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

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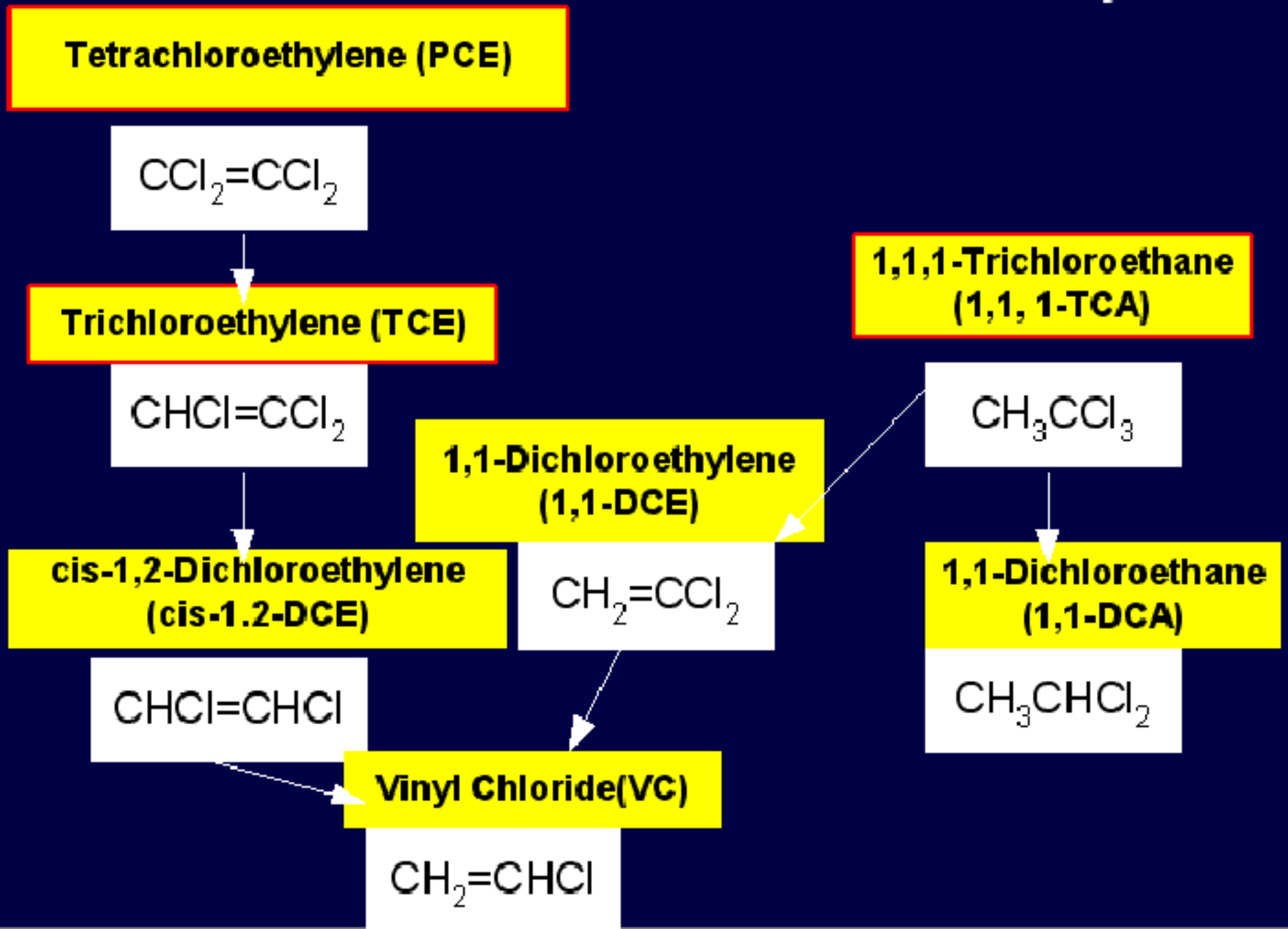
Background

- 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



Pit dug for washing underground soil and water

Clean up action

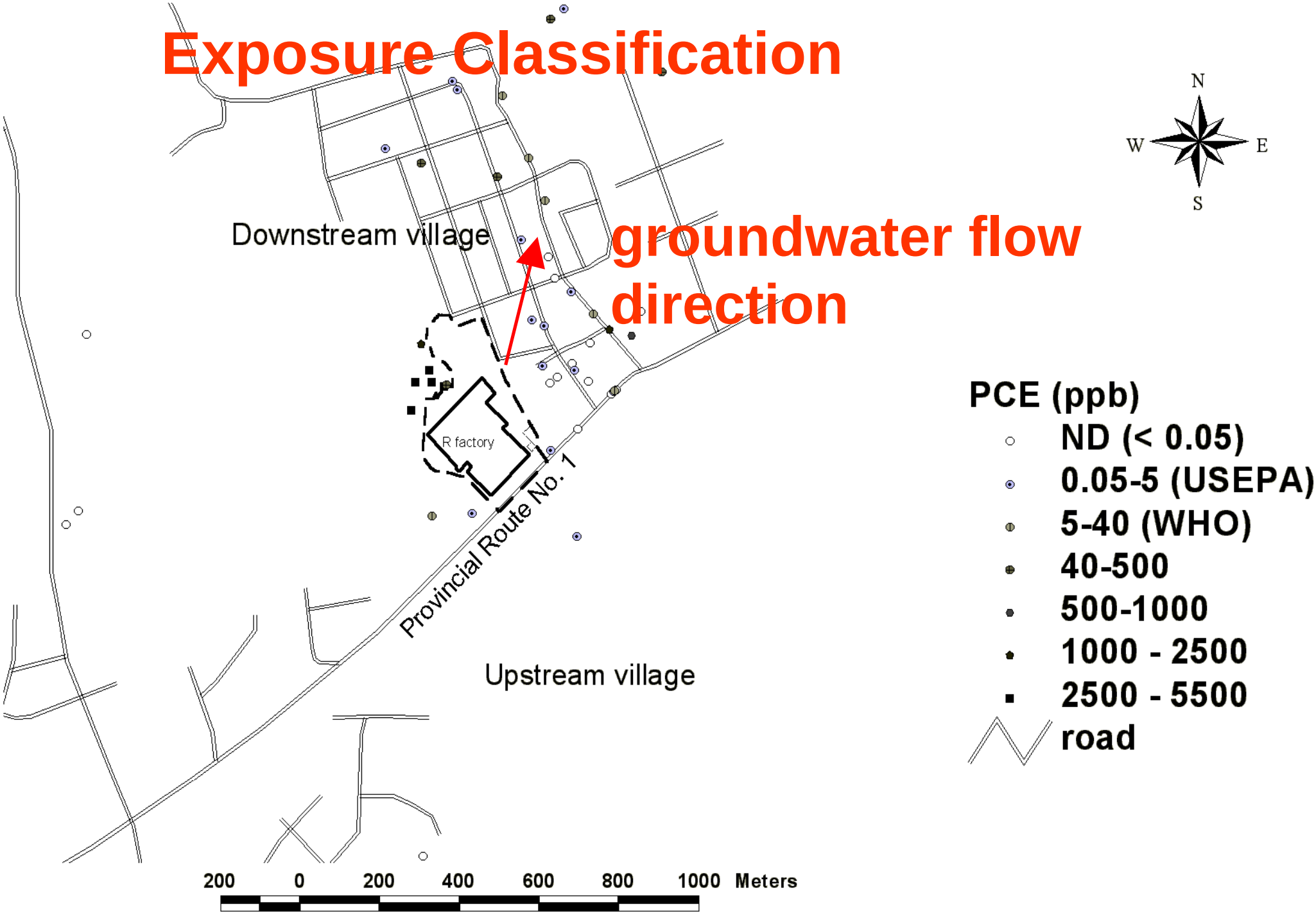
Objective

- 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

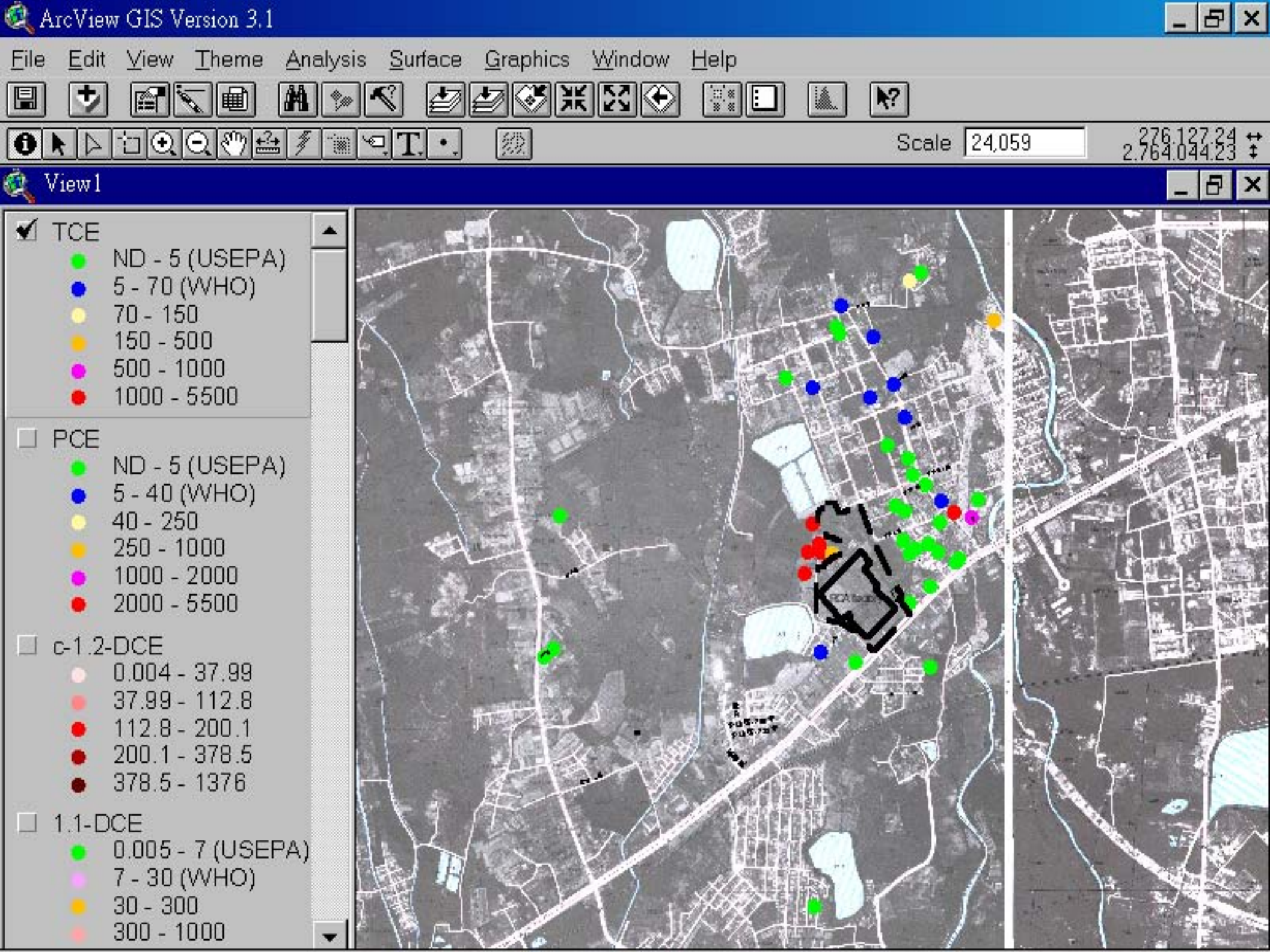


Concentrations & distribution of chlorinated hydrocarbons

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**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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
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7 - 30 (WHO)
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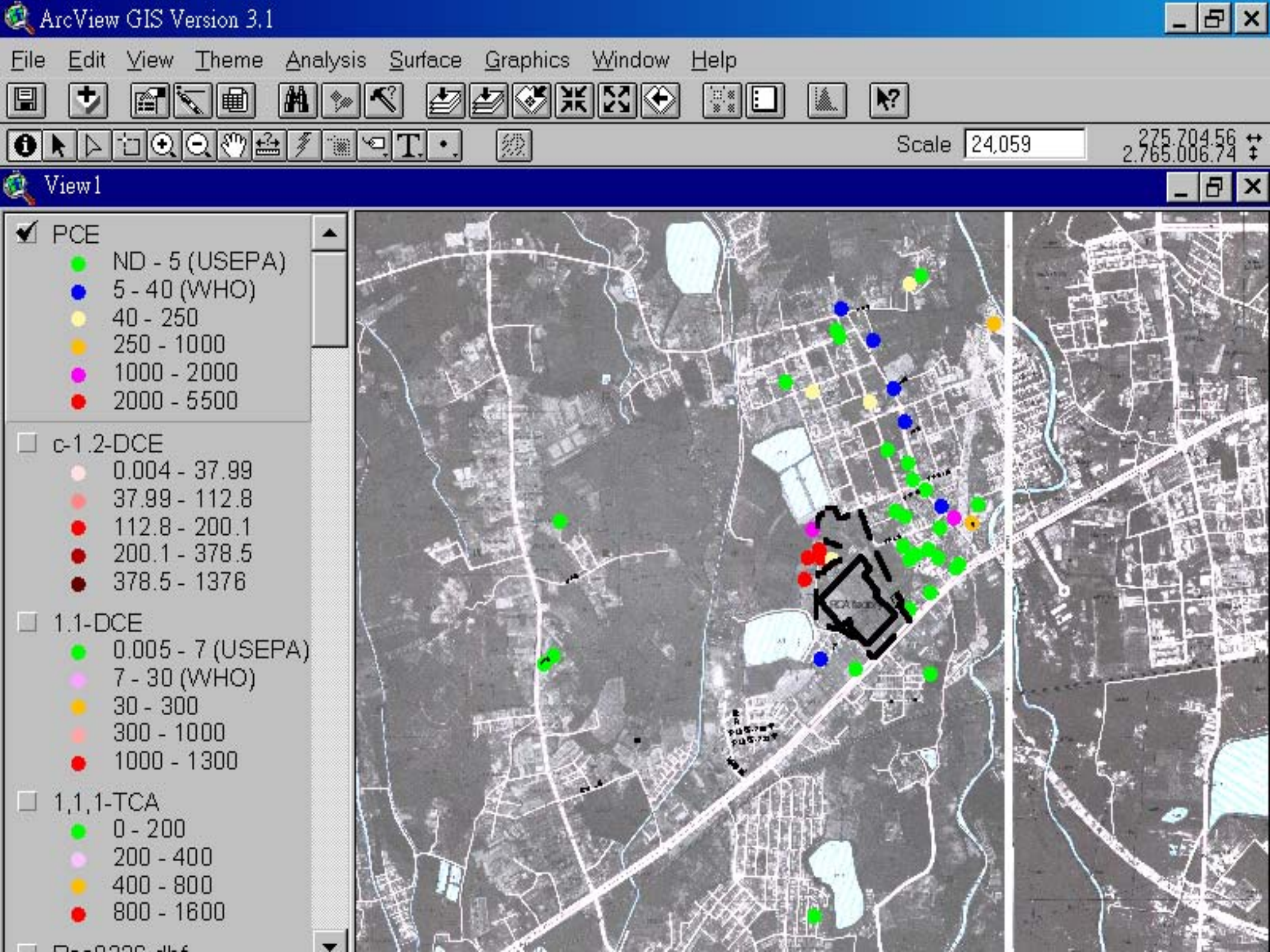
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37.99 - 112.8
112.8 - 200.1
200.1 - 378.5
378.5 - 1376
1,1-DCE
0.005 - 7 (USEPA)
7 - 30 (WHO)
30 - 300
300 - 1000
1000 - 1300
1,1,1-TCA
0 - 200
200 - 400
400 - 800
800 - 1600

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

		1966–79			1980–89			1990–97		
Gender	Cause of death	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 synergisitc effect on hepatitis B carriers
  - Alchocol, 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