R&S 027693

VINYL CHLORIDE

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OUTLINE OF DISCUSSION

I. VINYL CHLORIDE

- A. Introduction
- B. Known Cases Worldwide of ASL Associated with VCM
- C. CMA/EHA Study
- D. Dow Study
- E. The Sir Richard Doll Review
- F. Calculation of Risk
- G. Various Authors' Conclusions
- H. Miscarriages and Birth Defects
- I. Neuropathy

II. THE ST. GABRIEL MISCARRIAGE STUDY

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OPRAH WINFREY SHOW

JUNE, 1989

Quote from local audience member

"The chemical that they make more of here than anywhere else in the country is vinyl chloride and it causes that in the wives, it causes cancer and it causes rare liver disease and it is proven and they make it intentionally and it is immoral and criminal to produce a chemical that is known to kill."

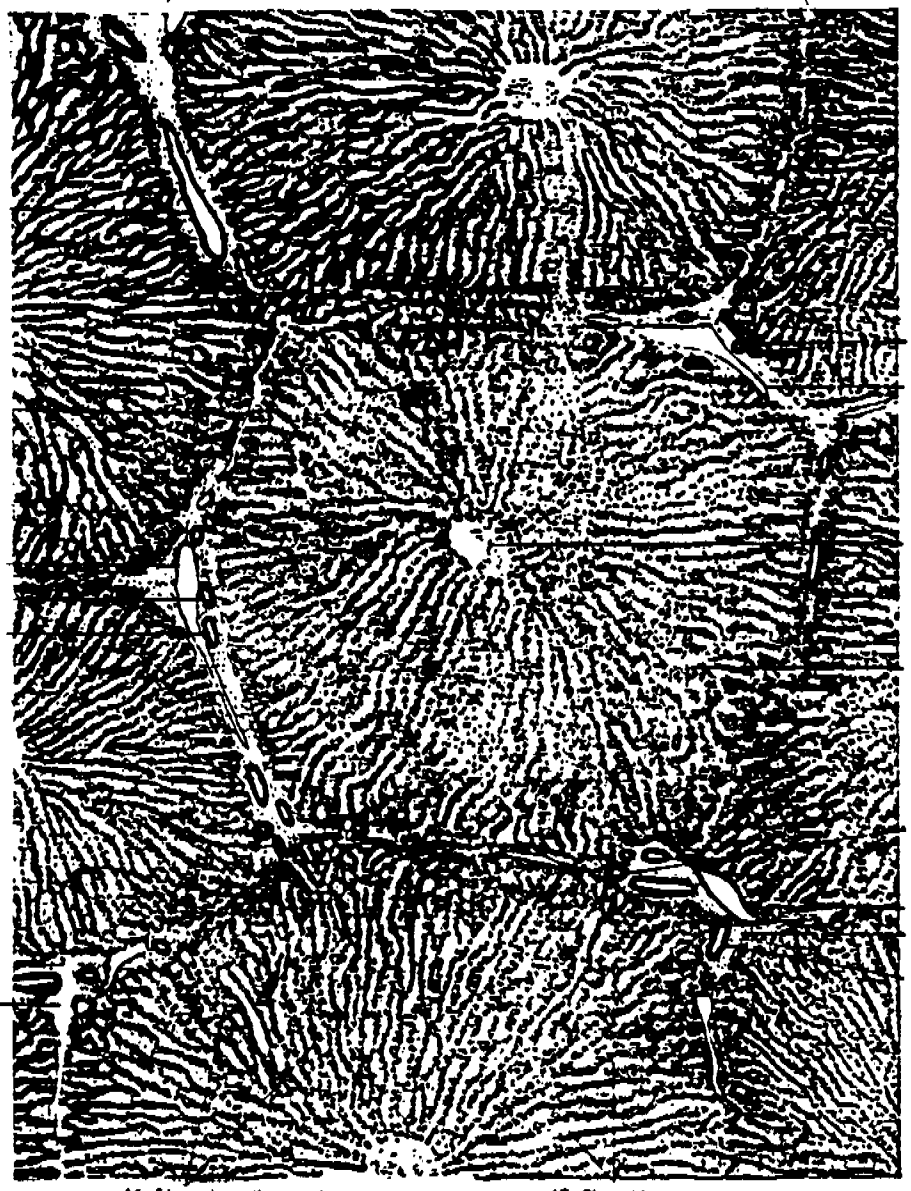
THREE PHASES IN PVC PRODUCTION

- VCM production
- PVC polymerization
- PVC fabrication

CHRONOLOGY OF PVC PRODUCTION AND HEALTH RISKS

1942	Start of commerical PVC production in U.S.
1949	Earliest references to AOL and hepatic effects
1966-7	Detailed description of AOL
1960's	Reports of hepatomegaly
1971	First report of experimental carcinogenicity
1972-3	Detailed description of hepatotoxicity
1974	First cluster of HAS

LIVER LOBULE (PANORAMIC VIEW)



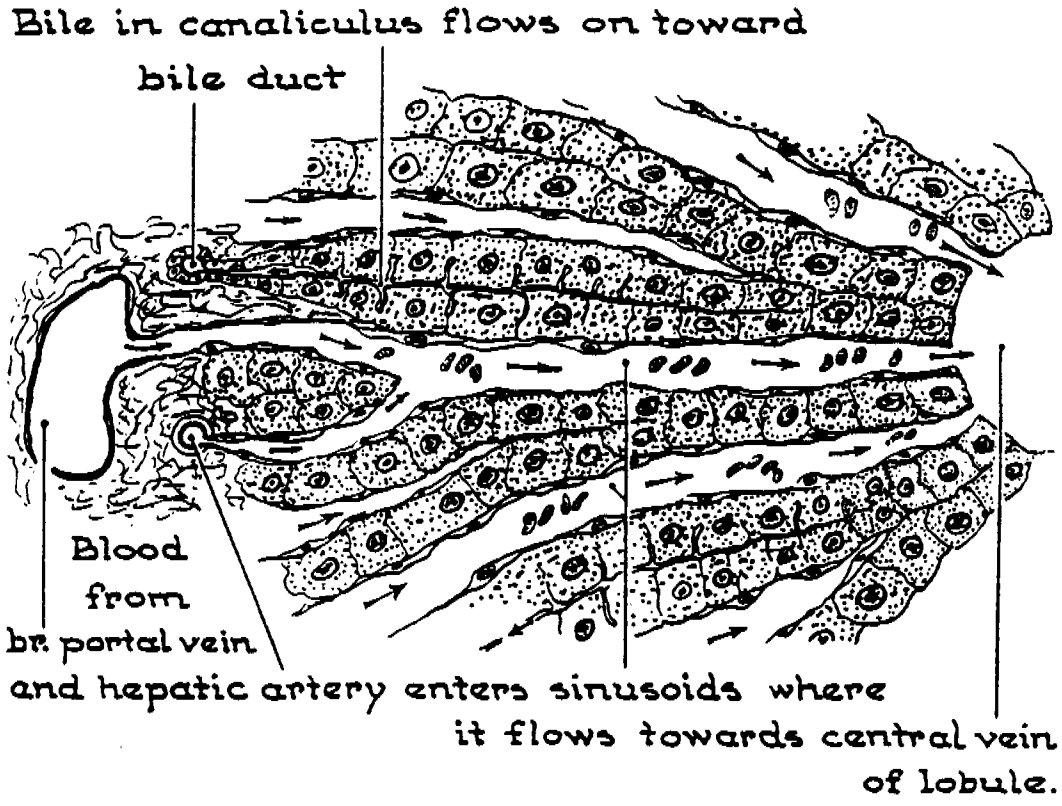
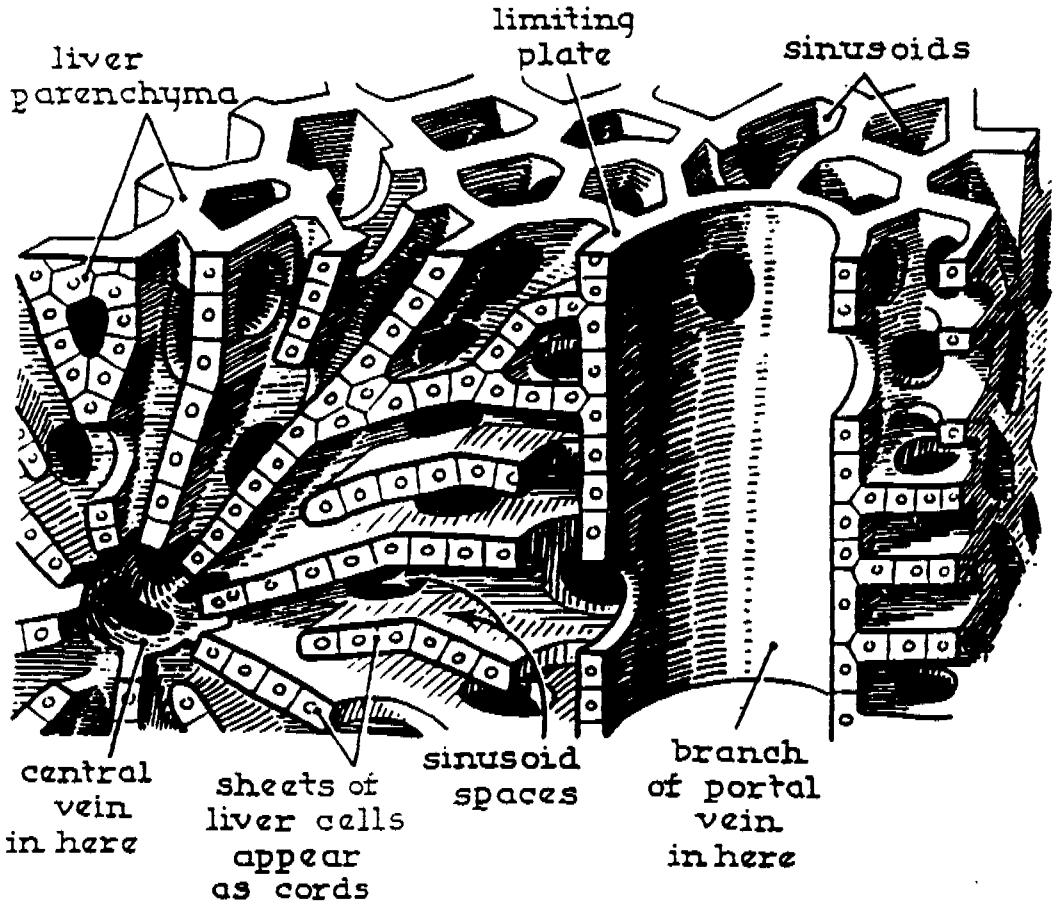


FIG. 25-7. Drawing (at high-power magnification) to show how blood from the portal vein and the hepatic artery (*left*) flows into sinusoids, lined by reticuloendothelium, that lie between liver cords, and empties into the central vein (*right*). The way that bile travels in the opposite direction in canaliculi to empty into bile ducts in portal areas is also shown.


liver parenchyma
limiting plate
sinusoids
central vein in here
sheets of liver cells appear as cords
sinusoid spaces
branch of portal vein in here

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is the standard for vinyl chloride, with a time-weighted average for all exposures not to exceed 50 ppm (Fig 64–1).

Acro-osteolysis

Acro-osteolysis consists of localized areas of bone necrosis and absorption. These lesions are nontender and are not associated with a periosteal reaction. The hands and fingers are most commonly involved. In a majority of cases, acro-osteolysis is associated with Raynaud's phenomenon and scleroderma-tous skin changes.

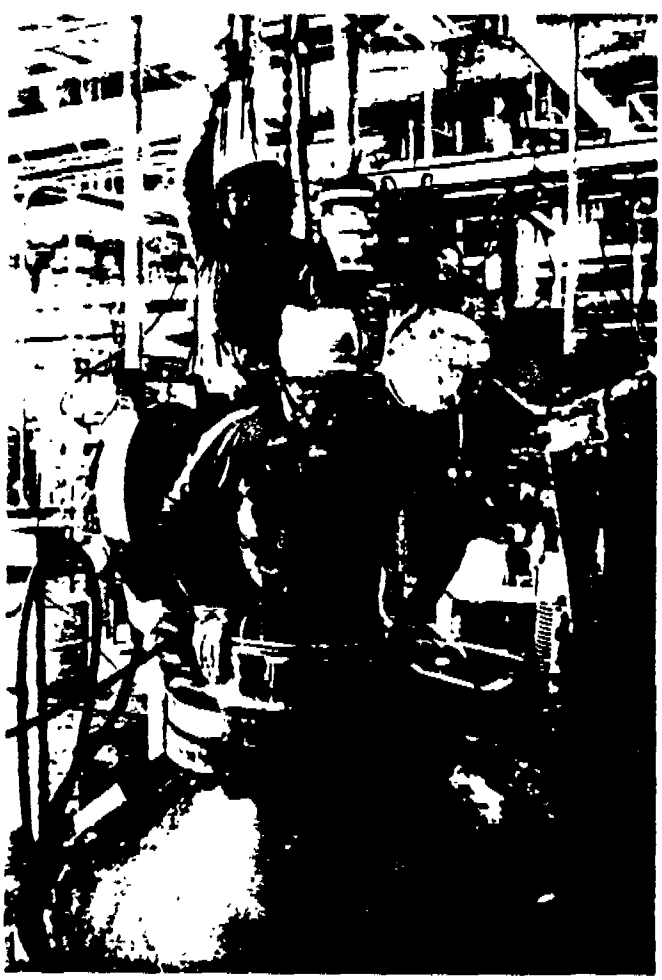

FIG 64–1.
A worker entering a PVC reactor vessel to clean out caked polymer adhering to the inner surfaces. During the polymerization reaction, sludge from the slurry has a tendency to form a crust on the impeller mechanism as well as the tank inner surfaces. The caked polymer is periodically hand-chipped by workers inside the tank, and this is the operation that subjected workers to the highest concentrations of vinyl chloride. Current practice requires that flexible ducts be used for purging with clean air before the worker enters. In addition, workers in this operation must be provided with positive-pressure air-supplied respirators, preferably the hood type. Demand-type respirators have been used, but may not offer the same protection as the continuous-flow type of hood respirator. (Courtesy of Maurice N. Johnson, M.D., B.F. Goodrich Company, Akron, Ohio. Photographer—H. Groskinski.)

...at two workers.

Of the 533 PVC ... workers in this plant ... clave cleaners, two cases were identified ... hands of these workers. The terminal phal... patella, and the phalanges of the feet we... workers, also autoclave cleaners, demonstr... companied by Raynaud's phenomenon.

Wilson[70] studied 31 cases of acro-osteol... the hands of workers engaged in vinyl chlor... cesses. Most of these workers had worked ... walls and other equipment in the polymer... olysis was localized to the distal phalanges ... was associated with Raynaud symptoms. ... disorder resulted from a combination of ph... insult, and personal idiosyncrasy, and were ... ethe causes. Prevalence was reported to be ... employees performing similar work, and n... workmen processing the polymer or manufac... ins. More than 100 workers handled the m... processed it into plastic products did not d... acro-osteolysis.

In 1970 and 1971, Dinman [...] of the Inst... and Industrial Health at The University of ... comprehensive study of acro-osteolysis in w... compounding vinyl and PVC. The epidemi... resented more than 5,000 workers in 32 pl... were discovered, of which 25 had a definite ... 16 suspicious diagnoses of acro-osteolysis ... hand cleaning of the polymerizers.

Dodson[79] determined that work practi... specific agent or combination of agents, app... occurrence of the disease. He thought the dis... rather than localized in nature, but was unal... logic agent or portal of entry, suggesting sen... sitization of susceptibility." An industrial h... epidemiologic investigation[1] revealed vinyl ch... in the reactor before ventilating to be about 3... ation of the containers, the vinyl chloride con... reactors during scraping was found to be unde... ally around 50 ppm. It was found that scrapin... polymerized vinyl chloride so that levels of 100... found close to the hands during these oper... potentially high worker respiratory inhalation. ... stituents of the scrapings of the reactor vessel ... polymerized resins, unreacted catalysts, addit... the polymerized vinyl chloride. No serious dis... ported in any of the above-mentioned cases ... been partially disabled because of hand sore... striction in manual activity. With proper p... and careful hygiene measures, all these ca... (Fig 64–2).

Veltman et al.[72] reported findings in 70 w... toclaves and centrifuges, during drying and sa...

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FIG 64–2.
The solid, caked polymer must be removed by chisels, hammers, and handpicks. Neither workers nor management may be aware of the hazard involved when a spark is generated by steel on steel. It is not uncommon to open a pocket of the cake lining the vessel. The pocket may contain liquid vinyl chloride monomer. It is very possible that the lower explosive limit for vinyl chloride monomer (33,000 ppm) can be reached during the chipping with steel on steel. Reactor vessels have exploded, leaving nothing but a crater in the ground where the plant once stood. Reactor chipping or cleaning tools should be of the nonsparking type. To minimize worker entry, some companies use high-pressure water guns to remove the caked polymer. These water guns may operate from 9,000 to 13,000 pounds of pressure per square inch. This in itself may produce a serious safety hazard. Some attempts in the United States to remove the caked slurry have utilized closed solvent cleaning systems in which solvents such as tetrahydrofuran are used. To date, such solvent cleaning systems have been relatively unsuccessful. Recently completed production systems using 30,000-gallon reactor vessels have been utilizing automatic high-pressure water cleaning guns and solvent systems to minimize or eliminate the need for worker entry into reactor vessels. Older reactor vessels, which contain cooling vanes of heat exchangers, complicate the cleaning process and high-pressure water guns and solvent systems cannot be used in these tanks. (Courtesy of Maurice N. Johnson, M.D., B. F. Goodrich Company, Akron, Ohio. Photographer–H. Groskinski.)

people in a group of 267 workers nylchloride polymerization plant, signs of abnormal peripheral cir much more frequently in those sure. Findings included numbnes to cold, pain, cyanosis, involven syndrome. An abnormal Allen tes ers, pseudoclubbing in 3.75%, changes in 6.4%.

The specific effect of VCM culminates in neural, dermal, and been in doubt. The superficial sclerosis (scleroderma) has prompt a report of 22 PVC workers by 1976, 6 workers had prodromal s non, 10 had typical Raynaud's sy scleroderma-like changes in the n ysis of the distal phalanges and syndrome was described as sympt esthesia in the fingers with metac digital arteries. Cryoglobulinemia immunoglobulins (22.7%) were p plasma proteins. Those with m more likely to have immunologic in 5 of 22 and IgM in 1 of 22. In be elevated in 67%.[4]

Cryoglobulins were also see Ward et al.[27] These workers we patients with vinyl chloride disea ical findings encompassing abn blood, nervous system, lungs, a possible VCD; and 35 vinyl chlori oglobulins were seen in 66%. RF found in 55%, 27%, and 0%. Th IgG, C3, and fibrinogen. Rheum patients when measured by the lat positive in low titer by hemagglu definite VCD and 22.7% of those orescent examination of skin and with definite VCD showed the pre within the lumen of small blood cular endothelium. These author VCM binds to IgG-producing ag immune complexes during cold e stimulate complement activation and the conversion of fibrinogen t ies and small blood vessels.

Liver

A hepatitis-like effect has be posure. In a study of 70 workers

CAUSES OF ASL

- VCM
- Inorganic arsenic
- Thorotrast
- Androgenic - anabolic steroids

TOXICOLOGY

1. HAS is linked to the amount of VCM metabolized rather than to VCM concentration.

2. Reactive intermediates, particularly the epoxide (chloroethylene oxide) found by oxidative metabolism of carbon/carbon double bond, are most likely the carcinogenic agents.

3. Short-lived metabolites are formed in the hepatocyte but are carcinogenic in the adjacent cells to which they migrate presumably because their cells have less detoxification potential.

4. Reactive metabolites covalently bond to macromolecules such as DNA.

VCM-INDUCED VS. CLASSIC HEPATOTOXICITY

VCM-induced hepatotoxicity:

- relatively silent progression
- not detected early by standard liver function tests
- effective screening tests lacking
- least common of all causes of hepatotoxicity
- various parts of spectrum seen with VCM, Thorotrast, arsenic, and steroids (androgenic-anabolic)

Classic hepatotoxicity:

- clincial signs and symptoms appear early
- hepatic effects noted by enzyme changes, and other readily available laboratory tests
- many clinical screening tests are used
- wide array of hepatotoxins have been identified

RETROSPECTIVE ESTIMATES OF TYPICAL TWA 8-HOUR PERSONAL EXPOSURES

Estimate	Year
1000	1945-1955
400-500	1955-1960
300-400	1960-1970
150	Mid 1973
5	1975

VINYL CHLORIDE ILLNESS

1. Enlargement of liver and spleen with a specific histologic appearance.
2. Patchy infiltration of the skin resembling scleoderma.
3. Many changes in the tips of the fingers described as acroosteolysis.
4. Peripheral circulatory changes identical with the classical picture of Raynaud's syndrome.

R&S 027708

ASSOCIATION OF PLASTICS MANUFACTURERS IN EUROPE WORLDWIDE REGISTRY OF ASL RESULTING FROM EXPOSURE TO VCM

- Begun in 1974
- Cases must be histologically confirmed
- Mean age at diagnoses = 52 years
- Incidence of ASL reaches a peak of 20-29 years after exposure
- 43% of affected individuals were autoclave cleaners

R&S 027709

NUMBERS OF VINYL CHLORIDE RELATED CASES OF ANGIOSARCOMA OF THE LIVER BY DATE OF DEATH

Period	Number of Deaths
1955-59	2
1960-64	4
1965-69	9
1970-74	23
1975-79	46
1980-84	34
Total	118

ASL REGISTRY UPDATE - THROUGH 1987

	Cases
1985	5
1986	3
1987	4

Of 50 cases in North America, 42 have occurred at 4 factories.

Louisville (15)
Shawinigan (12)
S. Charleston (10)
Niagara Falls (5)

DISTRIBUTION OF CASES BY COUNTRY

Country	Number of Cases	Number of Factories Reporting Cases
United States	35	10
West Germany	26	6
France	18	5
Canada	10	1
United Kingdom	9	2
Sweden	5	1
Italy	4	4
Yugoslavia	4	1
Czechoslovakia	2	1
Japan	2	1
Belgium	2	1
Norway	1	1
Total	118	34

EHA UPDATE
COHORT DEFINITION

- 9,370 men who had worked at least one year in jobs involving exposure to vinyl chloride prior to January 1, 1973.

- 32 U.S. plants

- Observed through December 31, 1982

EHA STUDY
OBSERVED AND EXPECTED DEATHS BY CAUSE, SMRS AND 95% CONFIDENCE LIMITS

Cause	OBS	EXP	SMR	95% CL
All Causes	1536	1705.3	90	86-95
All Cancers	359	341.7	105	94-117
Liver and Biliary Tract*	37	5.8	641	450-884
Lung	111	115.9	96	76-116
Brain and CNS	23	12.8	180	114-271
Lymphatic and Hematopoietic System	37	36.3	102	72-141
Nonmalignant Respiratory Disease	70	87.6	80	62-101
Emphysema, incldlng COPD	41	22.8	180	129-244

*7 Biliary tract cancers versus 2.7 expected (SMR = 256; 95% CL = 245-511).

R&S 027714

EHA STUDY
SUMMARY OF CANCER OF LIVER AND BILIARY TRACT

Duration of Expsoure

≤10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
6	182	20	1235*	11	1284*

Years Since First Exposure

≤20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
10	386*	11	590*	16	1218*

Year of First Expsoure

≤1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
27	780*	7	440*	3	419

Type of Plant

VCM		PVC	
OBS	SMR	OBS	SMR
1	326	31	693*

R&S 027715

EHA STUDY

SUMMARY OF ALL CANCER EXCLUDING LIVER AND BILIARY TRACT

Duration of Expsoure

<10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
174	92	94	102	54	100

Years Since First Exposure

<20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
120	87	122	105	80	96

Year of First Expsoure

<1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
166	93	107	105	49	90

Type of Plant

VCM		PVC	
OBS	SMR	OBS	SMR
23	110	241	94

EHA STUDY
SUMMARY OF CANCER OF THE LUNG

Duration of Expsoure

≤10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
59	93	37	114	15	75

Years Since First Exposure

≤20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
44	104	45	105	22	72

Year of First Expsoure

≤1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
54	90	39	106	18	96

Type of Plant

VCM		PVC	
OBS	SMR	OBS	SMR
1	-	29	-

EHS STUDY
SUMMARY OF CANCER OF BRAIN AND CNS

Duration of Expsoure

≤10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
13	165	4	121	6	386

Years Since First Exposure

<20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
13	184	6	158	4	210

Year of First Expsoure

≤1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
9	156	7	164	7	256

Type of Plant

VCM		PVC	
OBS	SMR	OBS	SMR
2	220	16	169

EHA STUDY
SUMMARY OF LYMPHATIC AND HEMATOPOIETIC CANCER

Duration of Expsoure

≤10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
20	91	12	128	5	104

Years Since First Exposure

≤20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
16	88	14	130	7	97

Type of Plant

VCM		PVC	
OBS	EXP	OBS	EXP
0	-	31	114

Year of First Expsoure

≤1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
19	107	13	114	5	71

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EHA STUDY
SUMMARY OF EMPHYSEMA MORTALITY

Duration of Expsoure

≤10 Years		10-19.9 Years		20+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
25	209*	11	167	5	117

Years Since First Exposure

≤20 Years		20-29.9 Years		30+ Years	
OBS	SMR	OBS	SMR	OBS	SMR
11	158*	17	198*	13	179

Year of First Expsoure

≤1950		1950-1959		1960+	
OBS	SMR	OBS	SMR	OBS	SMR
24	174*	12	189	5	187

Type of Plant

VCM		PVC	
OBS	SMR	OBS	SMR
1	83	29	163

DOW CHEMICAL
VINYL CHLORIDE MORTALITY STUDY

Michigan Division

- 593 employees who were potentially exposed to vinyl chloride monomer
- 1942-1982
- 17,114 person-years
- 28.9 person-years average per person

R&S 027721

OBSERVED AND EXPECTED DEATHS FOR SELECTED CAUSES EXCLUDING EMPLOYEES WITH PRIOR EXPOSURE TO ARSENIC INSECTICIDES, 1942-1982

Cause of Death (ICD-8)	Obs	Exp	SMR†	95% CI⊕
All causes	130	151.9	86	72-102
All cancers (140-209)	27	31.7	85	56-124
Digestive system cancer (150-159)	9	8.5	106	48-201
Liver cancer (155, 156)	1	0.6	- §	4-899
Respiratory system cancer (160-163)	10	11.3	89	42-163
Brain cancer (191, 192)	2	1.1	- §	23-682
All circulatory diseases (390-458)	65	75.4	86	67-110
All nonmalignant respiratory diseases (460-519)	9	8.6	104	48-198
All accidents (E800-E949)	8	10.9	74	32-144

* Expected numbers are based on calendar time and age-specific mortality rates of U.S. white men.
† Standardized mortality ratio; observed divided by expected number of deaths X 100.
⊕CI, confidence interval of Obs/Exp.
§ Not calculated when expected number of deaths fewer than 5.

Liver cancer was an introkepatic bile duct carcinoma.

DOSE-RESPONSE RELATIONSHIP

- Undetermined
- Less than 25 ppm
- 25-200 ppm TWA
- 200+ ppm TWA
- Based on highest rated job assignment for at least 1 month

Men with at least 5 years of exposure above 200 ppm (7 observed versus 2.8 expected). No predominant tumor site or unique histologic type.

R&S 027723

A

VCM REVIEW BY

SIR RICHARD DOLL

1988

OBSERVED AND EXPECTED NUMBER OF DEATHS FROM DIFFERENT CANCERS REPORTS IN THE FOUR PRINCIPAL STUDIES (0 = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS)

Type of Class of Cancer	United States O[a]	United States E	United Kingdom O	United Kingdom E	Canada O	Canada E	Italy O	Italy E
Buccal cavity and pharynx	13	11.55	4	3.58	0	0.64	1	0.8
Stomach	11	16.01	26	23.91	-	-	3	3.0
Large intestine	21	28.79	9	13.94	-	-	0	1.2
Liver	-	-	11	1.94	8	0.14	1	0.6
Liver and gallbladder	39	5.77	-	-	-	-	-	-
Pancreas	17	18.40	7	9.88	-	-	0	0.7
Lung	118	115.87	81	92.12	2	5.78	12	6.1
Melanoma	-	-	2	1.74	-	-	0	0.2
Testis	-	-	2	1.38			-	-
Bladder	5	8.46	14	8.00			1	0.7
Kidney	12	9.06	3	4.10	1	1.33	-	-
Other and unspecified urinary	-	-	3	4.29			-	-
Brain	25	12.76	4	6.18			-	-
Eye and central nervous system	-	-	-	-	0	0.60	-	-
Thyroid	-	-	2	0.43			-	-
Lympho- and reticulosarcoma	12	7.98	4	2.35	-	-	-	-
Hodgkin's disease	3	5.45	3	2.50			0	0.4
Leukemia	14	13.94	7	5.16	1	1.67	0	0.7
Multiple myeloma	11	8.37	2	2.35			-	-
Other lymphatic			-	-			-	-
Other	46	40.50	18	8.12	2	0.95	9	4.5
All cancers	383	341.73	235	228.60	20	16.37	30	21.1

[a] Observed deaths multiplied by 1.0674 and rounded off to the nearest integer to allow for deaths without discovered cause.

NUMBERS OF DEATHS FROM NONMALIGNANT AND ALL CAUSES REPORTED IN THE FOUR PRINCIPAL STUDIES (O = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS)

Type of Class of Cancer	United States		United Kingdom		Canada		Italy	
	O[a]	E	O	E	O	E	O	E
Ischemic heart disease	521	597.73	276	288	25	31.67	19	27.4
Other circulatory disease	157	123.55	105	141				
Bronchitis[b]	44	22.83	36	44				
Pneumonia	16	31.94	40	61	6	3.21	3	5.0
Other respiratory disease	15	32.84						
Cirrhosis of the liver	37	56.06	5	5	4[c]	3.85	4	5.2
Other digestive disease	27	39.52	-	-			3	2.7
Other diseases	67	115.68	43	76	2[d]	5.40	2	7.0
All nonmalignant causes	1153	1363.54	545	665	36	54.76	36	56.4
All causes	1536	1705.27	894	894	59	71.07	6	77.5

[a] Observed deaths multiplied by 1.0674 and rounded off to the nearest integer to allow for deaths without discovered cause.
[b] Emphysema in data from the United States.
[c] Includes two cases certified as cirrhosis of the liver which proved to be angiosarcoma of the liver.
[d] Includes one case with cause unknown.

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MORTALITY FROM VARIOUS CANCERS AMONG VINYL CHLORIDE WORKERS IN 49 PLANTS IN THE FOUR PRINCIPAL STUDIES COMBINED

(O = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS, SMR = STANDARDIZED MORTALITY RATIO))

Type or Class of Cancer	O	E	SMR
Mouth and pharynx	18	16.57	109
Digestive system (other than liver)	125	154.59	81
Respiratory system	223	229.36	97
Lung	211	214.09	99
Genitourinary system	70	62.81	111
Melanoma	2	1.94	-
Brain	29	19.54	148
Thyroid	2	0.43	-
Lymphatic and hematopoietic system	57	50.87	112
Other	83	63.24	131
All other than of the liver	609	599.35	102

MORTALITY FROM CANCER OF THE LIVER AND OTHER CAUSES AMONG VINYL CHLORIDE WORKERS IN 49 PLANTS IN THE FOUR PRINCIPAL STUDIES COMBINED

(0 = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS, SMR = STANDARDIZED MORTALITY RATIO))

Cause of death	O	E	SMR
Cancer of the liver [a]	59	8.45	698
Cancer of other sites	609	599.35	102
Other diseases	1547	1844.89	84
Accidents, poisonings, and violence	226	295.15	77
All causes	2441	2747.84	89

[a] Including cancers of the gallbladder in the series from the United States.

MORTALITY FROM SELECTED NONMALIGNANT CAUSES AND ALL CAUSES IN THE FOUR PRINCIPAL STUDIES COMBINED

(0 = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS, SMR = STANDARDIZED MORTALITY RATIO))

Type of Disease	O	E	SMR	Source of Information [a]
Bronchitis, emphysema	80	66.83	120	1, 2
Other respiratory disease	71	125.78	56	1, 2
All respiratory disease	160	200.82	80	1, 2, 3, 4,
Ischemic heart disease	797	885.73	90	1, 2
Other circulatory disease	252	264.55	95	1, 2
All circulatory disease	1103	1209.35	91	1, 2, 3, 4
Cirrhosis of the liver	46	66.26	69	1, 2, 4
Other disease	238	368.07	65	1, 2, 3, 4
All nonmalignant disease	1547	1844.50	84	1, 2, 3, 4
All external causes	226	295.15	77	1, 2, 3, 4
All nonmalignant causes	1773	2139.65	85	1, 2, 3, 4
All causes	2441	2747.85	89	1, 2, 3, 4

[a] 1 = United States study, 2 = United Kingdom study, 3 = Canadian study, and 4 = Italian study.
[b] Bronchitis in the United Kingdom study, emphysema in the United States study.
[c] Includes cerebrovascular disease in the United Kingdom and Italian studies.

MORTALITY FROM LUNG CANCER IN THE SERIES FROM THE UNITED STATES (US) AND THE UNITED KINGDOM (UK) BY CHARACTERISTICS RELEVANT TO AN OCCUPATIONAL HAZARD

(O = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS, SMR = STANDARDIZED MORTALITY RATIO))

Data Characteristic [a]	Category 1			Category 2		
	O [b]	E	SMR	O [b]	E	SMR
Observed 20 years or more after first employment (1), others (2)	114	113.96	100	85	93.83	91
Employed 10 years or more in the US (1), others in the US (2)	55	52.45	105	63	63.44	99
Employed before 1956 in the UK (1), others in the UK (2)	52	51.39	101	29	40.50	72
Ever employed as autoclave worker in the UK (1), others in the UK (2)	16	17.08	94	65	74.82	87

[a] The numbers in parentheses designate the category.
[b] Expected numbers are based on calendar time and age-specific mortality rates of U.S. white men.

MORTALITY FROM CHRONIC OBSTRUCTIVE LUNG DISEASE[a] IN THE SERIES FROM THE UNITED STATES AND THE UNITED KINGDOM BY CHARACTERISTICS RELEVANT TO AN OCCUPATIONAL HAZARD

(0 = OBSERVED NUMBER OF DEATHS, E = NUMBER OF DEATHS, SMR = STANDARDIZED MORTALITY RATIO))

Data Characteristic[b]	Category 1			Category 2		
	O	E	SMR	O	E	SMR
Observed 20 years or more after first employment (1), others (2)	30	15.8	190	11	7.0	157
Employed 10 years or more in the US (1), others in the US (2)	16	10.9	147	25	12.0	208
Employed before 1956 in the UK (1), others in the UK (2)	26	30.17	86	10	13.60	74
Ever employed as autoclave worker in the UK (1), others in the UK (2)[c]	3	6.55	46	33	37.22	89

[a] Described as emphysema in the US study and as bronchitis in the United Kingdom study.
[b] The numbers in parentheses designate the category.
[c] Men ever employed as a bagger or drier, occupations which would have caused the greatest occupational exposure to polyvinyl chloride dust, experienced one death from bronchitis against 4.98 expected.

CALCULATION OF RISK

Calculations based on the amount of material metabolized on human data have produced exposure values of about 1 ppm for a 10^{-6} lifetime risk.

CALCULATION OF RISK

Studies of the quantitative aspect of VCM metabolism have shown that there is a dose dependency in the rate of metabolism.

As the dose of VCM increases, the proportion exhaled increases and that excreted in the urine and feces decreases.

CALCULATION OF RISK

In rats, VCM has been shown to be metabolized extensively. The highly reactive intermediate in the metabolic process, chloroethylene oxide, reacts with cellular macromolecules, including DNA to produce the actural lesions leading to mutations/induction of cancer.

CALCULATION OF RISK

Estimation of the exposure levels likely to cause a lifetime risk of ASL of 10^{-6} on laboratory date may range as low as 3.9×10^{-7} ppb (Multi-hit) or as high as 1400 ppb (log-probit). Reasons for this variability include: 1) rate of VCM conversion is limited at high levels of exposures giving inaccurate estimates of the slope of the dose response-relationships; 2) has not been able to estimate the rate of conversion in man; 3) variability of subsets of experimental data used on mathematical models; 4) various differences in assumptions of mathematical models and 5) assumptions used in applying the models.

CALCULATION OF RISK

Although there was considerable variability in the dose-response relationship in the different experiments reported, in all cases a total metabolized dose equivalent to an inhalation of 200 ppm was required to produce an elevation in ASL incidence.

R&S 027736

HOW MANY MORE ASL CASES ARE EXPECTED TO DEVELOP WORLDWIDE DUE TO VCM EXPOSURE IN NEXT 30 YEARS?

	Estimated New Cases
Forman et al	200-250
Purchase et al	150-350
Nicholson	1500

There has not been a reported death of angiosarcoma of the liver for any Dow employee or employee of a Louisiana chemical plant.

VCM
OCCUPATIONAL STUDY CONCLUSIONS

VCM caused angiosarcoma of the liver in occupations which had high exposures prior to 1974.

Cancer

Sir Richard Doll (1988), "There is too little evidence to confirm or refute the suggestion that vinyl chloride might cause melanoma or cancers of the thyroid, brain, and lymphatic and hematopoietic systems. None of the small excesses that have been recorded point specifically to an occupational hazard . . . and most are likely to be the sort of chance effect that is certain to be observed when many types of cancers are examined in many different studies.

VCM
OCCUPATIONAL STUDY CONCLUSIONS

Sir Richard Doll (1988, continued), "The combined data for the mortality from respiratory cancer fall, at first sight, to support the hypothesis regarding lung cancer (SMR 97). Higher ratios for lung cancer have, however, been observed consistently in the subgroups in which the effect of an occupational hazard would be most likely seen (that is, men employed for more than 10 years, exposed to higher than average concentrations, or observed more than 20 years after first exposure). In two of the supplementary studies, it was also noted that the mortality from lung cancer was specifically increased among the most heavily exposed workers."

VINYL CHLORIDE COMMUNITY HEALTH CONCLUSIONS

Sir Richard Doll (1988), "A very small risk of angiosarcoma may have occurred as a result of vinyl chloride escaping into the environment around plants handling vinyl chloride in the past, but the evidence indicates that the current risk to the general public (if any) must be negligible."

VCM
OCCUPATIONAL STUDY CONCLUSIONS

Jones et al (British study, 1988), "This study does not offer any anecdotal or statistical evidence for an association between brain cancer and VCM exposure."

Jones et al (1988), "The results of the study do not demonstrate any association between VCM and lung cancer deaths."

Wu et al (NIOSH, 1989), "Our data do not support the hypothesis the excess risk of lung cancer and brain cancer which had been observed at this plant is associated with exposure to either VCM or PVC dust. The lack of significant findings in the cohort analyses for these two cancers was further supported by the lack of a dose response in the case-control studies for exposure to either VCM or PVC dust.

VCM
OCCUPATIONAL STUDY CONCLUSIONS

Purchase et al (1987), "For brain cancer the association between exposure to VCM and an increased incidence was less clear because of the lower relative risk. Neoplasms of the respiratory tract, digestive system, lymphatic and hematopoietic system, buccal cavity and pharynx, cardiovascular system and colon/stomach were reported to show an increased incidence in one or more studies, but to show no increase, or in some cases a decrease, in incidence in other studies."

VCM
OCCUPATIONAL STUDY CONCLUSIONS

Wong et al (1987), "Contrary to our observation on liver cancer, a higher brain cancer mortality risk was found among those who were exposed after age 35 and who were exposed in or after 1960 than those who were exposed before 1960 and at a younger age. Based on the limited exposure information available in this mortality study, the implication of this difference in risk profile is not clear at this point."

"For the entire cohort, 115 deaths were due to cancer of the respiratory system, compared to 122.25 expected. The corresponding SMR was 94.5. Our study, at the 0.05 significance level, has 80% statistical power to detect an SMR for cancer of the respiratory system as small as 124. Therefore, we can conclude that our study has clearly demonstrated that there is no relationship between occupational exposure to vinyl chloride and cancer of the respiratory system."

VCM
OCCUPATIONAL STUDY CONCLUSIONS

Wong et al (1987), "In our study, 37 deaths were due to lymphatic and hematopoietic cancer, compared to 36.28 expected. The corresponding SMR was 102.0. Our study, at the 0.05 significance level, has 80% power to detect an SMR for lymphatic and hematopoietic cancer as small as 145. Therefore, our study has adequate power to detect an increased risk in lymphatic and hematopoietic cancer as small as 45%. Since we did not see any excess in the cohort as a whole or in any other specific analysis by length of exposure or latency, we conclude that there is no relationship between occupational exposure to vinyl chloride and an increased risk of lymphatic and hematopoietic cancer.

MISCARRIAGES

AND

BIRTH DEFECTS

R&S 027746

INFANTE ET AL 1976 STUDY
MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C. EXPOSURE

	Controls	Primary VCM Exposure
Prior to husband's exposure:		
Number of families	95	70
Mean paternal age at conception (yr.)	23.0	26.4
Number of fetal deaths among wives	11	15
Number of pregnancies	159	148
Age-adjusted fetal deaths/100 pregnancies	6.9	6.1
Subsequent to husband's exposure:		
Number of families	113	62
Mean paternal age at conception (yr.)	30.4	30.2
Number of fetal deaths among wives	24	23
Number of pregnancies	273	139
Age-adjusted fetal deaths/100 pregnancies	8.8	15.8

R&S 027747

INFANTE ET AL 1976 STUDY
MEAN PATERNAL AGE, NUMBER OF PREGNANCIES, AND FETAL DEATH-RATES ACCORDING TO HUSBAND'S V.C. EXPOSURE EXCLUDING PREGNANCIES OF WOMEN WITH >3 FETAL DEATHS

	Controls	Primary VCM Exposure
Prior to husband's exposure:		
Mean paternal age at conception (yr.)	23.0	26.3
Number of fetal deaths among wives	11	9
Number of pregnancies	159	141
Age-adjusted fetal deaths/100 pregnancies	6.9	3.1
Subsequent to husband's exposure:		
Mean paternal age at conception (yr.)	30.2	30.8
Number of fetal deaths among wives	18	14
Number of pregnancies	265	120
Age-adjusted fetal deaths/100 pregnancies	6.8	10.8

INFANTE ET AL 1976 STUDY
PATERNAL AGE DISTRIBUTION FOR FETAL DEATHS ACCORDING TO HUSBAND'S V.C. EXPOSURE

	Controls			Primary exposure		
Paternal age (yr)	Pregnancies	Fetal deaths		Pregnancies	Fetal deaths	
Before exposure:						
<20	31	2	(6.5%)	7	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		27	5	(18.5%)
>35	4	0		14	1	
All ages, crude rate	159	11	(6.9%)	148	15	(10.1%)
Mean paternal age at conception	23.0 yr.	-		26.4 yr.	-	
Age-adjusted rate*	-	-				(6.1%)
After exposure:						
<20	1	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	30.4 yr.	-		30.2 yr.	-	
Age-adjusted rate*	-	-	(8.8%)	-	-	(15.8%)

* Fetal mortality-rates for primary V.C. exposure group are direct age adjusted to the paternal age distribution of the pregnancies in the control group.

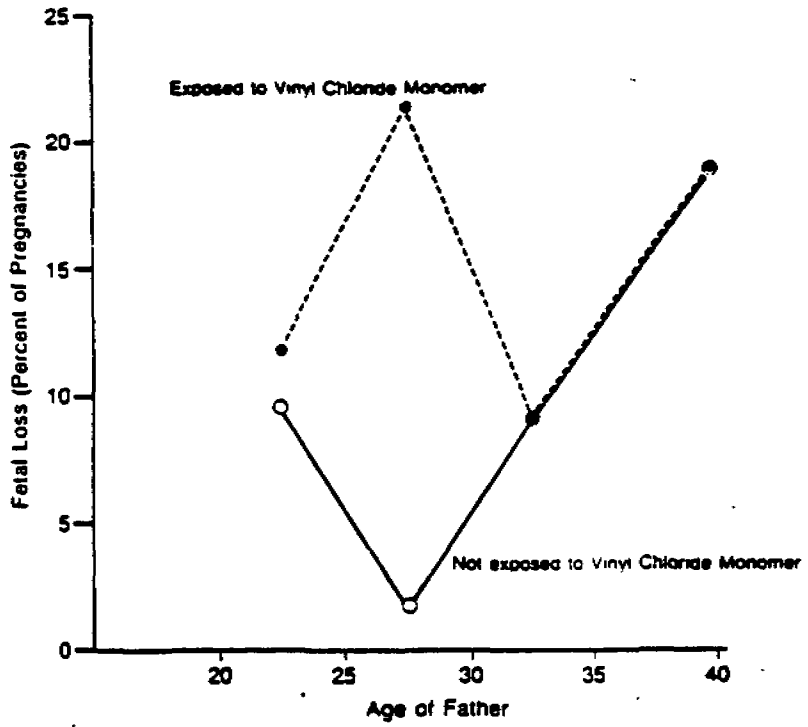

FIG. 1. Fetal deaths according to paternal age for men exposed and not exposed to vinyl chloride monomer [adapted from Ref. (6)].

VCM REPRODUCTIVE TOXICOLOGY

Animal studies have shown that exposure to high levels of VCM during pregnancy resulted more often in high rates of fetal loss and miscarriage than in birth defects.

COMMENTS REGARDING THE INFANTE ET AL (NIOSH) STUDY

(late) Reuel Stillones (Dean - Public Health - Univ. of Texas)

"The problem may be viewed in different ways, but no matter how it is viewed, that analyses is wrong, for it implies that the hazard affects the entire age span, and it intentionally dilutes the strong association in persons ages 25-29 with the zero associations in the other age groups."

R&S 027752

COMMENTS REGARDING THE INFANTE ET AL (NIOSH) STUDY

David Schottenfeld (Dept. Chair - Epidemiology, Univ. of Mich.)

"While the authors felt that these observations were likely to reflect a real difference in pregnancy outcome not attributable to either interviewer or patient recall bias, the conclusions were based on indirect sources of information and could not take into account the multiplicity of material factors known to affect pregnancy outcome. The study design precluded documenting in even the crudest manner the validity of pregnancy histories. Without such adjustments and validation, the inferences made by Infante and colleagues cannot be sustained and little light is shed on the possible association of abnormal pregnancy outcome with paternal occupational exposure to VCM."

R&S 027753

THERIAULT ET AL 1983 STUDY
BIRTH DEFECT STUDY
SHAWINIGAN, CANADA

FOUR OBJECTIVES

1. Document birth-defect rate previously observed
2. Correlate monthly and seasonal variations of length defects with VCM in the environment
3. Correlate geographic variations in birth-defect rates with estimates of VCM in the air
4. Compare a group of parents who gave birth to malformed infants with a control group with respect to residential and occupational histories.

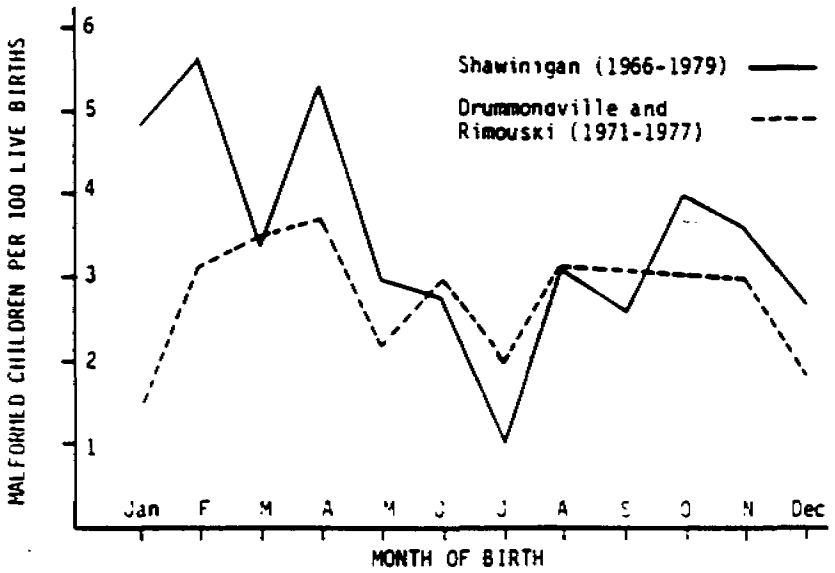

Fig. 1. Monthly distribution of birth-defect rates.

THERIAULT ET AL 1983 STUDY
COMPARISON OF TOTAL BIRTH DEFECTS AND CNS BIRTH DEFECTS BETWEEN SCHOOL DISTRICTS WITH HIGH AND LOW ATMOSPHERIC VINYL CHLORIDE CONCENTRATION

	School Districts With High VCM Levels	School Districts With Low VCM Levels	Total
Births with defects	87	70	157
Births without defects	2,285	2,125	4,410
Births with CNS defects	16	13	29
Births without CNS defects	2,356	2,182	4,538
Total births	2,372	2,195	4,567

R&S 027756

THERIAULT ET AL 1983 STUDY
DISTRIBUTION OF CASES AND CONTROLS BY DISEASES OF THE MOTHERS DURING PREGNANCY

Mother's Occupation	Before Pregnancy	During Pregnancy	Before Pregnancy	During Pregnancy
Work outside home without exposure to chemicals	41	22	42	20
Work in VCM industry	0	0	0	0
Work outside home with exposure to chemicals	2	1	2	1
Stay at home	25	45	24	47
Total	68	68	68	68

THERIAULT ET AL 1983 STUDY
DISTRIBUTION OF CASES AND CONTROLS BY FATHER'S OCCUPATION

Father's Occupation	Cases	Controls
Ever worked in vinyl chloride industry	0	0
Ever worked in industries with exposure to chemicals	20	25
Never worked in industries with exposure to chemicals	43	39
Unknown	5	4
Total	68	68

THERIAULT ET AL CONCLUSION

"We were unable to substantiate the presence of an association between VCM in the air and birth defects in the exposed community. In view of the high numbers of angiosarcoma of the liver observed among production workers and the possible large emissions of VCM, it can mean that such an association does not exist. It can also be the result of a small number of observations. The probability of finding an excess of birth defects in the highly exposed districts twice as high as in the poorly exposed ones was 80%. The probability would have been 99% had the excess been three times as high."

POLYNEUROPATHY

Vinyl chloride has not undergone scrutiny as a neurotoxic chemical. However, lifetime animal toxicology studies have not reported, on an incidental basis, polyneuropathy.