



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Preliminary Carcinogen Risk Assessment
for Vinylidene Chloride

FROM: *Elizabeth L. Anderson*
Elizabeth L. Anderson, Executive Director,
Carcinogen Assessment Group (RD-689)

TO: Joseph Padgett, Director
Strategies and Air Standards Division, MD-12

As requested in your original memorandum of March 31, 1977, and later re-scheduled requests on November 17, 1977 and March 28, 1978, the Carcinogen Assessment Group has finished the Type I preliminary risk assessment for vinylidene chloride. We are transmitting the report to you.

Attachment

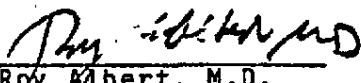
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S. Jellinek
W. Barber
J. Padgett
J. McGinnity
D. Denney
M. James
D. Barth
H. Beale

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THE CARCINOGEN ASSESSMENT GROUP'S

PRELIMINARY RISK ASSESSMENT ON

VINYLDENE CHLORIDE


Roy Albert, M.D.
Chairman

Participating Members

Elizabeth L. Anderson, Ph.D.
Charles B. Hiremath, Ph.D.
Robert E. McGaughey, Ph.D.
Lakshmi C. Mishra, Ph.D.
Ruth Pertel, Ph.D.
Dharm V. Singh, DVM, Ph.D.
Wade T. Richardson, J.D.
Todd W. Thorslund, Sc.D.
Adrienne J. Zahner, Ph.D.

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I. Summary

Vinylidene chloride (VDC) administered via inhalation has induced kidney adenocarcinomas in male Swiss mice at 25 ppm and mammary fibroadenomas and carcinomas in female Sprague-Dawley rats at 150 ppm and less with an incidence significantly higher in treated than in control groups according to one report. Although negative results have been reported in rats via inhalation exposure by three other authors, the short time of observation in one case and the lack of complete histological analysis in the other two cases make the negative results not conclusive. In two relatively well-executed studies of chronic oral administration at dose levels of 28 mg/kg/day and less, no carcinogenic effect was observed. In an occupational study of 138 workers exposed to VDC vapors no excess occurrence of cancer was observed. Several reports have shown that with metabolic activation VDC causes both base substitution and frame shift mutations in Salmonella typhimurium. It is also mutagenic in E. coli with metabolic activation.

The positive carcinogenic response to VDC in both rats and mice, along with its ability to induce mutations in bacteria with metabolic activation and its structural similarity to vinyl chloride constitute sufficient evidence that VDC is a possible human carcinogen.

A quantitative risk analysis based on the animal studies and assuming a lifetime continuous exposure to 1 ug/m^3 showed an individual lifetime risk of less than 3×10^{-5} .

II. Introduction

Vinylidene chloride is a volatile liquid with a boiling point of 37°C. Its structure is $\text{H}_2\text{C} = \text{CCl}_2$ (1,1-dichloroethylene), which is similar to vinyl chloride. It is used in the production of methyl chloroform and in the formation, along with other monomers, of plastics useful in food packaging sheets and other applications. An estimated 265 million pounds were produced in 1974 (EPA, 1976).

A detailed review of the toxicology and biochemistry of VDC has prepared (EPA, 1976). No attempt is made here to repeat that information. It is toxic to the liver at high doses and it mutagenic in Salmonella typhimurium and E. Coli with metabolic activation.

III. Carcinogenesis Studies

A. Maltoni (1977)

Maltoni reported the interim results of four chronic studies:

- a. Inhalation in Sprague-Dawley rats at doses of 0, 10, 25, 100, 150 ppm for 4 hrs/day, 4-5 days/wk for 1 year. To date, 82 weeks or 1.6 years of observation have been made.
- b. Inhalation in Swiss mice at doses of 0, 10, 25 ppm for the same dose schedule. Results are available after 82 weeks.
- c. Oral (gavage) in Sprague-Dawley rats at 0, 0.5, 5, 10, 20 mg/kg, for 4-5 days/wk for 1 year. Results are available after 82 weeks.
- d. Inhalation in Chinese hamsters at 0 and 25 ppm for the same dose schedule. Results are available after 74 weeks=1.4yrs.

The Results of the Maltoni study are as follows:

a. Rat Inhalation

The tumors observed were: 1) mammary tumors (fibroadenomas and carcinomas) in both the treated and control groups; 2) one Zymbal gland carcinoma in the 100 ppm group (none in control and 3) leukemia in both treated and control groups at the rate of about 1 per 50 animals.

A summary of the mammary tumor incidence is tabulated below.

Table 1 - Incidence of Mammary Tumors in Rats Inhaling Vinylidene Chloride (VDC)

	Dose (ppm)					
	<u>0</u>	<u>10</u>	<u>25</u>	<u>50</u>	<u>100</u>	<u>150</u>
<u>Number with tumors</u> <u>Number initially</u>	32/100	15/30	12/30	15/30	18/30	35/60
Incidence	0.32	0.50	0.40	0.50	0.60	0.58
p value		0.21	0.45	0.21	0.044	0.007

b. Mice Inhalation

The following tumors were observed: 1) kidney carcinomas at the highest dose (25 ppm) with a large incidence in males but in only one out of 112 females. None were observed at 10 ppm. The time when the first animal was observed with a kidney adenocarcinoma was 55 weeks; 2) mammary adenocarcinomas in females at 25 ppm; 3) leukemia, pulmonary adenomas and miscellaneous tumors scattered equally in control and treated groups. The observations are summarized in tables 2 and 3.

Table 2 - Incidence of Kidney Adenocarcinomas in Mice Inhaling VDC

	<u>Males</u>			<u>Females</u>		
	<u>0 ppm</u>	<u>10 ppm</u>	<u>25 ppm</u>	<u>0 ppm</u>	<u>10ppm</u>	<u>25 ppm</u>
<u>Number with tumors</u> <u>Survivors at time of</u> <u>first tumor</u>	0/126	0/25	16/98	0/158	0/26	1/112
Incidence	0	0	0.163	0	0	0.0089
p value			8.5x10 ⁻⁷			0.41

Table 3 - Incidence of Mammary Adenocarcinomas in Female Mice
Receiving VDC Via Inhalation

	<u>0 ppm</u>	<u>10 ppm</u>	<u>25 ppm</u>
<u>Number with tumors</u> <u>Survivors at time of</u> <u>kidney adenocarcinomas</u>	2/158	1/26	7/112
Incidence	0.013	0.039	0.063
p-value		0.068	0.029

Therefore in this mouse strain a strong carcinogenic response is seen in the kidney of males and a moderate response is observed in the mammary gland of females.

c. Rats, oral (gavage):

Mammary carcinomas were observed with an incidence of between 22% and 42% in both treated and control groups. Other tumors at miscellaneous sites were observed but not at significantly higher rates than control groups.

d. Hamsters, inhalation

No tumors were observed.

B. Viola and Caputo

Wistar albino rats were exposed via inhalation to VDC at a concentration of 200 ppm for 5 months, then 100 ppm for an additional 7 months, then held for observation for the remainder of their lifespan. The exposures lasted 4 hrs/day, 5 days/week. Reticulum cell sarcomas were observed in the abdominal cavity with a frequency of about 30% in females and 15% in males, with no difference in incidence between control and treated animals.

The authors also exposed Sprague-Dawley rats to concentrations of 75 ppm and 100 ppm via inhalation, presumably using the same dosage schedule as above. Subcutaneous fibromas were seen grossly in females in 50% to 60% of both control and treated animals, and in males miscellaneous tumors were observed in treated and control groups. The tissues had not been examined microscopically when the report was written.

C. Lee, et al (1978)

Albino CD-1 mice and CD rats (Charles River) were exposed to 55 ppm of VDC for 6 hours/day, 5 days/week until the terminal sacrifice at 12 months. In mice the following tumors were observed in both males and females with slightly higher incidence in the treated than in the control groups: bronchioloalveolar adenomas, hemangiosarcoma of the liver and hepatoma. The differences were not statistically significant. In rats hemangiomias were seen in two of 36 treated males, but no tumors were seen in either control or treated females. A longer time for observation might have revealed the presence of additional tumors.

D. Dow studies (preliminary reported by Norris, 1977)

According to the advance text of a presentation to have been delivered in January 1977, (Norris, 1977) the Manufacturing Chemists Association is sponsoring the following chronic studies: a) 90-day and 2-year drinking water studies at 60, 100 and 200 ppm and b) 90-day and 2-year inhalation studies in rats at 10 and 40 ppm initially, but increased to 25 and 75 ppm after 30 days of the lower exposure. The 2-year drinking water study has been described in detail by Humiston, et al. (1977) and is discussed below (part E). In the inhalation studies the only adverse effects found were minimal microscopic changes in the liver with a higher incidence at 75 ppm than at 25 ppm. In all other respects there was no observed difference between control and treated groups.

E. Humiston, et al. (1977)

Sprague-Dawley rats were given VDC at concentrations of 0, 50, 100 and 200 ppm in drinking water for 24 months. Complete data on food and water consumption, body weights, blood and urine chemistry, and histological examination of 37 tissues were reported. The result is that no adverse effect was observed in any of the treated groups compared to controls with two exceptions. In females the 50 ppm group had a statistically significant higher incidence of pituitary gland adenomas than controls. This was not considered an effect of the treatment, since it was not dose-related and the historical spontaneous rate of these tumors is high and variable in Sprague-Dawley rats. The other effect was a dose-related

statistically significant incidence of liver lesions, described as fatty degeneration, which was more marked in female than males. Accompanying this was atrophy of the centrilobular cells and hypertrophy of the periportal liver cells. Treatment related necrosis of cells was not observed.

F. Summary of Carcinogenesis Studies

Of the 5 reports on chronic studies only Maltoni's studies showed positive results. The principal findings are tabulated below. The tabulation shows that in both studies where VDC was given orally in Sprague-Dawley rats, no carcinogenic response occurred. In the inhalation studies with Sprague-Dawley rats there is an apparent conflict between Maltoni's findings of mammary carcinomas and the Viola and Caputo, Lee, et al. and Norris reports which report no carcinogenic response. However, the negative findings of the latter authors can be explained by different factors. No microscopic examination of the tissues was reported in the Viola and Caputo and the Norris papers, and the almost complete lack of any effect in the Norris (and Humiston) experiment raises the question of whether the dose was high enough. In the Lee, et al. studies the duration of observation was too short to observe the development of tumors. For these reasons, the Maltoni, et al. findings of carcinogenicity in rats and mice are not contradicted by the negative results of the other studies.

Results of Carcinogenesis Assays of Vinylidene Chloride

<u>Author</u>	<u>Species</u>	<u>Dose</u>	<u>Route of Administration</u>	<u>Duration of Observations</u>	<u>Significant Findings</u>
Bottoni, et al. (1977)	Sprague-Dawley rats	10, 25, 50, 100, 150 ppm for 12 months	Inhalation	82 weeks	Mammary carcinomas, dose-related excess over controls.
	Swiss mice	10, 25 ppm for 12 months	Inhalation	82 weeks	Kidney carcinomas (none in controls) Mammary tumors at 25 ppm
	Sprague-Dawley rats	.32, 3.2, 6.4, 13 mg/kg/day	Oral (gavage)	93 weeks	None
	Chinese Hamsters	25 ppm	Inhalation	74 weeks	None
Viola and Caputo	Wistar albino rats	142 ppm 12 month average	Inhalation	Lifetime	None, no histology
	Sprague-Dawley rats	75, 100 ppm 12 months	Inhalation	Lifetime	None, no histology
Lee, et al. (1978)	CD rats	55 ppm	Inhalation	52 weeks	None
	CD-1 mice	55 ppm	Inhalation	52 weeks	None
Harris	Rats	24, 74 ppm	Inhalation	104 weeks	None, interim result only
Reidston, et al. (1977)	Sprague-Dawley	9, 14, 28 mg/kg/day	Drinking water	104 weeks	None

IV. Risk Assessment

A risk assessment can be made independently for each of the observed positive responses. The risk of continuous inhalation of 1 ug/m^3 of VDC for a lifetime is calculated from the one-hit dose-response model with the dose in units of ppm. The ppm equivalent of 1 ug/m^3 VDC is found from the following formula, where M_{VDC} and M_{air} are the respective molecular weights;

$$\begin{aligned} 1 \text{ ug/m}^3 &= 10^{-3} / (1.2 \times M_{\text{VDC}} / M_{\text{air}}) \\ &= 10^{-3} / (1.2 \times 97 / 28.8) \\ &= 2.5 \times 10^{-4} \text{ ppm} \end{aligned}$$

A. Maltoni mouse kidney adenocarcinoma in males

The lifetime average exposure for the 25 ppm group

X_1 , is:

$$X_1 = 25 \times 4/24 \times 4.5/7 \times 1/2 = 1.34 \text{ ppm}$$

The dose-response slope of the one-hit curve is:

$$\begin{aligned} B &= (1/X_1) \ln [1/(1-P)] \\ &= (1/1.34) \times \ln(1/1-0.163) \\ &= 0.133 \end{aligned}$$

where X_1 is the lifetime average VDC concentration and P is the tumor incidence, $16/98 = 0.163$. Therefore, the risk at a lifetime exposure of $X_2 = 1 \text{ ug/m}^3$ is:

$$\begin{aligned} R &= BX_2 \\ &= 0.133 \times 2.5 \times 10^{-4} \\ &= 3.32 \times 10^{-5} \end{aligned}$$

$$\frac{3.32 \times 10^{-5} \times 10^6 \text{ (approx)}}{71} \approx 0.5/\text{yr}$$

B. Maltoni rat mammary tumors

The response at the two upper doses (150 and 100 ppm) can be used to get two independent estimates of the slope B. Since the control incidence, p_0 is not zero, the probability of tumors due to the 150 ppm treatment, P_1 , is:

$$\begin{aligned} P_1 &= (p_t - p_0) / (1 - p_0) \\ &= (35/60 - 32/100) / (1 - 32/100) \\ &= 0.39 \end{aligned}$$

The lifetime average exposure of the 150 ppm group, X_1 , is

$$\begin{aligned} X_1 &= 150 \times 4/24 \times 4.5/7 \times 1/2 \\ &= 8.04 \text{ ppm} \end{aligned}$$

Therefore one estimate of the slope B, is:

$$\begin{aligned} B_1 &= (1/X_1) \times \ln[1/(1-P_1)] \\ &= (1/8.04) \times \ln[1/(1-0.39)] \\ &= 0.061 \end{aligned}$$

In a similar calculation for the 100 ppm group, it is found that $B_2=0.099$, which is close enough to B_1 to verify that the one-hit model is not grossly inaccurate. Therefore the value of 0.099 is taken to be the slope. The risk at a continuous lifetime exposure of 1 ug/m^3 is therefore:

$$\begin{aligned} R &= BX_2 \\ &= 0.099 \times 2.5 \times 10^{-4} \\ &= 2.5 \times 10^{-5} \end{aligned}$$

The risk estimate based on the mice kidney data is only about 30 % higher than the estimate based on rat mammary tumor data.

References

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