HEALTH CONSULTATION

Review of Bladder Cancer and Leukemia Data

UPJOHN CHEMICAL COMPANY
(a/k/a UPJOHN COMPANY-FINE CHEMICALS DIVISION)

NORTH HAVEN, NEW HAVEN COUNTY, CONNECTICUT

EPA FACILITY ID: CTD001168533

Prepared by:

Connecticut Department of Public Health
Under a Cooperative Agreement with the
Agency for Toxic Substances and Disease Registry

CONTENTS

Background

The Upjohn Company operated the North Haven Fine Chemical (NHFC) plant in North Haven, Connecticut, from 1962 to 1993. From the mid-1940's through 1962, the Carwin Company operated the NHFC facility (1). The Upjohn Company still maintains ownership of the NHFC facility. All buildings except an administration building have been demolished. The facility is surrounded by fencing on three sides. The fourth side can be accessed via the Quinnipiac River. Signs indicating hazards and restricting trespassing have been posted in this area. Most of the NHFC facility is covered with asphalt (1). Figure 1 in Appendix B provides an overview of the area.

SRA Technologies completed a cancer incidence study of Upjohn workers in September, 1995 (2). The study was initiated by Upjohn after three workers developed bladder tumors after production of benzidine, a known bladder carcinogen, had been discontinued. The standardized incidence ratio (SIR) is the total number of observed cancer cases among Upjohn workers divided by the total number of expected cancer cases among Upjohn workers. The study found a statistically significant increase in the SIR for male bladder cancer. The SIR for male bladder cancer was 8.3 (95% confidence interval [CI] = 3.3, 17.0) (2). The study concluded that the increase in bladder cancer was associated with an occupational exposure (2).

Benzene was detected in the ambient air during off-site sampling in August 1989. Benzene was also detected in the ambient air on-site. The Upjohn facility had a history of benzene releases. Benzene releases occurred as fugitive emissions during production, as well as accidental releases. Some of the benzene releases were at or above levels of health concern. Benzene has been classified as carcinogenic to humans (3). There is an established link between exposure to benzene and the development of leukemia, specifically, acute myelogenous leukemia (3,4).

Based on the above information, the Agency for Toxic Substances and Disease Registry (ATSDR) and the Connecticut Department of Public Health (CT DPH) concluded, in a Public Health Assessment published March 8, 2000, that *this site represented a public health hazard in the past due to air exposures from the Upjohn NHFC facility* (1). The site currently represents no public health hazard.

Statement of Issues

Initially, the CT DPH was petitioned by the North Haven First Selectman to examine the health impacts of the Upjohn Facility on residents. This petition was driven by the release of an occupational study by SRA Technologies that found a statistically significant increase in the standardized incidence ratio for male bladder cancer. The community is concerned that residents around the Upjohn facility may be experiencing higher than expected bladder cancer rates. In order to address concerns of the citizens, a review of bladder cancer in the community around the Upjohn facility was conducted. Because of the documented link with benzene, leukemia was also be reviewed (3,4).

Methods

Tumor Data

Bladder cancer and leukemia data were obtained from the Connecticut Tumor Registry (CTR) for the time period 1983–1996. This time period was utilized because the data were available in electronic form and the latency period from exposure to disease onset would have been sufficient to capture cases possibly affected by the Upjohn facility.

Since the CTR does not capture information on people who do not develop tumors, non-case data were obtained from the 1990 U.S. Census. Population data were extracted from the Census's STF3A population file (5). The Census Referent Population Methodology (CRPM) was used to represent the population of North Haven (6). This methodology was used to model the location of the general population using the addresses from a digital phone book, the 1990 U.S. Census population data, and a series of sophisticated computer programs. The CRPM provides us with a more accurate model of the referent population location.

Time Periods

The analyses were stratified by two 5-year and one 4-year time periods (1983–1987, 1988–1992, 1993–1996). The 4-year time period was utilized because 1996 was the most current year data were available from the CTR when this work began. The total number of cases listed for each time period, by gender and tumor site, can be found in Table 1.

Exposure Model: Quarter-Mile Buffers

Distance was modeled as a categorical variable (buffer zones). An exposure radius was selected arbitrarily (1/4-mile buffers). Residences within a quarter-mile of the Upjohn facility were considered "exposed." This analysis was then repeated for residences from 1/4 to ½ mile, ½ to 3/4 mile, and 3/4 to 1 mile. Residences more than 1 mile from the Upjohn facility were considered "unexposed" and comprised the comparison population for the four buffer zones. These exposure classification schemes are shown in Figure 2. If distance of residence correlates with exposure, and exposure is associated with the disease under investigation, then one might expect decreasing odds of disease in concentric rings further from the waste sites. This exposure classification scheme does not take wind direction or velocity into account. An assumption is made that exposure would travel equally in all directions.

Logistic Regression Model

Regression models defining the association between exposure to Upjohn waste and cancer were developed, using the CTR for case information and the census for the reference group. The purpose of these models was to explore the possible association between exposure to Upjohn waste and the incidence of bladder cancer and leukemia. Since actual exposure

information was not available, the regression models utilize distance to the Upjohn facility as an exposure surrogate.

The results of the logistic regression models are expressed as odds ratios. For this study, the odds ratio shows the association between the risk factor, distance to the Upjohn facility, and a disease (bladder cancer and leukemia). This is accomplished by comparing the probability or chance of disease for those who live near the Upjohn facility to those who live farther away.

For the individuals with cancer, and the CRPM reference population, the actual distance from their home to the Upjohn site perimeter was calculated. Data were not available on some of the important risk factors for cancer. For example, although occupational exposures to bladder carcinogens is an important risk factor, the CTR files were lacking adequate occupational information. Most records had no occupation information at all. This important, potentially confounding, factor could not be included in the analyses. If a cancer case reported to the CTR was also a worker at the North Haven Upjohn facility, they would have had a greater chance to be exposed. This could have the effect of increasing the odds ratios in the community.

Smoking is another variable which should be considered, but CTR records were incomplete and/or inconsistent. The effect of age and gender were controlled for in the analysis of bladder cancer and leukemia, with age categorized in four age groupings.

Analyses were performed in the Statistical Analysis System (SAS®) software utilizing the PROC LOGISTIC function (7).

Disease Surface Models

Surface models were created for both bladder cancer and leukemia for each time period and by gender. These surface models provide an overall picture of bladder cancer and leukemia within North Haven over time.

The age-adjusted incidence rates were computed for three time periods (beginning in 1983 through 1996) for 1,365 lattice points or locations (X & Y coordinate pairs) within North Haven, spaced 1/8-mile apart. Rushton and Lolonis developed this method of exploratory spatial analysis for use with birth data (8). However, the CRPM provides us the ability to use tumor data for similar analyses.

The direct method of standardization was utilized. The rates were standardized to a standard population to control for the effects of population changes and age distributions over time[1]. The U.S. 1990 Standard Million was used as the reference population for the direct standardization analysis. Breslow and Day recommend utilizing a published set of weights for direct standardization as it promotes comparability between series (9). This enabled the analysis of trends in cancer incidence over time.

The tumor data were stratified into four age groups, <45, 45–64, 65–74, >74, and by gender. Race was not considered for the analysis, as all bladder cancer cases and all but one leukemia case reported their race as white. The age-adjusted rates give an indication of what is happening in North Haven over time. This type of analysis does not evaluate exposure from the Upjohn site. Once the age-adjusted rates were created for all 1,365 lattice points, a surface model of the rates across the study area was developed utilizing Geographic Information System (GIS) software.

Exposure Analysis/Assumptions

These analyses did not utilize a direct measure of exposure from the North Haven Upjohn facility. There are no direct measures of exposure, biological or environmental, available. Therefore, the surface models of disease rates were created without using exposure models. All residents of North Haven were assumed to have an equal chance of being exposed to the Upjohn facilities' emissions.

Results

The odds ratios for bladder cancer and leukemia can be found in Tables 2 and 3, respectively. For bladder cancer, there was only one significant odds ratio. It was found in females, in the ½– to 3/4–mile buffer zone, during the 1993–1996 time frame (OR 6.83 95% CI [1.51, 30.87]). The extremely wide range on the 95% confidence interval suggests a large degree of variability and should be interpreted with caution. When examining the buffer zones for a trend, it is clear that there is no relationship between proximity of residence to the Upjohn site and the odds of bladder cancer.

There were no significantly elevated odds ratios for leukemia for males or females. There was also no pattern or relationship between proximity of residence to the Upjohn site and the odds of leukemia.

The maps of bladder cancer rates can be found in Figure 3. Because of the small numbers of tumors in each gender-time period category, maps of the rate surface models could not be presented for female bladder cancer, and male and female leukemia. The number of tumors by site, gender, and time-period can be found in Table 1. In each of these situations, the maps may have divulged confidential patient information. Because of this, the information can not be released.

Discussion

Researchers are often criticized when cancer data are analyzed by town. Citizens want to see the data analyzed for smaller areas such as neighborhoods and streets. For this review of bladder cancer and leukemia, methods were utilized to conduct the analyses in areas smaller

than the town. While this addresses the issue of what is happening within the town of North Haven, an additional methodological problem rises–the time series, gender-stratified analysis suffers from small numbers.

There is a significant female bladder cancer odds ratio reported in Table 2 for the ½– to 3/4–mile buffer zone, during the 1993–1996 time frame. This odds ratio has an extremely wide 95% confidence interval (OR 6.83 95% CI [1.51, 30.87]). This is due in part to the very small sample size (n=3). The wider the confidence interval range, the less precise the estimate will be. Additionally, the smaller the sample size, the less precise the estimate will be. When the same buffer zone is examined with female bladder cancer data from 1983–1996, the sample size increases to five. The odds ratio is still elevated, but no longer significant (OR 2.59 95% CI [0.96, 7.02]).

In order to conduct analyses that are at a geographic level smaller than the town, the results become less precise. It is a tradeoff between smaller geographic areas being studied and poor precision, versus larger geographic areas being studied and greater precision. The time series maps do show areas within the town where male bladder cancer occurred. However, because of the very small numbers, none of the results were significant and care must be taken when reviewing the data.

When examining the three maps for male bladder cancer (Figure 3), over time, the pattern of disease changes. Although maps of female bladder cancer and male and female leukemia were not included in this consultation, they were created. Because of concerns of confidentially, they can not be released to the public. In accordance with CGS 19a-25, Confidentiality of Data, all epidemiologic information which identifies an individual and which is gathered by the state or local health department in connection with the investigation of reported cases or suspected cases of disease or during the investigation of outbreaks of disease shall be kept in compliance with current confidentiality statutes (10).

The maps of female bladder cancer and male and female leukemia were reviewed and no recognizable pattern was found.

Limitations

This work utilized existing data from the Connecticut Department of Public Health. While tumor records were complete and accurate, these data were not collected specifically for this study. Information concerning many potential risk factors for cancer was not available for analysis (including specific information on exposure to chemicals from the Upjohn facility).

The latency period between exposure and disease onset for the cancer cases can be 10 to 20 years or longer. Because of this long latency period, issues such as estimation of exposure based on one residential address become particularly problematic. The mobility of the population over time is a concern because of the long latency between exposure and tumor

diagnosis. The cancer study rests on the assumption that the location of the individual at the time of cancer diagnosis is the address they lived at years earlier when relevant exposures may have occurred.

A major limitation of the cancer analysis is the inability to track the movement of cases over time. An assumption is made that all the cases lived in the same house for the entire study period. If a cancer patient moved prior to diagnosis, the address reported on the medical record would not reflect where the individual lived during the relevant exposure period.

As long as the movement occurs equally in both groups, exposed moving away from exposed areas and non-exposed moving into exposed areas, the bias will be non-differential. This has the effect of moving the point estimate towards the null. If movement is different between groups, more people move in than out or more people move out than in, the bias will be differential. This will have an unpredictable effect on the point estimate (11).

Information regarding residential history on cancer cases was not available from the CTR records. A few cases had residential information if they moved and continued to receive treatment for their cancer. However, the address change only represented the address at the time medical care was received and not when the case moved. When the address at cancer diagnosis is used to approximate exposure, residential mobility becomes an important limitation.

The tumor registry database did not include the occupational history of the patient in a consistent manner for the duration of the study period, and this important, potentially confounding, factor could not be included in the analyses. If a cancer case reported to the CTR was also a worker at the North Haven Upjohn facility, they would have had a greater chance to be exposed. This could have the effect of increasing the odds ratios in the community. In this scenario, the true exposure would have been occupational and not environmental.

Conclusions

There were no major findings for male and female bladder cancer. There were no major findings for male or female leukemia. There does not appear to be a relationship between living near the North Haven Upjohn facility and leukemia and bladder cancer.

Recommendations

The study conclusions should be released to the public in a timely manner. Additional community outreach and education should be conducted as needed.

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Table 1: Number of cancer cases by tumor site, time category, and gender for North Haven, Connecticut, 1983–1996.

Tumor Site	Gender	Time Period	Number of Cases
Bladder	Male	1983–1987	30
		1988–1992	30
		1993–1996	26
	Female	1983–1987	6
		1988–1992	13
		1993–1996	9
Leukemia	Male	1983–1987	6
		1988–1992	13
		1993–1996	8
	Female	1983–1987	5
		1988–1992	4
		1993–1996	6

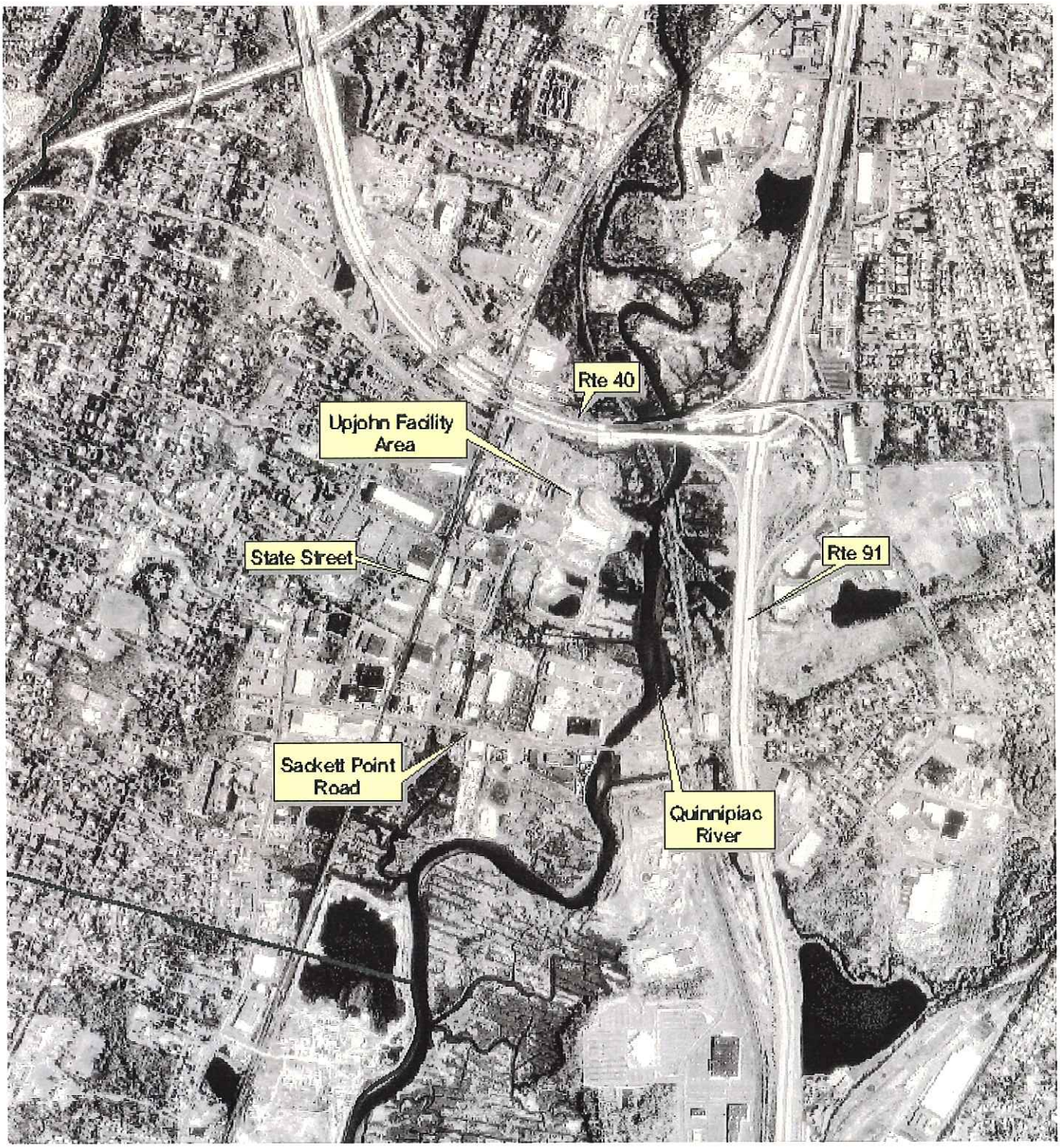
Table 2: Bladder Cancer Odds Ratios by Gender and Time Period for 1/4-Mile Buffer Zones Around the Upjohn Facility, North Haven, Connecticut, 1983–1996.

Gender	Time Period	Buffer Zone in Miles	Number of Cases	Number of non-Cases	Odds Ratio	95% Confidence Interval	
						Lower	Upper
Male	1983–1987	0–0.25	1	156	2.57	0.33	19.84
		0.25–0.5	1	517	0.88	0.12	6.68
		0.5–0.75	3	750	1.09	0.32	3.37
		0.75–1	5	1,157	1.69	0.63	4.55
		> 1	20	8,281	–	–	–
	1988–1992	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	1	517	0.69	0.09	5.23
		0.5–0.75	4	750	1.33	0.45	3.91
		0.75–1	3	1,157	0.93	0.28	3.15
		> 1	22	8,281	–	–	–
	1993–1996	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	0	517	0.00	0.00	0.00
		0.5–0.75	6	750	2.06	0.81	5.27
		0.75–1	1	1,157	0.34	0.05	2.59
		> 1	19	8,281	–	–	–
	1983–1996	0–0.25	1	156	0.98	0.13	7.25
		0.25–0.5	2	517	0.52	0.13	2.18
		0.5–0.75	13	750	1.51	0.81	2.79
		0.75–1	9	1,157	0.99	0.49	2.03
		> 1	61	8,281	–	–	–
Female	1983–1987	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	0	416	0.00	0.00	0.00
		0.5–0.75	1	781	3.08	0.32	29.92
		0.75–1	2	1,189	4.25	0.70	25.73
		> 1	3	8,929	–	–	–
	1988–1992	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	0	416	0.00	0.00	0.00
		0.5–0.75	1	781	0.89	0.12	6.91
		0.75–1	0	1,189	0.00	0.00	0.00
		> 1	12	8,929	–	–	–
	1993–1996	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	0	416	0.00	0.00	0.00
		0.5–0.75	3	781	6.83	1.51	30.87
		0.75–1	2	1,189	2.96	0.54	16.29
		> 1	4	8,929	–	–	–
	1983–1996	0–0.25	0	152	0.00	0.00	0.00
		0.25–0 .5	0	416	0.00	0.00	0.00
		0.5–0.75	5	781	2.59	0.96	7.02
		.75 - 1	4	1,189	1.34	0.45	3.97
		> 1	19	8,929	–	–	–

Table 3: Leukemia Odds Ratios by Gender and Time Period for 1/4-Mile Buffer Zones Around the Upjohn Facility, North Haven, Connecticut, 1983–1996.

Gender	Time Period	Buffer Zone in Miles	Number of Cases	Number of non-Cases	Odds Ratio	95% Confidence Int.	
						Lower	Upper
Male	1983–1987	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	1	517	4.47	0.45	44.31
		0.5–0.75	1	750	2.06	0.21	20.14
		0.75–1	1	1,157	2.13	0.22	20.68
		> 1	3	8,281	-	-	-
	1988–1992	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	1	517	1.62	0.20	12.76
		0.5–0.75	0	750	0.00	0.00	0.00
		0.75–1	2	1,157	1.42	0.31	6.51
		> 1	10	8,281	-	-	-
	1993–1996	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	0	517	0.00	0.00	0.00
		0.5–0.75	2	750	3.36	0.64	17.78
		0.75–1	1	1,157	1.42	0.17	12.20
		> 1	5	8,281	-	-	-
	1983–1996	0–0.25	0	156	0.00	0.00	0.00
		0.25–0.5	2	517	1.84	0.42	7.93
		0.5–0.75	3	750	1.30	0.38	4.48
		0.75–1	4	1,157	1.54	0.52	4.58
		> 1	18	8,281	-	-	-
Female	1983–1987	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	1	416	6.15	0.68	55.87
		0.5–0.75	0	781	0.00	0.00	0.00
		0.75–1	0	1,189	0.00	0.00	0.00
		> 1	4	8,929	-	-	-
	1988–1992	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	1	416	10.74	0.97	118.89
		0.5–0.75	0	781	0.00	0.00	0.00
		0.75–1	1	1,189	3.82	0.34	42.33
		> 1	2	8,929	-	-	-
	1993–1996	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	0	416	0.00	0.00	0.00
		0.5–0.75	0	781	0.00	0.00	0.00
		0.75–1	1	1,189	1.28	0.15	11.12
		> 1	5	8,929	-	-	-
	1983–1996	0–0.25	0	152	0.00	0.00	0.00
		0.25–0.5	2	416	4.26	0.94	19.36
		0.5–0.75	0	781	0.00	0.00	0.00
		0.75–1	2	1,189	1.25	0.27	5.67

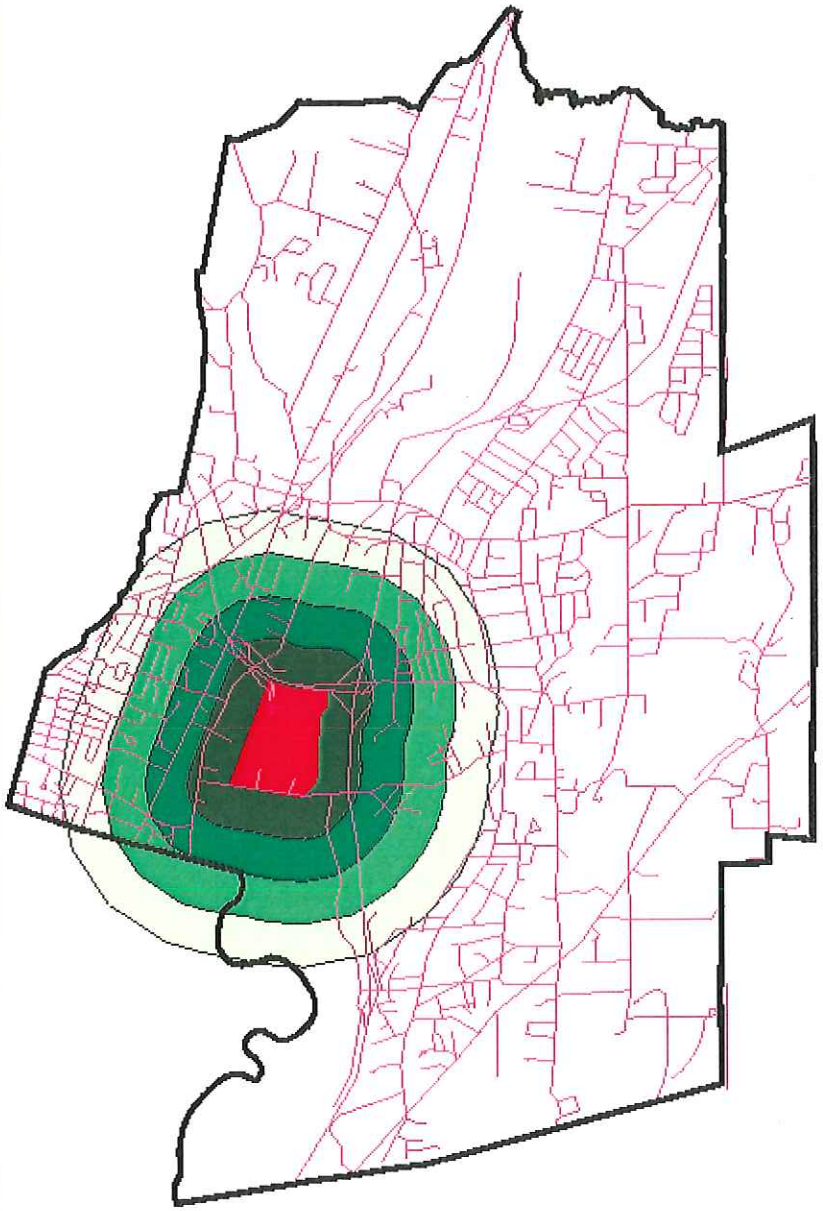
Figure 1 North Haven Connecticut and the Upjohn Facility



The 1990 orthophoto data obtained from the CT Department of Environmental Protection.

August 4, 2001

Figure 2 Quarter-Mile Buffer Zones Around the Upjohn Facility, North Haven, Connecticut

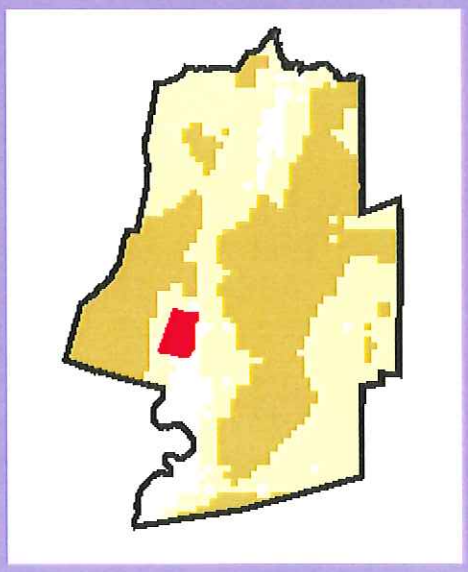


July 16, 2001

Figure 3 Male Bladder Cancer Age Adjusted Rate per 1,000* 1983 - 1996 North Haven, Connecticut

Town Boundaries
Upjohn Facility
Male Bladder Cancer Rate
0 - 2.403
2.403 - 4.806
4.806 - 7.209
> 7.209

Population Density

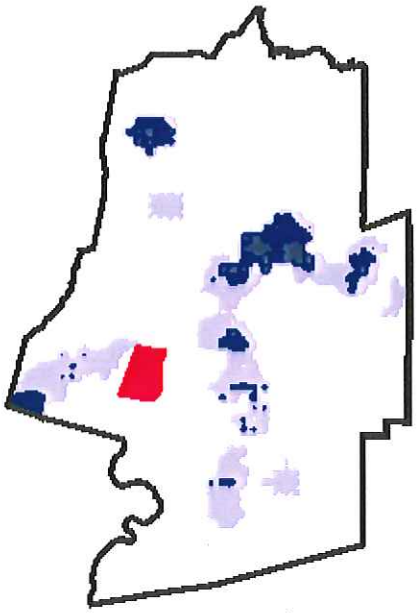


Town Boundaries
Upjohn Facility
Population Density per Square Mile
0 - 100
101 - 1,000
1,001 - 10000
> 10,000

*None of these rates were statistically significant.

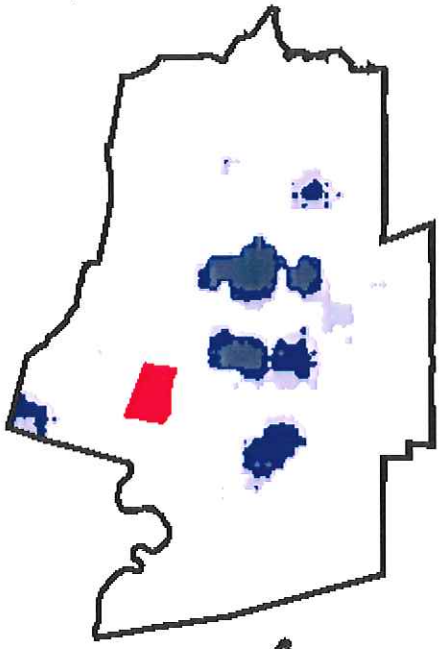
1983 - 1987

Number of Bladder Cancer Cases: 30



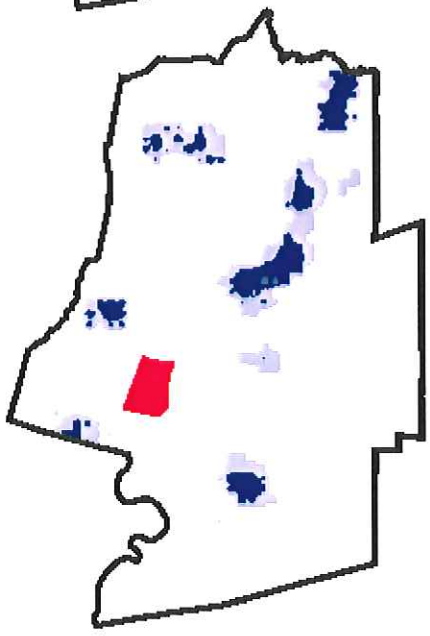
1988 - 1992

Number of Bladder Cancer Cases: 30



1993 - 1996

Number of Bladder Cancer Cases: 26



1 0 1 2 3 4 5 Miles

July 16, 2001