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CARCINOGENIC, MUTAGENIC AND TERATOGENIC RISKS ASSOCIATED WITH VINYL CHLORIDE

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Summary

The data presented demonstrate clearly that vinyl chloride (VC) is related to a significant excess of mortality from cancer of the liver, lung and brain among workers occupationally exposed to VC. The risk of dying from cancer of the lymphatic and hematopoietic system also appears to increase with an increase in latency. These cancer sites could have been predicted by the animal bioassay conducted by Maltoni. With regard to the liver, even the histopathologic type of cancer (angiosarcoma) was observed first in experimental animals. A study of cancer mortality among populations residing proximate to VC polymerization facilities also demonstrated an increased risk of dying from CNS and lymphatic cancer. These latter findings raise cause for concern about out-plant emissions of VC, but without further study these cancers obviously cannot be interpreted as being related to out-plant exposure to VC.

Various test systems now have elicited a positive mutagenic response to VC. Thus, our observations of a significant excess of fetal mortality among the wives of males, who were occupationally exposed to VC, raise public health concern that VC may be mutagenic in humas.

With regard to the teratogenicity of VC, observations of a significant excess of children born with birth defects were reported among populations residing proximate to VC polymerization facilities. Additional epidemiologic study is needed to determine whether a repeated pattern of excessive numbers of children born with birth defects can be observed in other communities with VC polymerization facilities.

Introduction

In 1930, the first adverse health effects of vinyl chloride (VC) were reported [22]. Since then, numerous investigators have reported the toxic effects of VC on the central nervous system, the liver, the bones of the fingers and the lungs

[2,5,9—12,18,20,28]. More recently, the study of VC toxicity has broadened to assess the spectrum of carcinogenesis [2,15,16,21,26,29,30], mutagenesis [1,3,4,6,13,14,23,24]. and teratogenesis [8]. These efforts were stimulated by the work of Viola et al. [29] who, in 1971, reported the induction of tumors of the skin, lungs and bones in rats exposed by inhalation to 30,000 ppm of VC over a period of twelve months. Widespread concern for the carcinogenic activity of VC, however, did not occur until early 1974, when Creech and Johnson [2] reported four deaths from angiosarcoma of the liver among workers employed in the manufacture of polyvinyl chloride (PVC) resins. It was later learned that Maltoni had previously demonstrated VC-induced hepatic angiosarcomas, lung adenomas, brain neuroblastomas, lymphomas and various other tumors in mice, rats and hamsters [15,16].

With regard to mutagenicity, several investigators have induced mutations via microbial test systems [1,14,24]. Also, VC metabolites have induced mutations in mammalian cells [6]. In addition, reports from several countries have demonstrated significant excesses of chromosomal aberrations among workers exposed to VC as contrasted with those not exposed [3,4,13,23]. Because of these observations and of the widespread exposure to VC among both workers and the general population, the National Institute for Occupational Safety and Health (NIOSH) in the U.S.A. undertook an epidemiologic program to evaluate the magnitude and spectrum of VC toxicity to humans. This program was 4-fold in nature and sought to evaluate: (1) The site-specific risk of cancer among workers exposed to VC [30]. (2) The risk of some cancers among populations residing proximate to VC polymerization facilities [8]. (3) The site specific risk of congenital anomalies among populations residing proximate to VC polymerization facilities [8]. (4) The risk of fetal wastage among the wives of workers occupationally exposed to VC [7].

Cancer risk among workers exposed to VC

To assess the neoplastic risk of workers exposed to VC, a population consisting of employes from four VC polymerizing facilitates was selected for cohort mortality study [30]. Since occupationally induced cancers often take many years to become manifest, the study cohort was restricted to workers who had achieved five or more years of employment and for whom at least 10 years had lapsed since initial employment. Thus, the exposure period was five or more years and the latency period was 10 or more years. Follow-up for study cohort members was greater than 99%.

Table I shows the total mortality experience among the study cohort. The expected numbers are based on United States mortality data applied to NIOSH's modified life-table method. For all malignant neoplasms, there were 35 observed vs 23.5 expected, the SMR was 149. This excess was significant at the $P < 0.05$ level of confidence. For total mortality, 136 deaths were observed vs 126.3 expected. Selecting a cohort with at least five years work experience and 10 years latency eliminated the "healthy worker effect" [19] and so there were more total deaths than expected and this was mostly at the expense of cancer mortality.

Table II shows cancer mortality experience by greater than 10 and 15 year latency periods. At the greater than 10 year latency period, only biliary and

TABLE I

MORTALITY EXPERIENCE AMONG COHORT WORKERS EXPOSED TO VINYL CHLORIDE

Cause of death	ICD code [a]	Observed	Expected	SMR [b]
All malignant neoplasms	(140—205)	35	23.5	149 [c]
Heart	(400—443)	57	54.7	104
Non-malignant respiratory diseases	(470—527)	6	3.4	176
Cirrhosis	(581)	2	4.0	50
All other causes		36	40.7	88

[a] ICD, International Classification of Diseases, 7th revision.
[b] SMR, standardized mortality ratio.
[c] Significant at $P < 0.05$.

liver cancer deaths were significantly in excess; however, when the sub-cohort with 15 years of latency since initial employment was used, deaths from three categories of cancer were significantly in excess. The excess in mortality from cancer of the lymphatic and hematopoietic systems was not significant; however, the SMR increased from 159 to 176 with an increase in latency. These comparisons show the importance of latency when looking for occupationally-induced cancers.

TABLE II

CANCER MORTALITY BY INTERVAL SINCE INITIAL EXPOSURE AMONG WORKERS EXPOSED TO VINYL CHLORIDE

Site of malignancy		10+ years		15+ years
All malignant neoplasms	Obs. [a]	35		31
	Exp. [b]	23.5		16.9
	SMR [c]	149 [d]	<	184 [e]
Brain and CNS cancer	Obs.	3		3
	Exp.	0.9		0.6
	SMR	329	<	498 [d]
Respiratory system cancer	Obs.	12		11
	Exp.	7.7		5.7
	SMR	156	<	194 [d]
Biliary and liver cancer	Obs.	7		7
	Exp.	0.6		0.4
	SMR	1155 [e]	<	1606 [e]
Lymphatic and hematopoietic system cancer	Obs.	4		3
	Exp.	2.5		1.7
	SMR	159	<	176
All other malignant neoplasms	Obs.	9		7
	Exp.	11.7		8.4
	SMR	77	<	83

[a] Obs., observed.
[b] Exp., expected.
[c] SMR, standardized mortality ratio.
[d] Significant at $P < 0.05$.
[e] Significant at $P < 0.01$.

In laboratory studies, Maltoni has induced hepatic angiosarcomas, lung adenomas, brain neuroblastomas and lymphomas [16]. Therefore, the predictive value of animal bioassay studies can be demonstrated, not only by the observation of a significant excess of angiosarcoma of the liver among VC workers, but also by significant excesses of lung and brain tumors.

Cancer risks in populations residing near VC polymerization facilities

The risk of some cancers among adult populations residing in the only three Ohio communities with VC polymerization facilities was assessed [8]. All three communities had at least one facility in operation by 1954 and Painesville had a second plant in operation by 1967. The community population sizes varied from 12,000—24,000. Between 1960—70 the population had remained stable in Painesville and Ashtabula, but had increased by 30% in Avon Lake. As reported previously, for the three communities taken as a whole, there were no apparent differences in racial origin or family income as compared to the average for the State [8].

As a result of previous findings [26], cancers of the central nervous system, lymphatic and hematopoietic systems, were selected for study. Because of possible error in death certificate data in terms of metastases from other primary sites, data for lung and liver cancers were not analyzed.

Table III shows data for observed versus expected CNS cancer deaths in the white population by sex for the period 1958—73. North Ridgeville is the only community shown which does not have a PVC polymerization facility. It was included in the analyses of the cancer data because it is located contiguous to Avon Lake and because it had a high incidence of children born with birth defects [8]. If North Ridgeville had not been included in the analyses of cancer mortality, little difference in the results would have been observed. Expected values are based on the occurrence in the balance of the counties over the same period of time. As shown in Table III, there was a significant excess of CNS cancer deaths in males. The excess was greatest in Painesville and North Ridgeville. With all communities combined, there were 27 CNS cancer deaths observed in males versus 14.1 expected; the SMR was 191. The difference was significant at $P < 0.01$.

In females, with all groups combined, there was only a slight excess. With sex groups combined, the excess was significant at $P < 0.01$. It may be noteworthy that one father-daughter combination for CNS tumor deaths occurred in Painesville. The daughter died of a papillary ependymoma in 1963 at the age of 16. The father died two years later of a glioblastoma multiforme at the age of 58. It would be difficult to determine whether this observation is the result of genetic or environmental factors.

Table III also shows deaths from lymphomas. Although the differences between observed and expected deaths in males were not significant, there was a consistent excess in each community. In females, there were excess lymphoma deaths in two of the four communities. With sex groups combined, a significant excess of lymphoma deaths was observed in Ashtabula. With sex groups and communities combined, the number of observed deaths was 61 versus 48.7 expected. The SMR was 125. This was significant at

TABLE III

OBSERVED AND EXPECTED DEATHS FOR THREE TYPES OF CANCER FOR RESIDENTS 45 YEARS AND OLDER IN THE OHIO COMMUNITIES WITH VINYL CHLORIDE POLYMERIZATION FACILITIES, 1958—73

Expected numbers of cancer deaths based on occurrence over the same period of time in the balance of the counties in which the communities are located.

	Males		Females		Sexes combined	
	Obs./Exp.	SMR	Obs./Exp.	SMR	Obs./Exp.	SMR
	CNS cancer (191—192)[a]					
Ashtabula	7/ 6.1	115	6/ 3.8	158	13/ 9.9	131
Painesville	12/ 3.8	316 [d]	2/ 2.8	71	14/ 6.6	212 [b]
Avon Lake	2/ 2.3	87	1/ 1.8	56	3/ 4.1	73
N. Ridgeville	6/ 1.9	316 [b]	2/ 1.5	133	8/ 3.4	235 [b]
Communities Combined	27/14.1	191 [c]	11/ 9.9	111	38/24.0	158 [c]
	Leukemia and aleukemia (204—207)[a]					
Ashtabula	13/14.7	88	11/ 8.6	128	24/23.3	103
Painesville	8/ 7.1	113	7/ 6.8	103	15/13.9	108
Avon Lake	1/ 3.6	28	5/ 2.2	227	6/ 5.8	103
N. Ridgeville	2/ 3.2	63	0/ 1.9	0	2/ 5.1	39
Communities Combined	24/28.6	84	23/19.5	118	47/48.1	98
	Lymphomas (200—203)[a]					
Ashtabula	18/12.6	143	14/ 5.8	241 [c]	32/18.4	174 [c]
Painesville	12/10.4	115	4/ 8.3	48	16/18.7	86
Avon Lake	4/ 3.3	121	5/ 2.9	172	9/ 6.2	145
N. Ridgeville	3/ 2.8	107	1/ 2.6	38	4/ 5.4	74
Communities Combined	37/29.1	127	24/19.6	122	61/48.7	125

[a] International Classification of Diseases, 8th revision codes.
[b] $P < 0.05$.
[c] $P < 0.01$.
[d] $P < 0.002$.

$0.05 < P < 0.10$. Data were then analyzed for leukemia and aleukemia mortality. As shown in Table III, the observed versus expected mortality was virtually identical.

Birth defects among populations residing near VC polymerization facilities

The occurrence of birth defects was studied [8] for the same three Ohio communities with VC polymerization facilities. Birth data for residents of North Ridgeville were not combined with data for the three index communities in the initial analyses (Table IV) because the high incidence of birth defects in North Ridgeville, which lies contiguous to Avon Lake, was identified in subsequent analyses [8]. Data for North Ridgeville, however, were included in subsequent analyses (Table V) for specific birth malformations. The observations among community residents were compared to both the occurrence in

TABLE IV

RESIDENT BIRTHS, MALFORMATION RATE PER 1000 LIVE BIRTHS IN OHIO AND IN THREE SELECTED COMMUNITIES AND OBSERVED VERSUS EXPECTED NUMBERS OF MALFORMATIONS IN EACH CITY, YEARS COMBINED, 1970—73

Malformations are based on codes 740—759 of the International Classification of Diseases, 8th revision, 1968.

Area	Births	Malformations			
		Rate/10^3	Number observed	Number expected [a]	χ^2
Entire state of Ohio	719, 287	10.1	7295	—	—
Ashtabula city	1900	17.4	33	19.3	9.78 [b]
Painesville city	1381	18.1	25	14.0	10.29 [b]
Avon Lake city	738	20.3	15	7.5	7.56 [b]
All three communities combined	4019	18.2	73	40.8	27.13 [c]

[a] Expected numbers are based on state rate per 1000 live births.
[b] $P < 0.01$.
[c] $P < 0.001$.

the balance of the counties in which the communities are located and to the occurrence in the State for the period 1970—73. Between 1970—73, the rate for birth defects changed from 9.3 to 11.3 per 1000 live births for the balance of the counties, from 9.6 to 10.8 for the entire state, whereas, the rate for the three index cities combined changed from 17.0 to 22.5. Thus, the incidence of birth defects for children born in the index cities was almost twice as great as the incidence in the balance of the counties or in the entire State, and the differences appear to be increasing with time.

Table IV shows data for malformation rates in each index community versus the rate for the entire State. These differences were all highly significant. The rates ranged from 17.47 in Ashtabula to 20.33 in Avon Lake, as compared to 10.14 for the entire State. When the community experience was compared to the occurrence in the balance of the counties in which the communities were

TABLE V

OBSERVED, EXPECTED AND RELATIVE RISK FOR SPECIFIC CONGENITAL ANOMALIES IN INDEX AREAS INCLUDING N. RIDGEVILLE, 1970—73 [a]

Defect category	Number of defects		RR [b]
	Observed	Expected	
All defects (740—756, 758, 759) [c]	109	56.0	1.95
Central nervous system (740—749)	17	5.6	3.02
Cleft palate and lip (749)	10	6.5	1.53
Genital organs (752)	16	8.4	1.90
Clubfoot (754)	23	8.2	2.79
All other defects	43	27.2	1.58

[a] Excludes skin, hair and nails (757).
[b] RR, relative risk (observed/expected).
[c] International Classification of Disease codes, 8th revision, are shown in parentheses.

located, the differences remained significant. Therefore, whether you compare the occurrence in the communities to the expected, based on the average for the State, or for the balance of the counties, the excess of children with congenital anomalies in the communities appears to be significant.

Table V shows observed versus expected numbers and the relative risk for total and selected malformations. Although an increase in most organ systems was observed, the greatest excess of severe defects included malformations of the CNS, cleft lip and palate, club foot and genital organs. These observations have been reported previously in more detail [8].

Fetal mortality among wives of workers exposed to VC

Since VC had elicited a positive mutagenic response via microbial test systems [1,6,14,24] and also had been associated with significant excesses of chromosomal aberrations in the lymphocytes of workers occupationally exposed to VC [3,4,13,23], concern was expressed that VC may induce germinal mutations. Thus, a questionnaire-interview survey was conducted to ascertain the incidence of fetal loss (defined as any product of conception not born alive) among wives of workers exposed to VC [7a]. All current VC polymerization and polyvinyl chloride (PVC) fabrication workers were included for study together with a similar number of current rubber workers selected from work areas relatively free from known toxic materials and matched as a group to the VC workers by age. No interviews were conducted with workers' wives and no data were obtained concerning maternal age, except indirectly through paternal age. Group participation rates ranged from 62—77 percent. Data for the wives of VC polymerization workers (study group) were contrasted with data for the wives of PVC fabrication and rubber workers ("controls"), who were known to have had very low or no VC exposure, respectively.

The data in Table VI show the paternal age distribution for fetal deaths according to the husband's exposure. Prior to husband's exposure, the crude fetal death rates for the control and study group were 6.9 and 10.1%, respectively. Subsequent to husband's exposure, the crude rates were 8.8 and 16.5%, respectively.

As can be seen in Table VI, the excess in fetal mortality subsequent to husband's exposure, was associated with younger-aged husbands. For husbands 30 years of age and older, the rates for the control group 17/142 (12.0%) and primary VC exposure group 9/69 (13%) were about the same; whereas, for husbands less than 30 years of age, the rates for the control group 7/131 (5.3%) and primary VC exposure group 14/70 (20.0%) were significantly different, $P < 0.001$, $\chi^2 = 10.52$, with one degree of freedom (df). The excess of fetal mortality among wives of younger-aged husbands may be a reflection of a practice of placing newly hired personnel because of little or no seniority, in jobs where occupational exposures to VC may have been worse. This hypothesis, however, needs further assessment in other working populations. Since parental age was positively correlated with fetal mortality in this population and in a previous study [25], fetal mortality rates for the study group were adjusted to the age-distribution of the control group.

TABLE VI

PATERNAL AGE DISTRIBUTION FOR FETAL DEATHS ACCORDING TO HUSBAND'S VC EXPOSURE

Paternal age group (years)	"Controls"			Primary VC Exposure		
	Pregnancies	Fetal deaths		Pregnancies	Fetal deaths	
	(N)	(N)	(%)	(N)	(N)	(%)
	Prior to husband's exposure					
<20	31	2	6.5	7	0	0.0
20–24	80	4	5.0	44	2	4.5
25–29	38	4	10.5	56	7	12.5
30–34	6	1	16.7	27	5	18.5
≥35	4	0	0.0	14	1	7.1
All ages crude rate	159	11	6.9	148	15	10.1
Mean paternal age at conception (year)	23.0			26.4		
Age-adjusted [a] rate			(6.9)			(6.1)
	Subsequent to husband's exposure					
>20	1	0	0.0	0	0	0.0
20–24	43	4	9.3	22	3	13.6
25–29	87	3	3.4	48	11	22.9
30–34	87	7	8.0	36	3	8.3
≥35	55	10	18.2	33	6	18.2
All ages crude rate	273	24	8.8	139	23	16.5
Mean paternal age at conception (year)	30.4			30.2		
Age- adjusted [a] rate			(8.8)			(15.8)

[a] Fetal mortality rates for primary VC exposure group are direct age-adjusted to the paternal age-distribution of the pregnancies in the control group (shown in parentheses).

TABLE VII

MEAN PATERNAL, NUMBER OF PREGNANCIES AND AGE-ADJUSTED FETAL DEATH RATES ACCORDING TO HUSBAND'S VC EXPOSURE

	"Controls" [a]	Primary VC exposure [b]
	Prior to husband's exposure	
Number of families	95	70
Mean paternal age at conception (years)	23.0	26.4
Number of fetal deaths among wives	11	15
Number of pregnancies	159	148
Age-adjusted fetal deaths/100 preg. [c]	6.9	6.1
	Subsequent to husband's exposure	
Number of families	113	62
Mean paternal age at conception (years)	30.4	30.2
Number of fetal deaths among wives	24	23
Number of pregnancies	273	139
Age-adjusted fetal deaths/100 preg. [c]	8.8	15.8 [d]

[a] Rubber and PVC fabrication workers.

[b] VC polymerization workers.

[c] Rates age-adjusted to "control" group paternal age distribution.

[d] Subsequent to husbands' exposure, the frequency of fetal deaths among wives was significantly greater in the primary VC exposure group as compared to the "controls" ($P < 0.05$) or to the frequency in the study group prior to husband's exposure ($P < 0.02$) by age-adjusted Chi-square testing.

The data in Table VII show fetal death rates per 100 pregnancies for the wives of male workers in the control and study groups. Prior to their husband's exposures, the rates were 6.9% and 6.1% for the control and study groups, respectively. Subsequent to husband's exposure, however, the rates were 8.8% for the control group versus 15.8% for the study group. This difference was significant at the $P < 0.05$ level by Mantel-Haenszel Chi-square testing [17] ($\chi^2 = 4.84$, df = 1). Further, the before and after exposure comparisons indicated changes in rates from 6.9 to 8.8% for the control group as compared to a change from 6.1 to 15.8% for the study group. The rates for before and after husband's exposure in the study group were significantly different ($P < 0.025$, $\chi^2 = 5.78$, df = 1). For the study group, it may be noted that before exposure age-adjustment reduced the crude rate from 10.1 to 6.1%; whereas, after exposure the crude rate was reduced from 16.5 to 15.8%. The greater reduction in rates for the before exposure age-adjustment resulted from a difference in the age distribution of the husbands in the two groups. As can be seen in Table VII, prior to husband's exposure, the mean paternal age in the study group was 26.4 years as compared to only 23.0 years for the control group, whereas, subsequent to husband's exposure, the mean ages of the two groups were virtually the same, i.e., 30.4 years versus 30.2 years. In both situations mean age was a good measure of central tendency.

To determine whether women who had chronically experienced abortions might have weighted the results in favor of a higher fetal mortality rate in the primary VC exposure group, data for the pregnancies of women who had two, three or four or more spontaneous abortions were eliminated. The data were then recalculated to determine whether or not the trend of a greater miscarriage rate could be maintained. As shown in Table VIII, the trend was maintained for each analysis.

TABLE VIII

NUMBER OF PREGNANCIES AND AGE-ADJUSTED FETAL DEATH RATES ACCORDING TO HUSBAND'S VC EXPOSURE EXCLUDING PREGNANCIES IN WOMEN WITH ≥2, 3 OR 4 FETAL DEATHS

Rates for the primary VC exposure group are age-adjusted to the Control group

	Controls		Primary VC exposure	
	Number of pregnancies	Fetal death rate	Number of pregnancies	Fetal death rate
	≥2 Fetal deaths excluded			
Before husband's exposure	155	5.8%	126	1.7%
After husband's exposure	255	4.7%	111	6.2%
	≥3 Fetal deaths excluded			
Before husband's exposure	159	6.9%	141	3.1%
After husband's exposure	265	6.8%	120	10.8%
	≥4 Fetal deaths excluded			
Before husband's exposure	159	6.9%	142	5.8%
After husband's exposure	265	6.8%	127	11.8%

As reported previously [7a], additional analyses suggested that the significant excess in fetal mortality after the husband's exposure would not seem to be the result of bias from interviewers nor from respondents. Because of the highly volatile nature of vinyl chloride [27], carry-home exposure to the wife would seem unlikely. Therefore, the leading possibility for the mechanism involved would seem to be germ-cell damage in the male through direct VC exposure.

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