

Increased Mortality Odds Ratio of Male Liver Cancer in a Community Contaminated by Chlorinated Hydrocarbons in Groundwater

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Background



- **A former electronics factory, the R factory, was in operation from 1970 to 1992.**
- **In 1994, the Taiwan EPA declared it as a hazardous waste site because of soil & groundwater contamination.**

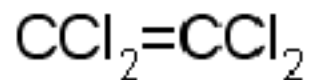
Disposal of waste solvents

- **Chlorinated** solvents as **degreasers**, including trichloroethylene (TCE), tetrachloroethylene (PCE), and 1,1,1-TCA.
- Dense non-aqueous phase liquids (**DNAPL**)

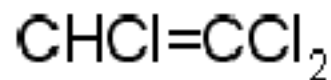


Major contaminants in the groundwater downstream of the R factory

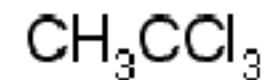
Tetrachloroethylene (PCE)



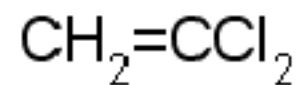
Trichloroethylene (TCE)



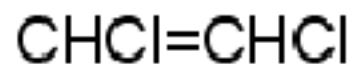
**1,1,1-Trichloroethane
(1,1,1-TCA)**



**1,1-Dichloroethylene
(1,1-DCE)**



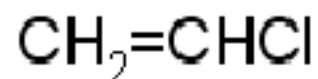
**cis-1,2-Dichloroethylene
(cis-1.2-DCE)**



**1,1-Dichloroethane
(1,1-DCA)**



Vinyl Chloride (VC)



Pit dug for washing underground soil and water



Clean up action



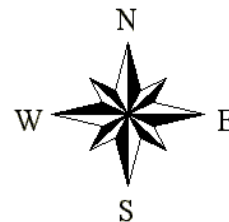
Objective

- to investigate the association between **cancer mortality** risk and exposure to **chlorinated hydrocarbons** in groundwater of a downstream community near the R factory

Methods: Epi Investigation

- **Death certificates** collected from two adjacent villages for 1966-97
 - Linkage with National Cancer Registry using identification number
- **Underlying cause of death** was coded without knowledge of exposure by nosologists using ICD-9
- **Cancer** as the diseases of interest **cardiovascular-cerebrovascular (CV-CB)** diseases as the reference diseases

Exposure Classification



Downstream village

groundwater flow direction

R factory

Provincial Route No. 1

Upstream village

PCE (ppb)

- ND (< 0.05)
- ◐ 0.05-5 (USEPA)
- ◑ 5-40 (WHO)
- 40-500
- 500-1000
- 1000 - 2500
- 2500 - 5500

road

200 0 200 400 600 800 1000 Meters

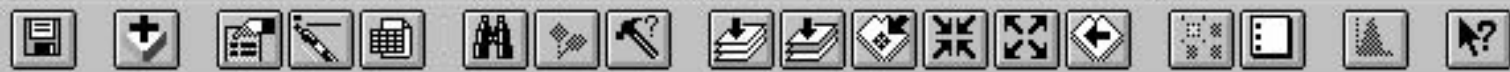


Concentrations & distribution of chlorinated hydrocarbons

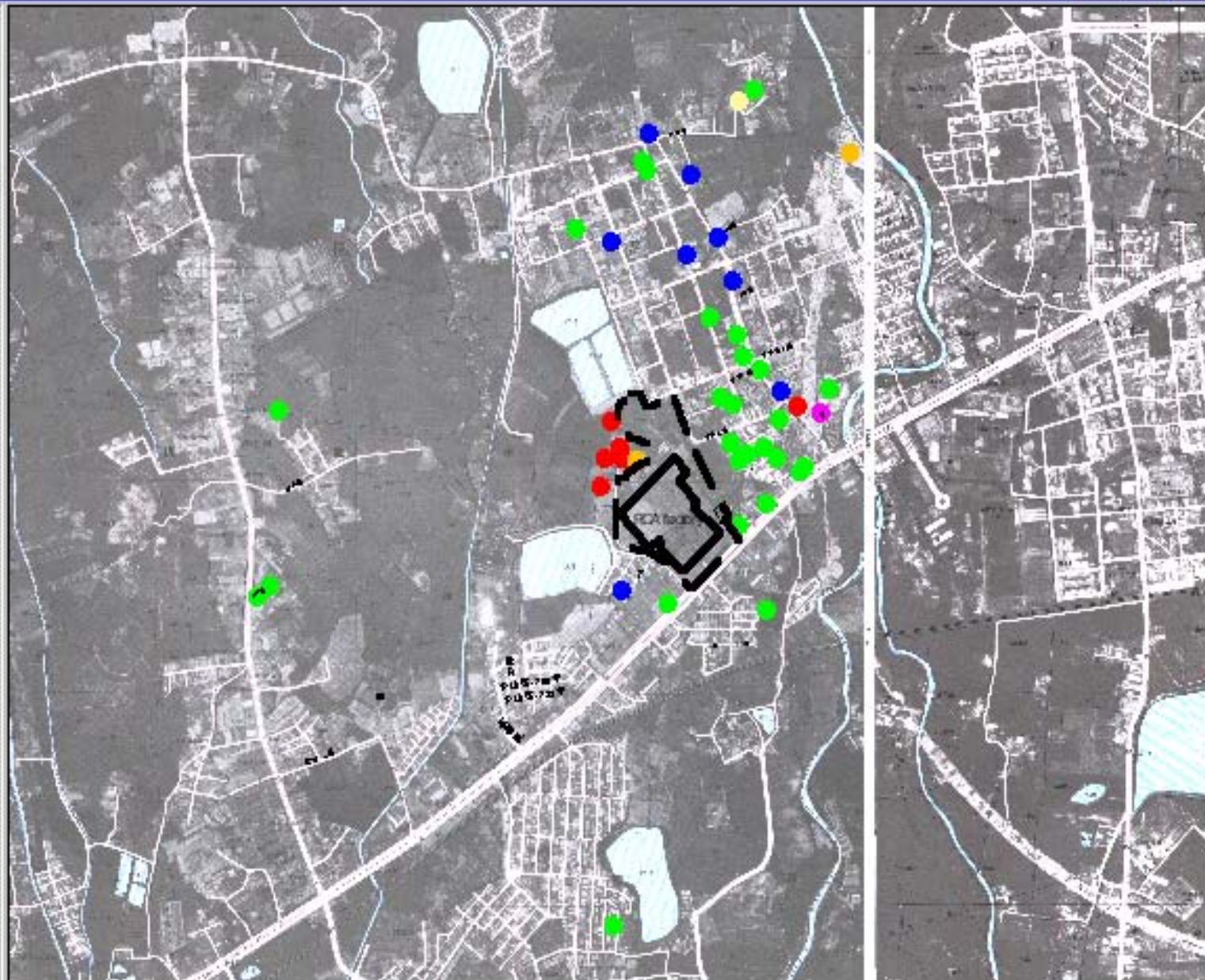
Chemicals	IARC Group	Downstream area (to the north of the Route No. 1 and the factory)		Upstream area	
		Well water concentration (N=44)		Well water concentration (N=2)	
		Median (range) (µg/L)	Percentage above MCL	Median (range) (µg/L)	Percentage above MCL
Vinyl chloride	1	0.003 (ND-72.3)	29.5%	ND	0
Tetrachloroethylene	2A	2.95 (ND-5228.3)	45.5%	0.05 (ND-0.1)	0
Trichloroethylene	2A	28.43 (ND-1790.7)	65.9%	0.1 (0.1-0.1)	0
1,1-Dichloroethylene	3	1.35 (ND-1240.4)	27.3%	ND	0
1,1,1-Trichloroethane	3	0.67 (ND-1504.4)	11.4%	ND	0
c-1,2-Dichloroethylene	NA	3.05 (ND-1376.0)	15.9%	ND	0
1,1-Dichloroethane	NA	1.81 (ND-227.9)	NA	0.05 (ND-0.1)	NA

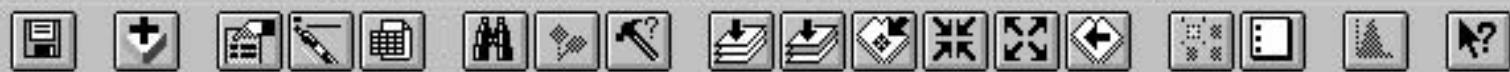
Exposure classification

- **Groundwater flow direction**
 - Towards the north & northeast in the first aquifer
- Classified as **exposed (downstream)** and **unexposed (upstream)**
- Verified with contaminant concentrations in **49** residential wells
- Location of residence on the death certificate – exposure status of each decedent



- TCE
 - ND - 5 (USEPA)
 - 5 - 70 (WHO)
 - 70 - 150
 - 150 - 500
 - 500 - 1000
 - 1000 - 5500
- PCE
 - ND - 5 (USEPA)
 - 5 - 40 (WHO)
 - 40 - 250
 - 250 - 1000
 - 1000 - 2000
 - 2000 - 5500
- c-1,2-DCE
 - 0.004 - 37.99
 - 37.99 - 112.8
 - 112.8 - 200.1
 - 200.1 - 378.5
 - 378.5 - 1376
- 1,1-DCE
 - 0.005 - 7 (USEPA)
 - 7 - 30 (WHO)
 - 30 - 300
 - 300 - 1000



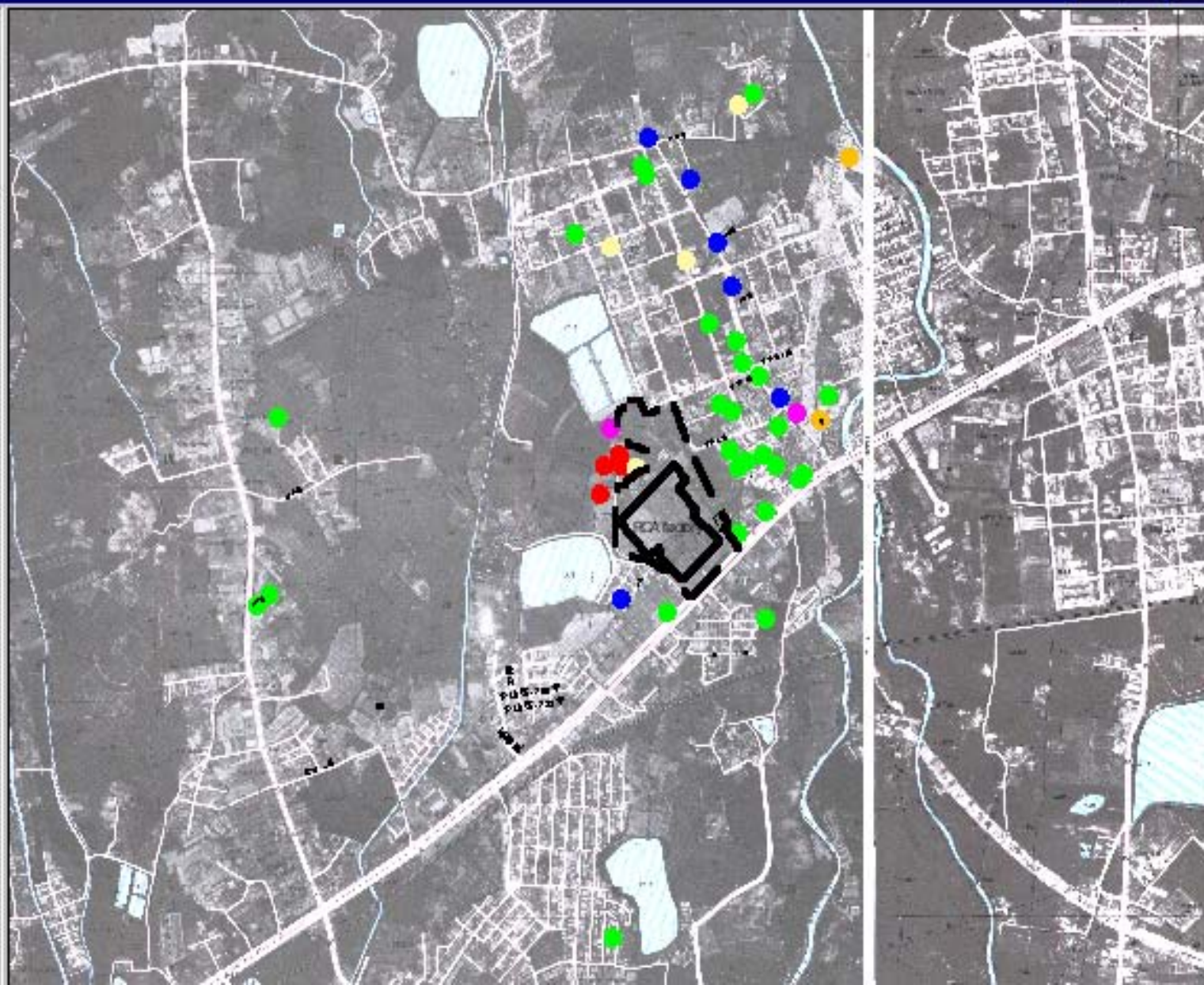


Scale 24,059

275,704.56
2,765,006.74

View1

- PCE
 - ND - 5 (USEPA)
 - 5 - 40 (WHO)
 - 40 - 250
 - 250 - 1000
 - 1000 - 2000
 - 2000 - 5500
- c-1,2-DCE
 - 0.004 - 37.99
 - 37.99 - 112.8
 - 112.8 - 200.1
 - 200.1 - 378.5
 - 378.5 - 1376
- 1,1-DCE
 - 0.005 - 7 (USEPA)
 - 7 - 30 (WHO)
 - 30 - 300
 - 300 - 1000
 - 1000 - 1300
- 1,1,1-TCA
 - 0 - 200
 - 200 - 400
 - 400 - 800
 - 800 - 1600
- PCE-0326.dta



$$\frac{a/c}{b/d} = \frac{a \times d}{b \times c}$$

Mortality Odds Ratio (MOR): a special case of case-control study

	Exposure (+)	Exposure (-)
Disease of interest	a	b
Reference disease	c	d

Person-years

N1

N0

- $MOR = ad/(bc)$
- Assumption: $c/N1 = d/N0$

MOR design

- Appropriate **reference diseases**
 - No causal association with exposure
 - Comparable mortality between exposed and unexposed populations
 - Select **CV-CB diseases**, excluding arrhythmia related deaths
 - All **non-cancer diseases** as alternative choices

Methods

- **MORs** for various kinds of cancers after stratified by gender, age, and calendar period
 - Period: 1966-75 (historical control), 1976-85, 1986-97, test for time trend
 - Age: <30, 30-49, 50-69, >70
- Summary Odds Ratio controlling for age with **Mantel-Haenszel method**
- **Multiple logistic regressions** adjusted for age and period

MOR for liver cancer vs. CV-CB or Non-cancer diseases

Gender	Cause of death	1966-79			1980-89			1990-97		
		E(+)	E(-)	MOR‡ (95% CI)	E(+)	E(-)	MOR (95% CI)	E(+)	E(-)	MOR (95% CI)
Male†	Liver cancer	3	3	0.82 (0.15 to 4.44)	13	6	3.19 (0.99 to 10.32)	10	7	3.34 (1.00 to 11.13)
	CV-CB diseases*	30	22		25	36		19	34	
	Non-cancer diseases	104	56	0.59 (0.12 to 2.88)	104	86	1.78 (0.64 to 4.94)	67	97	2.33 (0.84 to 6.50)
Female	Liver cancer	0	1	-	1	2	1.02	3	2	2.09 (0.35 to 12.59)
	CV-CB diseases*	25	18		28	21		13	15	
	Non-cancer diseases	53	40	-	62	41	0.64 (0.06 to 6.56)	45	45	1.96 (0.33 to 11.50)

Increased MOR of male liver cancer

Adjusted MOR (95% CI) for cancer in men by residential area and time period

Cause of death (ICD-9)	Residential area		Period of death		
	Upstream village	Downstream village	1966-79	1980-89	1990-97
All cancer (140-208)	1	2.07 (1.31-3.27)	1	1.93 (1.08-3.46)	2.26 (1.24-4.13)
Liver cancer (155)	1	2.57 (1.21-5.46)	1	3.96 (1.36-11.51)	4.17 (1.41-12.38)
Stomach cancer (151)	1	2.18 (0.97-4.89)	1	1.43 (0.52-6.87)	1.66 (0.59-4.69)
Colorectal cancer (153-154)	1	0.83 (0.24-2.89)	1	0.64 (0.12-3.28)	1.24 (0.29-5.30)
Lung cancer (162)	1	1.75 (0.79-3.89)	1	3.66 (1.12-11.96)	3.01 (0.87-10.46)

Discussion (1): Main findings

- **Significant period effect in the downstream village**
- **Neighboring communities: similar socioeconomic characteristics**
 - % high education & white collar workers--
downstream > upstream (**less likely to be exposed to occupational carcinogens**)
- **BUT not all potential confounders could be controlled, because**
 - Limited data on death certificates

Discussion (2): Biological plausibility

- **Supportive evidence from health risk assessment : (Lee et al., J Toxicol Environ Health 2002;65:219-35)**
 - **Corroborated evidence from animal study on ICR mice exposed to mixture of halogenated hydrocarbons:**
 - Hepatocellular neoplasm in male ↑**
 - Mammary adenocarcinoma in female ↑**
- (Wang FI, et al., J Toxicol Environ Health 2002;65:279-91)**

Estimates of Exposure and Cancer Risk

Route	Chemicals	Lifetime intake (mg/kg-day)	Slope factor (mg/kg-day) ⁻¹	Source	Cancer risk
Dermal absorption	VC	2.67E-06	7.20E-01	IRIS (2000)	1.92E-06
	PCE	2.05E-03	5.20E-02	NCEA (1995)	1.07E-04
	TCE	3.11E-04	7.33E-02	NCEA (1995)	2.28E-05
Inhalation	VC	4.19E-04	1.54E-02	IRIS (2000)	6.45E-06
	PCE	4.25E-02	2.00E-03	NCEA (1995)	8.50E-05
	TCE	1.93E-02	6.00E-03	NCEA (1995)	1.16E-04
Risk estimates			VC (IARC 1)		8.4E-06
			PCE (IARC 2A)		1.9E-04
			TCE(IARC 2A)		1.4E-04

Discussion (3)

- **Chemical hepatocarcinogens may cause synergistic effect on hepatitis B carriers**
 - **Alcohol, Aflatoxins**
 - **Mixtures of chlorinated hydrocarbons?**
- **Persistent DNAPL pollution**
 - **Difficult to clean up**
 - **Proper precaution: life-cycle of a product's manufacturing**

Conclusion

- **Significant association between residence at a groundwater contaminated community and male liver cancer**
- **But limited by lack of individual information on groundwater exposure and potential confounders**
- **Biologically plausible from other evidence**

THANK YOU FOR YOUR ATTENTION

