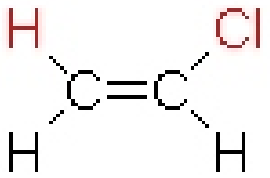
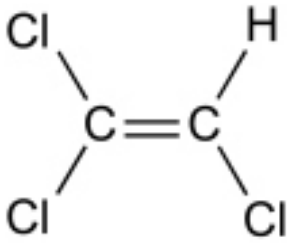
Two examples (1 cause-and-effect; 1 [almost certainly] coincidence):

1. **Vinyl chloride** at B.F. Goodrich plant, Louisville, Kentucky and **liver cancer** (angiosarcoma of the liver)



2. **Trichloroethylene** in East Woburn, MA, and **childhood leukemia** (as in, *A Civil Action*)



How / why are people exposed to *vinyl chloride*?

Vinyl chloride (monomer) is polymerized to make polyvinyl chloride (PVC) polymer.
Commercial production began in the **1930's**.
Worldwide production is enormous:
currently ~ **18 million tons** annually.

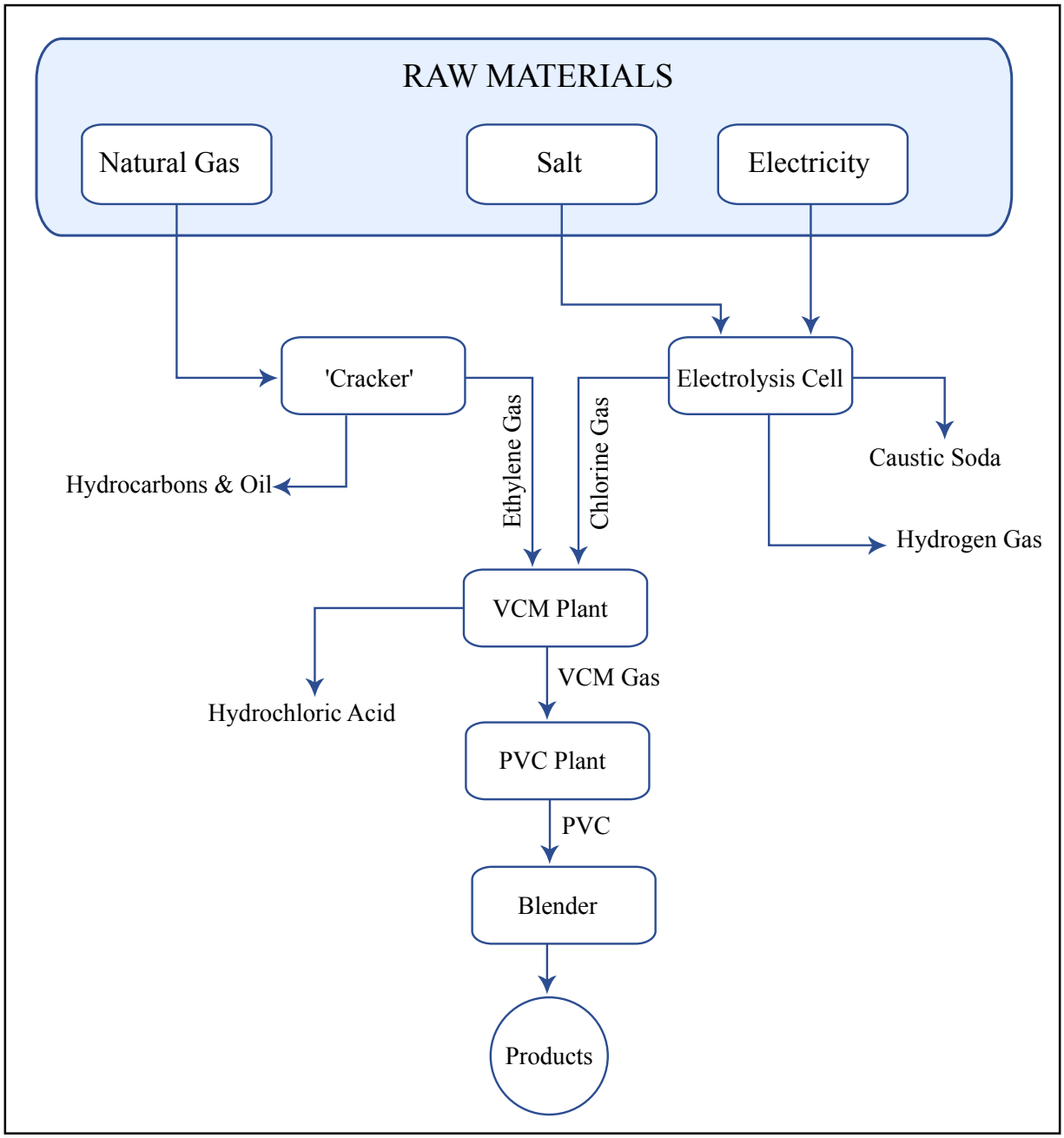


Figure by MIT OCW.

Properties of vinyl chloride: Colorless gas; sweet odor.
*No obvious **acute** toxicity* from early occupational exposures.

Early occupational guideline for allowable exposures (pre-OSHA):
1961: American Council of Government and Industrial Hygienists (ACGIH): TLV of 500 parts per million (ppm, v/v), 8-hr. TWA. Basis?

Research at Dow Chemical (Torkelson *et al.*, **1961**): rodents develop **liver and kidney** toxicity following exposure to 500 ppm;
NOAEL = 50 ppm. Recommend reduction in TLV to 50 ppm. Little action taken.

Mid-1960's: **Acroosteolysis** appears in some Goodrich workers (**bone** erosion at fingertips). Noticed by plant's occupational physician, John Creech, M.D. (1967). Workers were screened and their hands x-rayed. Some changes made in work procedures (at least at Goodrich) to reduce exposures.

Cancer case reports:
1971: one BF Goodrich (Louisville, KY) VCM worker dies of angiosarcoma of the liver (ASL; rare form of cancer: only about 25 cases per year in U.S. expected).
1973: a second BF Goodrich worker dies of ASL, and another worker is diagnosed with ASL.
Search of company death certificates: a 4th case may have occurred in 1968. (Creech and Johnson [Goodrich's company docs], 1974).
Total workforce at this plant ~ 300.

Case reports of Angiosarcoma of the Liver among Polyvinyl Chloride Workers B.F. Goodrich Plant, Louisville, Kentucky

		Dates of:			
Case	**Age at illness onset**	**Illness onset**	**Diagnosis**	**Death**	**Years worked with vinyl chloride before illness**
1	**43**	Aug. 1967	Sept. 1967	Jan. 7, 1968	**17**
2	**36**	Jan. 1970	May 1970	Sept. 27, 1971	**14**
3	**41**	Jan. 1964	Mar. 1973	Mar. 3, 1973	**14**
4	**58**	July 1973	Dec. 1973	Dec. 19, 1973	**27**

Bioassays in lab rodents (Italian researchers):

Rats exposed to **30,000 ppm** VCM develop various tumors (but not ASL: Viola; 1971).

Rats, mice, and hamsters exposed to VCM all develop some ASL and other tumors (**Maltoni, early-mid-1970's**)

Rat exposure-response data (Maltoni, 1977)*

			Number of Animals with Tumors	
Groups	**Concentration of vinyl chloride, ppm**	**No. of Animals (Sprague-Dawley rats)**	**Liver Angiosarcomas**	**Nephroblastomas**
I	**200**	120	**12**	**3**
II	**150**	120	**5**	**7**
III	**100**	120	**1**	**10**
IV	controls	120	0	0

*Exposure by inhalation to vinyl chloride in air, at 200, 150, 100 ppm. 4 hr/day, 5 days/week, for 52 weeks (half-lifetime). (Results after 143 weeks = end of the experiments.)

Regulatory responses

Spring 1974: OSHA PEL (which had been **500 ppm**) reduced to an "emergency temporary standard" (ETS) of **50 ppm**, and extensive air monitoring and respiratory protection mandated; ETS superseded within months (January 1, 1975) by a permanent standard of **1 ppm**.

Industry responses:
Ruling challenged in court -- claimed that PEL was infeasible and exorbitantly expensive (Court disagreed: OHSA won). *But* also (1) Industry sponsored proper epidemiologic studies, (2) U.S.-European VCM-ASL registry established, and (3) Industry-based process engineers quickly re-engineered (enclosed) VC reactors; "hand cleaning" of reactors eliminated; worker exposures *substantially* reduced.

Epidemiologic studies: Early 1980's and 1990's.

Wong *et al.* (**1991**). ["An industry-wide epidemiologic study of vinyl chloride workers, **1942-1982**."] Studied a cohort of 10,173 men who had worked for at least one year in jobs involving exposure to vinyl chloride prior to 1 January 1973. Men employed at 37 plants in the U.S., belonging to 17 companies. A total of 1,536 deaths: 15 deaths from angiosarcoma.

Was industry too slow to respond? Or was it "just" a "different" era?

May 12, 1959

Mr. W. E. McCormick, Director
Department of Industrial Hygiene and Toxicology
The **B.F. Goodrich Company**
500 South Main Street
Akron, OH

Dear Bill:

This is in reply to your letter of May 4 inquiring about the toxicological information we might have on vinyl chloride.

Insofar as I am aware, there is **no good toxicological data in the literature of the chronic toxicity of vinyl chloride.** As you know, the Conference of Governmental Industrial Hygienists **has for some time been recommending a maximum average of 500 ppm**. This figure is based upon the **acute** data of Patty, *et al.* and, hence, can not be relied upon to strongly when considering chronic exposures. Some years ago, we prepared a little writeup assuming that this figure was alright and a copy of it is enclosed to show you what we have said. I have added my comments to it for your information. I should add that **in the last month we have been investigating vinyl chloride a bit and find it to be somewhat more toxic when given by repeated daily inhalations but it is too early yet to tell what vapor concentrations will be without adverse effect. We feel quite confident, however, that 500 ppm is going to produce rather appreciable injury when inhaled 7 hours a day, five days a week for an extended period.**

As you can appreciate, this opinion is not ready for dissemination yet and I would appreciate it if you would hold it in confidence but use it as you see fit in your own operations. When more data becomes available, I will try to remember to pass it on to you.

Best regards.

Sincerely yours,

V.K. Rowe
Biochemical Research Laboratory

Inter-Company Correspondence

Company: **Union Carbide Company** Location: Mellon Institute

To: Dr. T.W. Wale Date: **November 24, 1959**
Location: New York Office

Attention
Copy To: Dr. E.R. Weidlein, Jr.
Dr. A.W. Downes

Dear Tom:

You will recall that the current threshold limit for vinyl chloride is 500 ppm, **based largely on single guinea pig inhalation studies by the Bureau of Mines about 25 years ago**.

An off-the-record phone call from V.K. Rowe gives me incomplete data on their current repeated inhalation study. **Six months at 500, 200 and 100 ppm has not found a no-effect level. Even 100 ppm produced organ weight changes and gross pathology, with micropathology expected. Vinyl chloride monomer is more toxic than has been believed.** Rowe expects to get more information before he decides whether or not this has any bearing on the safety of packaging uses of vinyl resins.

Dow has been distributed at sales efforts saying chloroform is less toxic than carbon tet. They have completed six months inhalation and find chloroform like carbon tet. This means its threshold limit will be lowered, as I have suggested for years. It was originally set by analogy with carbon tet, and never lowered when that for carbon tet was reduced.

I suggest that these personal communications not be quoted until Dow publishes.

Very truly yours,

Henry F. Smyth, Jr.

What is ***A Civil Action*** about?

A. Contaminated drinking water (from municipal wells);

B. A (space-time) cluster of childhood cancer ("discovered" by a mom and minister); and

C. The scientific question, "Did A cause B?"

D. [Other questions: Are such scientific questions best answered *via* lawsuits? Is "justice" thereby served? Who contaminated the water? Is the cluster "statistically significant"? etc. . .]

From: Cutler JJ, Parker GS, Rosen S, Prenney B, Healey R, Caldwell GG. 1986. Childhood leukemia in Woburn, Massachusetts. *Public Health Rep*. 101(2):201-5.

"Possible associations between environmental hazards and the occurrence of childhood leukemia were investigated in Woburn, MA, for the period 1969-79. Residents [parents and a minister] of Woburn were concerned over what they perceived to be a large number of childhood leukemia cases . . . Many believed that the elevated rate of childhood leukemia was related to . . . two city water wells that had been closed in 1979 when they were found to be contaminated by organic chemicals. . . This investigation ***confirmed an increase in incidence*** which was distributed uniformly over the 11-year period. . . . While the contaminants of Wells G and H, which had been closed, are not known leukemogens, it is not possible to rule out exposure to this water as a factor, particularly in the eastern Woburn residents."

How sizable / significant was the increased rate? (MA Cancer Registry only established in 1982).

Standardized Incidence Ratios (SIRs) for Leukemia (all types)
by Sex in Woburn, Massachusetts
January 1969 - December 1983

Sex	Number **Observed**	Number **Expected**	Ratio	95% Confidence Limits*
Male	12	3.99	3.00	1.55, 5.25
Female	4	2.02	1.98	0.54, 5.07
Both	**19**	**6.01**	**3.16**	**1.90, 4.93**

* Fisher exact.

Number of Observed and Expected Cases of Luekemia (all types)
by Census Tract in Woburn, Massachusetts
January 1969 - December 1983

Number of Cases	Census Tract					
	3331	3332	3333	**3334**	**3335**	3336
Observed	4	0	1	**7**	**6**	1
Expected	1.08	0.82	0.75	**.92**	**1.46**	1.00
Poisson Probability	0.02	---	0.53	**5.0×10^{-5}**	**0.004**	0.74

From: Cutter (1984)

Who contaminated the well water in East Woburn?

Plaintiffs' view:

Map removed for copyright reasons.

G and H = Wells G and H

Red Dots = homes of plaintiffs (each with a case of pediatric cancer)

U = Unifirst [Dry-cleaned commercial uniforms, using perc]

C = Cryovac (W.R. **Grace**) [Manufactured food processing and packaging equipment, 1960-1988; used TCE]

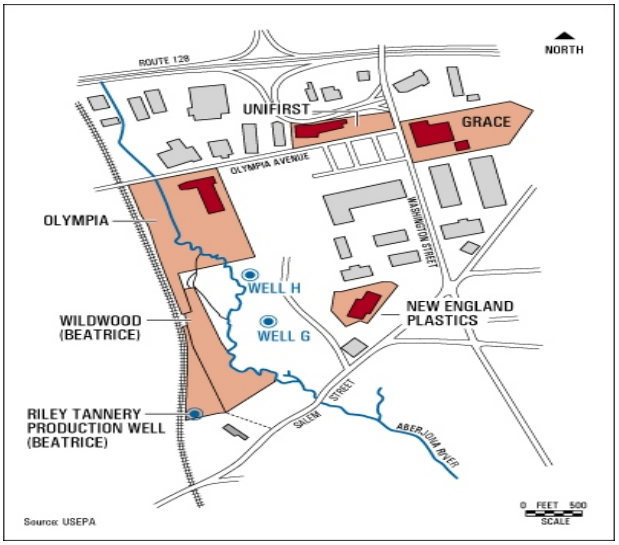
R = Riley Tannery [**1910-**1990's: property purchased by **Beatrice** Foods in 1978 (contamination discovered in 1979)]

Who contaminated the water?

Map removed for copyright reasons.

U.S. EPA view:

probably more complicated than this.



Courtesy of U.S. Environmental Protection Agency (EPA).

Woburn is an old city (**incorporated 1642**)

1800's: Manufacturing center, tanning leather, making shoes and boots.

1865: "Woburn was at the head of the tanning industry **in the country**."

1884: 26 large tanneries operating.

1901: Henry Thayer of Woburn originates chrome (Cr VI) tanning (replaces bark tanning)

By 1915: Some diversification: making ice cream, machine tools, mops, and paper boxes.

1920s: Groundwater wells for drinking water, the first in Massachusetts, began operating. [Eventually, 6 wells (A - F) drilled into the groundwater aquifer surrounding **Horn Pond** (**south-central** Woburn)]

Early 1960's: Population growing, water becoming scarce: city officials consider drilling wells in **groundwater-rich, swampy, industrialized East Woburn.**

1964: Drinking water Well G constructed (along the east floodplain of the Aberjona River)

1967: Well H constructed. Soon thereafter, recommendations to take wells G & H out of service due to bacterial contamination: heavily chlorinated instead. Resident: "The odor is almost like a clear bleach . . . ."

Early-mid 1970's: the State warns that water in Wells G & H is of poor quality, with elevated levels of nitrates, chlorides, sulfates, sodium, manganese, hardness, and elevated levels of carbon-chloroform extract [crude indication of organic contaminants]

1979: TCE and perc detected

What are our sources of drinking water in Massachusetts?

- Groundwater wells – public and private.
- Surface water – from reservoirs or rivers.

2004 Public Drinking Water System Reliance on Ground Water and Surface Water Sources in New England

	Ground Water		Surface Water	
State	Population	**% of Population**	Population	% of Population
Connecticut	462,052	17	2,231,612	83
Massachusetts	**2,065,285**	**43**	2,709,203	57
Maine	453,058	52	417,863	48
New Hampshire	595,129	56	474,976	44
Rhode Island	209,548	28	551,162	72
Vermont	345,659	56	266,510	44

What was the primary waterborne contaminant? (What about the *other* contaminants, chemical and microbiological . . .?)

Trichloroethylene (TCE)

Colorless, volatile liquid;
Versatile organic solvent
Reasonably chemically stable
Very low flammability: *no measurable flashpoint*
Not very toxic acutely; Not unpleasant odor

Widely used in industry (since about 1930)
metal cleaning / degreasing 55 %
chemical intermediate 41 %

Historically, use of TCE replaced use of CCl_4 and $CHCl_3$, which had replaced use of petroleum distillates.

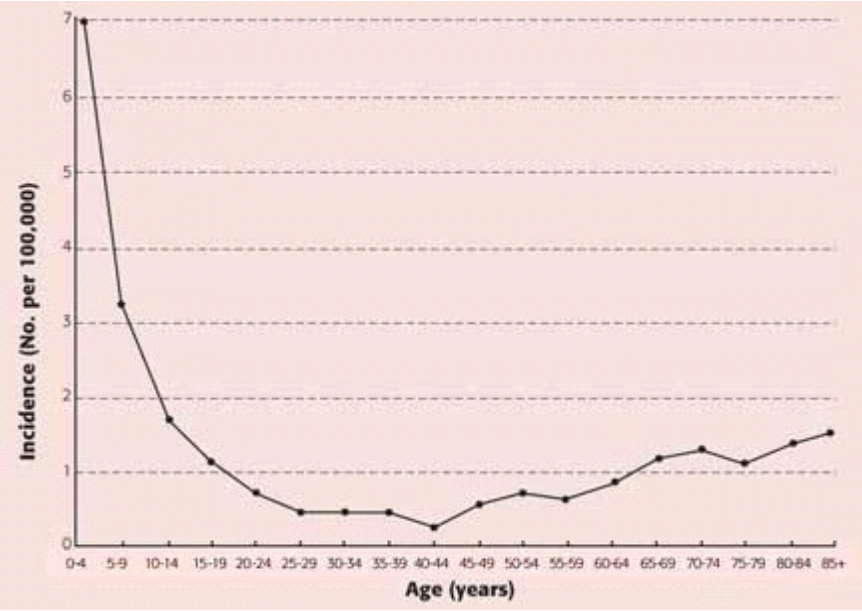
Concentration in Woburn water ≈ 260 µg / liter (260 ppb)
U.S. EPA "Maximum Contaminant Level" (MCL) = 5 ppb.
(TCE is a very common groundwater, hence drinking water, contaminant)

Does gross "exceedance" of MCL mean that children (fetuses) exposed to this water developed cancer as a result?

Leukemias: 4 basic types: lymphoid and myeloid (acute and chronic). All arise from cells in the **bone marrow** (soft inner part of some bones)

Three diagrams removed for copyright reasons.

What do we know about acute lymphoblastic leukemia (ALL)?



The horizontal axis shows 5-year age intervals. The vertical axis shows the frequency of new cases of ALL per 100,000 in a given age group. Note that the risk of ALL is greatest in the first 5 years of life. (Data from SEER Program of the National Cancer Institute.)

ALL is the most common of all **pediatric** cancers: ≈ 2,000 new cases of childhood ALL diagnosed annually in U.S.

Cause(s)? Unknown. Timing? "Mistakes" during fetal development? Exposures *in utero*? (Offspring of cigarette smoking moms: are they at excess risk of ALL?).

Possible causes:

Bad luck **Genetic predisposition (*e.g.*, Down syndrome)**
(Retro)virus(es)? (Analogy with other mammals) EMF?
Woburn: contaminated drinking water???

What do we know about cancer clusters *in communities*?

From: Caldwell GG. 1990. Twenty-two years of cancer cluster investigations at the Centers for Disease Control. *Am J Epidemiol.* 132(1 Suppl):S43-7:

> Beginning in 1961 [and spanning 20 years of investigation], the Centers for Disease Control investigated 108 cancer clusters . . . The clusters studied were of leukemia (38%), leukemia and lymphoma (30%), leukemia and other cancer combinations (13%), and all other cancer or combinations (19%). . . . Although 14 different categories of associations were reported [and despite lab tests for radiation, chemicals, viruses, and genetics], *no clear cause* was found for *any* cluster.

A reminder that, in *community (chronic) disease investigations*, *most* hypotheses are *wrong*.

Does TCE cause cancer in over-exposed factory workers? Lots of **epidemiologic** study of this question.

Answer: *Probably* not. . . "limited evidence." No "unusual" cancers. TCE not IARC "Group 1."

Overall Evaluations of Carcinogenicity to Humans (per IARC Monographs Volumes 1-88)

Group 1: Carcinogenic to humans (95): (Established via sufficient epidemiologic evidence)

AGENTS AND GROUPS OF AGENTS

Aflatoxins
4-Aminobiphenyl
Arsenic and arsenic compounds
Asbestos
Azathioprine
Benzene
Benzidine
Beryllium
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornaphazine)
Bis(chloromethyl)ether and chloromethyl methyl ether
1,4-Butanediol dimethanesulfonate (Busulphan; Myleran)
Cadmium and cadmium compounds
Chlorambucil
1-(2-Chloroethyl)-3-(4-methylcyclohexyl)-1-nitrosourea (Methyl-CCNU; Semustine)
Chromium[VI] compounds
Ciclosporin
Cyclophosphamide
Diethylstilboestrol
Epstein-Barr virus
Erionite
Estrogen therapy, postmenopausal
Estrogens, nonsteroidal
Ethylene oxide
Etoposide in combination with cisplatin and bleomycin
Formaldehyde
[Gamma Radiation: see X- and Gamma (g)-Radiation]
Gallium arsenide
Helicobacter pylori
Hepatitis B virus
Hepatitis C virus
Herbal remedies containing plant species of the genus Aristolochia
Human immunodeficiency virus type 1
Human papillomavirus type 16
Human papillomavirus type 18
Human T-cell lymphotropic virus type I
Melphalan
8-Methoxypsoralen (Methoxsalen) plus ultraviolet A radiation
MOPP and other combined chemotherapy including alkylating agents
Mustard gas (Sulfur mustard)
2-Naphthylamine
Neutrons
Nickel compounds
Opisthorchis viverrini
Oral contraceptives, combined
Oral contraceptives, sequential
Phosphorus-32, as phosphate
Plutonium-239 and its decay products as aerosols
Radioiodines, short-lived isotopes, including iodine-131, from atomic reactor accidents and nuclear weapons detonation
Radionuclides, a-particle-emitting, internally deposited
Radionuclides, b-particle-emitting, internally deposited
Radium-224 and its decay products
Radium-226 and its decay products
Radium-228 and its decay products
Radon-222 and its decay products
Schistosoma haematobium
Silica crystalline
Solar radiation
Talc containing asbestiform fibres
Tamoxifen

Group 1: Carcinogenic to humans (95), continued:

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin
Thiotepa
Thorium-232 and its decay products
Treosulfan
Vinyl chloride
X- and Gamma (g)-Radiation

MIXTURES
Alcoholic beverages
Analgesic mixtures containing phenacetin
Areca nut
Betel quid with tobacco
Betel quid without tobacco
Coal-tar pitches
Coal-tars
Mineral oils, untreated and mildly treated
Salted fish (Chinese-style)
Shale-oils
Soots
Tobacco products, smokeless
Wood dust

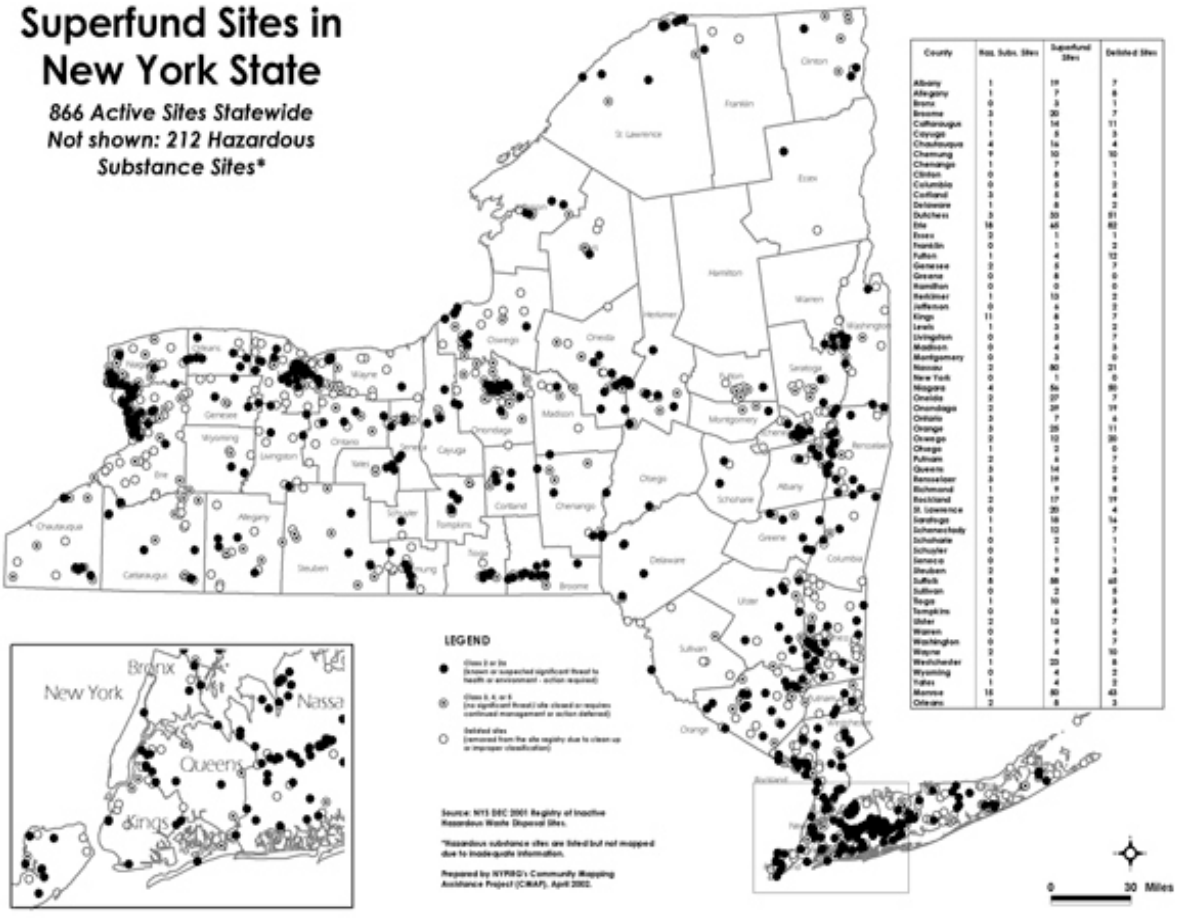
EXPOSURE CIRCUMSTANCES
Aluminium production
Arsenic in drinking-water
Auramine, manufacture of
Boot and shoe manufacture and repair
Coal gasification
Coke production
Furniture and cabinet making
Haematite mining (underground) with exposure to radon
Involuntary smoking
Iron and steel founding
Isopropanol manufacture
Magenta, manufacture of
Painter (occupational exposure as a)
Rubber industry
Strong-inorganic-acid mists containing sulfuric acid (occupational exposure to)
Tobacco smoking

What about results in lab rats and mice exposed chronically to TCE?

Table **Doses of trichloroethylene (TCE): toxicologic and other benchmarks**	
Endpoint	**TCE (mg/kg-day)**
Doses to people from water in Woburn	**??**
Worker's day-long exposure to CalOSHA PEL (25 ppm)	**??**
Mouse NOAEL: **liver cancer** (**half-lifetime** exposure; Herren-Freund *et al.*, 1987)	6
Rat NOAEL: **kidney cancer** (one-year exposure; Maltoni *et al.*, 1986)	250
Rat LOAEL: **kidney cancer** (NTP, 1988)	500
Mouse LOAEL: **liver cancer** (NTP, 1990)	1,000

TCE (and other solvents) elsewhere in groundwater in the U.S.

1980: Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA;), commonly known as "Superfund" enacted: money from a tax on the chemical and petroleum industries, mandates U.S. EPA "respond directly to releases or threatened releases of hazardous substances that *may* endanger public health or the environment." **> 1,400 National Priorities List (NPL) sites in U.S.**; TCE has been detected at some 850 of these!



Per the U.S. Agency for Toxic Substances and Disease Registry (ATSDR)

"Drinking or breathing high levels of trichloroethylene may cause nervous system effects, liver and lung damage, abnormal heartbeat, coma, and possibly death."

Are statements like this informative?
[ATSDR's motto: "To Protect America's Health from Toxic Exposures"]

What concentration of TCE in groundwater that serves (or may serve) as drinking water is *acceptably small*? (Aquifer clean up = "remediation" = improving public health?)

Quantitative health risk assessment for TCE: nothing (really) to do with Woburn. Based instead on results of **rat/mouse bioassays**, combined with **massive regulatory infrastructure** . . .

Huge $$ at stake.

TCE toxicology, mechanisms, and QRA for another time. . .

For now, by next Tuesday, Feb. 15, 2005, please do the following and email to me your answers:

Compare and contrast ***former occupational*** exposures to vinyl chloride in air with ***drinking water*** exposures to TCE in Woburn (and ***currently permissible workplace exposures*** to TCE). Express doses as mg/kg-day, with plausible ranges.

In air, **X** ppm = (**Y** mg/m3)(24.45)/(molecular weight)

In water, **x** ppb = **x** *u*g/L