fischer rat	M	Neg.	100(c)[a]	—		50	50	2
		Control	10(c)	—		50	50	1
	F	Neg.	100(c)	—		50	47	2
		Control	10(c)	—		50	50	1
A/J mouse	M	Neg.	100(c)	—		40	39	1
		Control	10(c)	—		50	50	
	F	Neg.	100(c)			50	50	1
		Control	10(c)	—		50	50	

[a](c) denotes control for corresponding dose above.

Table 3. VC multigeneration study, F_0 parents.[a]

Group	Compound	Dose[b]	Number of males	Numbe
I	Air	Control	25	
II	VC	Low dose (50 ppm)	25	
III	VC	High dose (500 ppm)	25	

[a]Sprague-Dawley/Wistar rats.
[b]Exposure to 50 or 500 PPM of VC 1 hr/day, 5 days/week for 10 weeks (49 exposures) before mating.

in mice the final sacrifice was at 20 months rather than 24 months. The change was made in consideration of the risk of animal loss through death and possible cannibalism. Tissues examined were lung, trachea, heart, liver, stomach, small intestines, spleen, kidney, bladder, bone marrow (sternum), adrenals, pancreas, duodenum, brain, eye, zymbal gland, ear, nose, muscle and bone (femur).

Electron Microscopic Studies. Groups of five male and five female Fisher (344) rats from each of the single 1-hr exposure studies (50, 500, 5000 and 50,000 ppm) with equal numbers of their corresponding control groups were sacrificed at 8, 16, 24 months.

Groups of five male and five female Fischer (344) rats from the multiple 1-hr exposure studies at 50 and 500 ppm VC along with equal numbers of control animals were sacrificed at 16 and 24 months.

Results

Toxicity During Exposure

Rats and mice exposed for 1 hr to concentrations of VC ranging from 50 to 50,000 ppm or for repeated exposures, i.e., 50 ppm or 500 ppm, produced no remarkable signs of toxicity with the exception of mice at the 50,000 ppm level. At 50,000 ppm VC 50% of the male mice exhibited hyperventilation at 45 minutes together with twitching and possible ataxia. Female mice became hyperactive after 40 min exposure, and respiratory difficulty and ataxia was observed in approximately 25% of the female mice after 55 min. Upon removal from the test atmosphere, all animals recovered to normal appearance within 24 hr. After exposure there were no consistent or dose-related differences between control and exposed (single or multiple) mice or rats in death rate, toxic signs or change in body weight.

[illegible] or repeatedly to VC at the higher dc 500, 5000 or 50,000 ppm.

Histological Examination of Mice: Single Exposure

Changes ascribable to vinyl chloric ent primarily in the lungs with th pulmonary adenomas and pneumoniti was evident in all animal groups w posed to VC at 500 ppm and above.

The development of bronchio-alve increased with exposure to higher VC. Tables 4 and 5 summarize the si logical changes observed in ICR mi months following single exposure to of VC.

Mice were more susceptible than monitis following exposure to VC. T ever was not incremental with do incidence of pneumonitis, adenoma in ICR mice following single exposur in Table 6. No correlation was obse the incidence of pneumonitis and pneumonitis and carcinoma. However, more prone to the induction of pneun ularly at 50,000 ppm, i.e., 34% M v 5000 ppm and below, male and femal equally sensitive.

There was an increase in bronchic nomas with exposure to higher doses condition manifests itself more frequ i.e., at 50,000 ppm: 51% M vs. 18% continued at the 5000 ppm: 22% M vs. and females were equally susceptibl 500 ppm and below. The upper res (nasal turbinates) and trachea reveal changes specifically attributable to V

Table 4. Histological examination of ICR mice at 8 and 18 months following a single (1-hr) exposure to vinyl chl

Vinyl chloride concentration, ppm	Histological changes attributable to vinyl chloride	
	Induction of pulmonary adenomas	Progression to car
50,000[a]	45/137 (33.3%)	3/137 (2.2%)
5,000[a]	24/143 (16.8%)	1/143 (0.7%)
500[a]	18/139 (12.9%)	1/139 (0.7%)
50	14/139 (10.1%)	0/139 (0%)
0 (control)	12/120 (10.0%)	0/120 (0%)

[a]Pneumonitis was evident in all animal groups which were exposed to VCM at doses of 500 ppm or more.

500 ppm, 10 days, 1 hr. Changes ascribable to VC were apparent in the lung only, primarily the induction of pulmonary adenomas. Bronchio-alveolar adenomas were induced in the test group with approximately equal frequency in males and females, i.e., 73.7% M vs. 75.6% F, respectively. The increase in incidence as shown in Table 7 for the test group over that of the controls was substantial, by

trols, 3/90 or 3.3%; 500 ppm, 22/166 or
animals scheduled for evaluation (surv
monary adenomas were observed as
months post exposure in 60% of males a
at 20 months, 75% of animals were affe

The incidence of pneumonitis, adenon
cinoma in A/J mice following multiple e
VC is presented in Table 8. Pneumoni
served more frequently in the control a

Table 5. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within the live ICR Swiss mice exposed to vinyl chloride in single inhalation exposures.

	Incidence of response for various vinyl chloride concns								
	0		50,000 ppm		5,000 ppm		500 ppm		
Tissue/response	M (62)[a]	F (77)[a]	M (74)[a]	F (82)[a]	M (76)[a]	F (82)[a]	M (72)[a]	F (75)[a]	M (8
Liver (number evaluated)	50	75	63	78	68	76	67	72	64
Hepatic cell necrosis	2	10	3	5	5	7	4	6	2
Hepatic cell vacuolation (lipidosis)	2	11		4	2	12	3	5	1
Hepatic cell hypertrophy	1		2	8		8	4	13	1
Hepatic cell hyperplasia					4	4			
Angiectasis				1		4			
Sinusoidal reticulosis				5					
Hepatic cell adenoma	2		1			1			2
Hepatic cell carcinoma	2		4	1	6	1	9		2
Hemangioma					1				
Hemangiosarcoma	1								
Lung (number evaluated)	50	70	61	76	65	78	66	73	71
Pneumonitis	1	6	21	10	13	17	19	15	4
Bronchio-alveolar adenoma	4	8	31	14	14	10	8	10	8
Bronchio-alveolar carcinoma			1	2	1			1	

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrificed (8 and month spontaneous deaths.

Table 6. Single inhalation exposure of ICR mice to vinyl chloride monomer.

		Lung tissue: incidence of response/number evaluated[a]		
VC exposure concn, ppm	Group	Pneumonitis	Adenoma	Carci
0 (control)	Male	1/50 (2%)	4/50 (8%)	0/50
	Female	6/70 (9%)	8/70 (11%)	0/70
	Combined (M + F)	7/120 (6%)	12/120 (10%)	0/120
50,000	Male	21/61 (34%)	31/61 (51%)	1/61
	Female	10/76 (13%)	14/76 (18%)	2/76
	Combined (M + F)	31/137 (23%)	45/137 (33%)	3/137
5,000	Male	13/65 (25%)	14/65 (22%)	1/65
	Female	17/78 (22%)	10/78 (13%)	0/78
	Combined (M + F)	30/143 (21%)	24/143 (17%)	1/143
500	Male	19/66 (29%)	8/66 (12%)	0/66
	Female	15/73 (21%)	10/73 (14%)	1/73
	Combined (M + F)	34/139 (24%)	18/139 (13%)	1/139
50	Male	4/71 (6%)	8/71 (11%)	0/71
	Female	7/68 (10%)	6/68 (9%)	0/68
	Combined (M + F)	11/139 (8%)	14/139 (10%)	0/139

[a]Total includes animals from scheduled sacrifice (8, 16, 20 months period) and spontaneous deaths.

are similar to those observed in the single exposure study.

50 ppm, 100 days, 1 hr. Again changes attributable to VC were apparent in the lung only, primarily pulmonary adenomas. However, the incidence in the induction of adenomas and progression to carcinoma are considered only marginal and not statistically significant.

Comparatively, the potential for development of pulmonary adenomas as shown in Table 7 was greater in A/J mice following multiple exposures at 500 ppm than at 50 ppm, i.e., incidence at 500 ppm, 74.7%; at 50 ppm, 44.1%, despite an equivalent total dose of 5000 ppm VC. Also, pulmonary adenomas were induced earliest (8 months) following multiple exposures at 500 ppm. It is also of interest that the

Table 7. Histological examination of A/J mice at 8, 16 and 20 months following multiple (1-hr) exposures to vinyl chloride monomer.

Number of exposures and concentration of VCM	Histological changes attributable to vinyl chloride monomer	
	Induction of pulmonary adenomas	Progression to carcinoma
0 (controls)	31/90 (34.4%)	3/90 (3.3%)
10 × 500 ppm[a]	124/166 (74.7%)	22/166 (13.3%)
0 (controls)	29/84 (34.5%)	2/84 (2.4%)
100 × 50 ppm[b]	65/158 (44.1%)	7/158 (4.4%)

[a]Highly significant difference in the number of pulmonary adenomas ($p \simeq 0.001$) observed at the 500 ppm × 10 hr exposure level versus control by Z test.

[b]No significant difference for pulmonary adenomas ($p < 0.14$) and carcinomas ($p \simeq 0.19$) observed at the lower multiple exposure level.

ppm, 34.4%; at 50 ppm, 34.5%.

Table 9 provides an overall summ
dence of histologically proven neop
in both strains of mice, i.e., ICR an
single and multiple exposures to V(
tic and nonneoplastic changes obser
and/or lungs of A/J mice following
sures to VC at 50 and 500 ppm are s
10 and 11. Although other neoplasi
plastic changes occurred variously i
organs and tissues, the response a
sporadically or was shared by all tes
ing controls. Relationship by inciden
to test exposure was not evident.
morphologic deviations were not u
mally observed in aging A/J mice m
standard laboratory conditions.

Electron Microscopic Result

In general, these studies indicate
to vinyl chloride increased organelle t
as loss of volume control (bleb for
creased lysosomal activity in the live
alterations progressively decreased a
exposure increased.

Hepatocellular carcinoma was se
Fischer rat which had received 10 e
ppm. Lymphosarcoma was noted
Fischer rat which had received a sin
500 ppm. Since these were indivi
since no cancers were seen at 5(
lymphosarcoma and the hepatocell
are not likely related to vinyl chlori

Table 8. Multiple inhalation exposure of A/J mice to vinyl chloride monomer.

VC Exposure			Lung tissue: incidence of response/number	
Frequency	concn, ppm	Group	Pneumonitis	Adenoma
10 × 1	0	Male	0/43 (0%)	15/43 (35%)
		Female	2/47 (4%)	16/47 (34%)
		Combined (M + F)	2/90 (2%)	31/90 (34%)
10 × 1	500	Male	0/76 (0%)	56/76 (74%)
		Female	0/90 (0%)	68/90 (76%)
		Combined (M + F)	0/166 (0%)	124/166 (75%)
100 × 1	0	Male	5/39 (13%)	11/39 (28%)
		Female	3/45 (7%)	18/45 (40%)
		Combined (M + F)	8/84 (10%)	29/84 (35%)
100 × 1	50	Male	4/77 (5%)	27/77 (35%)
		Female	5/81 (6%)	38/81 (47%)
		Combined (M + F)	9/158 (6%)	65/158 (41%)

[a]Total includes animals from scheduled sacrifice (8, 16, 20 months period) and spontaneous deaths.

Dawley/Wistar) were divided into three groups with equal numbers of males and females. These specific-pathogen-free, random bred animals were obtained from the Animal Resources Branch at Edgewood Arsenal. The rats were 12 weeks old when initially exposed to VC. One hundred rats were exposed as described and the remaining 50 were carried as unexposed controls. The parental generations of S-D/W rats were maintained 24 months post exposure for carcinogenic evaluation.

A complete gross and microscopic pathological examination of all tissues was performed on each control and exposed animal. Particular emphasis examined by electron microscopic techn

Neoplastic and nonneoplastic lesions we in approximately equal frequency in con parent generation of Sprague-Dawley/\ exposed to 50 ppm or 500 ppm of VC, 1 five days per week for 10 weeks (49 ex

The only lesions that occurred in high cy in the exposed animals than in contro eosinophilic cellular alterations presente areas. The appearance of these foci wa the dosage of VC. The nature of these le interest but as yet are controversial, inference can be drawn.

Table 9. Summary of incidence of histologically proven neoplasms observed within tissues of mice at various inter single or multiple exposures to vinyl chloride monomer.

Inhalation exposure	Exposure concentration, ppm	Number of neoplasms observed (scheduled sacrifice)				
		8 months	16 months	18 months	20 months	Totals
Single (1 hr)	50,000	5		24		29
	5,000	3		18		21
	500	1		29		30
	50	0		16		16
	0 (control)	0		14		14
Multiple (1 hr)	500 × 10	12	22		70	104
	0 (control)	0	2		38	40
	50 × 100	4	16		63	83
	0 (control)	1	5		27	33

[a]ICR strain used in single (1 hr) exposure studies; and A/J mice used in the multiple (1 hr) exposure studies.

Table 10. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within the mice exposed to vinyl chloride in multiple inhalation exposures.

Tissue/response	Incidence of response			
	Control (0 ppm), 100 × 1		Vinyl chloride, 50 p 100 × 1	
	M (39)[a]	F (47)[a]	M (81)[a]	F
Lung (number evaluated)	39	45	77	
Edema	2			
Congestion	4	1	1	
Focal hemorrhage	2		2	
Pneumonitis	5	3	4	
Bronchio-alveolar hyperplasia		3		
Osseous metaplasia				
Bronchio-alveolar adenoma	11	18	27	
Bronchio-alveolar carcinoma	2		3	
Reticulum cell sarcoma	—	—	—	
	13	18	30	

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrifice (8, 16, 20 mont spontaneous deaths.

of VC had been described by various investigators like Maltoni (*2,5*) and Lee et al. (*6*) to coincide with dose and length of exposure implies that the total dosage (concentration × exposure time) may be an important factor in the carcinogenicity of VC. Therefore, the inhaled dose was approximated by the Haber (*7*) concept. In its simplest form this concept states that the dosage, Ct is the product of C (concentration in milligrams/cubic meters) and t (time in minutes). The total concentration can also be expressed in parts per million (ppm) and the approximation of total inhaled dose useful, as is, for comparative purpos

In his experiments Maltoni (*5, 10*
and mice as shown in Table 12 to a se
VC ranging from 50 to 10,000 ppm
days per week for 52 weeks. The res
questionable carcinogenic effect at 5
dosage of 52,000 ppm-hr after 135 we
er experiment (BT3), Sprague-Dawl
ed in a similar fashion to BT1 but for
show after 86 weeks a negative ca

Table 11. Overall summary: incidence of nonneoplastic changes and histologically proven neoplasms within th of A/J mice exposed to vinyl chloride in multiple inhalation exposures.

	Incidence of response		
	Control (0 ppm), 10 × 1		Vinyl chloride, 50 10 × 1
Tissue/response	M (46)[a]	F (48)[a]	M (78)[a]
Liver (number evaluated)	45	48	78
Hepatic cell necrosis	4	6	6
Lymphoid cell infiltrate	1		1
Hepatic cell lipidosis	2		2
Neutrophil infiltrate	2		
Bile duct hyperplasia	1		
Granulomatous foci			1
Sinusoidal reticulosis			
Hepatocyst			
Amyloidosis			1
Angiectasis			
Hepatic cell adenoma	1		
Cholangiocarcinoma			1
	11	6	13
Lung (number evaluated)	43	47	76
Edema			
Pneumonitis		2	
Bronchio-alveolar hyperplasia	2	1	
Bronchio-alveolar adenoma	15	16	56
Bronchio-alveolar carcinoma		3	12
	17	22	68

[a]Numbers in parentheses denote animals per group. Total includes animals from scheduled sacrifice (8, 16, 20 m spontaneous deaths.

Table 12. Maltoni vinyl chloride studies.[a]

Test	Species	Results (carcinogenesis), ppm-hr
BT1	RATS	Questionable at 52,000
BT3	RATS	Negative at 17,000
		Questionable at 85,000
		Positive at 170,000; 850,000; 2,000,000; 3,000,000
BT6	RATS	Positive at 24,600,000
BT7	RATS	Negative at 52,000 and 260,000
		Questionable at 520,000
		Positive at 2,600,000; 6,200,000; 10,400,000
BT4	MICE	Positive at 30,000; 150,000; 300,000; 600,000; 1,500,000

experiment BT7, Wistar rats treated with VC at doses ranging from 50 to 10,000 ppm, for 4 hr daily, 5 days/week for 52 weeks in the same manner as described above show positive carcinogenic affects at total dosage of 2,600,000 ppm-hr. The author suggests from comparison of the experimental data obtained with two different strains of rats (BT1/BT3), Sprague-Dawley and (BT7) Wistar, that the strain seems to be a factor in neoplastic response. Based upon neoplastic lesions observed, the Wistar strain was less responsive than Sprague-Dawley. Experiment BT4 with Swiss mice, involving exposure to VC at 50 to 10,000 ppm, 4 hr per day, 5 days per week for 30 weeks produced carcinogenic effects with a total dosage *Ct* of 30,000 to 3,600,000 ppm-hr.

In the studies of Viola, Bigotti and Caputo (*1*), tumors were seen in rats which had been exposed to 30,000 ppm VC, 4 hr/day, 5 days/week, for 12 months. The total dose (*Ct*) of VC was 28,800,000 ppm-hr.

In the studies of Caputo, Viola and Bigotti (*8*), rats and rabbits were exposed to VC for 4 hr/day, 5 days/week for 12 months at six dose levels. The exposure to 50 ppm VC or total dose of 48,000 ppm-hr produced no tumors. Carcinogenic effects were observed at total dosage of 320,000 ppm-hr and above for rats and at 7,800,000 ppm-hr for rabbits.

Keplinger et al. (*9*) exposed rats, hamsters and mice to VC. Only the data on mice were sufficiently complete for examination of total dose effect. Total dosage of 56,000 ppm-hr and above produced tumors in mice. The final report on the rats and hamsters is still unavailable for evaluation.

Lee et al. (*6*) exposed mice and rats to three levels of VC: 50, 250 and 1000 ppm, 5 hr/day, 5 days/week for up to 12 months. All tests with a total dose of 48,000 ppm-hr and below were essentially

carcinogenic effect in rats may not app
total dose (*Ct*) of VC exceeds 50,000 p
single exposure study with ICR mice w
at 50 and 500 ppm-hr, borderline at 5
but did produce neoplastic lesions in
50,000 ppm-hr. The A/J mice exposed
doses of VC, i.e., 50 ppm × 100 days ×
ppm × 10 days × 1 hr for a total cumul
VC of 5000 ppm-hr show a significant
response, but only at the higher dose l

In our studies Fischer rats exposed
dosage of 50, 500, 5000, and 50,000 ppm
showed no chemically induced tumor res
ther did the Sprague-Dawley/Wistar rat
exposed to 500 ppm VC 1 hr/ day, 5 da
10 weeks (total dosage 24,500 ppm-hr).

Table 13 summarizes various investi
results, including our own, on vinyl ch
tests with ICR mice, single exposure t
an increased frequency of adenomas at t
of 5000 ppm-hr and above. For A/J mic
exposures to 50 and 500 ppm VC for a t
of 5000 ppm-hr shows a similar dose re
tern for adenomas. In general, in ter
dosage *Ct*, carcinogenic effects are seer
mice strains at *Ct* levels of 5000 to 50,(
Thus total dosage for carcinogenicity i
general agreement with Lee et al. (*6*) (78,
and Maltoni (*5*) (between 30,000 and 150,(
and other investigators.

There is no doubt that risk is related
exposure and hence total dose. In ou
much attention has been focused on
cancer associated with total dosage of V
er, the multiple exposure experiment a
ppm dose levels with A/J mice for an
total exposure to 5000 ppm-hr appears i
with the thesis of total dosage. Indeed

Table 13. Other vinyl chloride studies.

Authors	Species	Results (carcinogenesis), ppm-hr
Viola, Bigotti and Caputo (*1*)	Rats	Positive 28,800,000
Caputo, Viola and Bigotti (*8*)	Rats	Negative at 48,000 Positive at 320,000; 1,280,000; 3,200,000; 6,400,000
	Rabbits	Positive at 7,200,000
Keplinger et al. (*9*)	Mice (rats and hamsters)	Positive at 56,000
Lee (*6*)	Mice	All tests essentially negative below 78,000 and positive above 78,000
Consumer Product Safety Commission (1979)	ICR mice A/J mice	50 and 500, negative 5000, borderline positive 50,000 positive
	Fischer rats	50, 500, 5000 and 50,000, negative 24,500, eosinophilic loci, no cancers

basis of a number of factors, i.e., metabolism, detoxication, DNA repair or a time for tumor development for low level exposure beyond the animals' lifespan.

As is evident from Table 13, the two strains of rats, Fischer (344) and S-D/W, were more resistant to the adverse effects of single and multiple intermittent exposures of VC.

Our studies are in agreement as to the dose-time relationship for carcinogenesis related to the VC exposure. All of the continuous exposure studies considered collectively indicate that there is a lifetime total dose (Ct) for VC. However, from our own studies with single or intermittent low level exposures to VC we believe that concentration may be the most dominant factor in whether or not carcinogenic effects are observed. For single dose studies with VC in ICR mice, neoplastic lesions were produced at 5000 ppm. For multiple intermittent exposures studies with A/J mice the critical concentration for VC was 500 ppm, total dosage 5000 ppm-hr.

Approximate carcinogenic Ct levels of VC based on data for mice and rats are Ct = 5,000–50,000 ppm-hr, carcinogenic tendencies; 500,000 Ct > 50,000 ppm-hr, definite carcinogenicity; Ct > 500,000 ppm-hr, high incidence of carcinogenicity.

Considerations of Carcinogenicity of VC: Conclusions

Cancer seems dependent on total dose of vinyl chloride, especially in life-time exposure studies, but for short-term exposure the concentration may be the most critical factor.

There were apparent noncarcinog
the study.

Mice were more sensitive indicator
carcinogenic effects of vinyl chloride.

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