yield new insight into the mechanism of DES oncogenicity in target tissues such as the uterus and vagina.

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Cancer Incidence in the Love Canal Area

Abstract. *Data from the New York Cancer Registry show no evidence for higher cancer rates associated with residence near the Love Canal toxic waste burial site in comparison with the entire state outside of New York City. Rates of liver cancer, lymphoma, and leukemia, which were selected for special attention, were not consistently elevated. Among the other cancers studied, a higher rate was noted only for respiratory cancer, but it was not consistent across age groups and appeared to be related to a high rate for the entire city of Niagara Falls. There was no evidence that the lung cancer rate was associated with the toxic wastes buried at the dump site.*

The carcinogenic potential of environmental contamination from chemical wastes has focused public attention on the dumping sites that contain these wastes. Love Canal is among the most important of these sites. We report data on cancer incidence in the census tract surrounding the Love Canal for the period 1955 to 1977 (*1*).

Eighty chemicals were originally identified at the landfill (*2*), and the number has grown. These include benzene, which can induce leukemia in humans, seven compounds including trichloroethylene, which are carcinogenic in animals, and several toxic chemicals. Studies of the effects of benzene and halogenated hydrocarbons on animals and humans suggest that, if the chemical contamination at Love Canal has resulted in actual human exposure, the most likely resulting cancers would be liver cancer, lymphoma, and leukemia (*3–5*). Because of the uncertainty about exposure and the large number of chemicals dumped, we examined rates of all categories of cancer as well as the three most likely cancers.

The census tract surrounding the Love Canal (Fig. 1) provided a distinct population base from which to calculate cancer incidence rates. According to the 1970 census, the tract contained 4897 people. The census tract is bounded by streams to the north and west, by the Niagara River and a parkway to the south, and by a sparsely populated rural area to the east. The residences located on and adjacent to the dump site include approximately 225 households and 700 individuals. This area, referred to as rings 1 and 2 in an earlier report (*2*), is darkly outlined in Fig. 1.

Waste burial started in the 1920's and ended about 1953. Aerial photographs show that housing development increased after the dumping stopped, population of the tract grew rapidly. Major public concern about health hazards associated with the buried wastes started in early 1978. Because this concern marked the beginning of substantial changes in the size of the tract population and may also have resulted in changes in disease reporting, we analyzed data through 1977 only.

The source of the cancer incidence data was cases reported to the New York Cancer Registry, which has collected reports since 1940. In general, the data from 1966 on are of better quality than the earlier data; for example, before 1966 the reference date for each case was the date of the report, and since then it has been the date of diagnosis. We examined rates for all sites of cancer for the period 1966 to 1977; rates for the cancers of special interest (liver cancer, lymphoma, and leukemia) were examined for the period 1955 to 1965 as well.

The populations on which incidence rates were calculated were estimated from the two decennial censuses and a special census in 1967. We used the 1970 census count for the years 1970 to 1977; the 1960 and 1967 census count for those years; linear interpolation for all other years from 1960 to 1969; and extrapolation of the resulting trend for the years 1955 to 1959.

We calculated age- and sex-specific cancer incidence rates for ten major cancer sites and five age groups for each of the 25 census tracts in the city of Niagara Falls. Although the number of cases in each age- and sex-specific category was quite small, this analysis helped rule out the occurrence of large increased risks in subgroups of the study population. (Such a procedure seems essential to epidemiological investigations where the etiological mechanism underlying the disease is poorly understood, as is the case with environmentally caused cancer.) For each of these 50 age-site groups, the 25 rates were arrayed in rank order by census tract for males and females. Rates for the Love Canal tract appeared in the highest quintile 9 out of 50 times for males, and 8 out of 50 times for females. All rates in the highest quintile were examined further. For example, the bladder cancer rate among males 65 to 74 years old from the Love Canal tract was in the highest quintile, but this elevated rate was confined to that age group and was based on only three cases. In four instances for males and two for females the occurrence of one case put the Love Canal tract in the upper 20 percent of tracts. In our judgment there were no unusual patterns among the age-specific rates.

Standardized incidence ratios (SIR's) (*6–8*), based on registry data and census tract population estimates, were calcu-

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Table 1. Comparison of observed and expected numbers of cases of liver cancer, lymphoma, and leukemia in the Love Canal census tract between 1955 and 1977.

Cancer	Male cases				Female cases			
	Observed	Expected	5 percent confidence limits*	SIR†	Observed	Expected	5 percent confidence limits*	SIR†
			1955 to 1965					
Liver (155)‡	0	0.4	0 to 2	0.0	2	0.3	0 to 1	6.7
Lymphomas (200 to 202)	3	2.5	0 to 5	1.2	2	1.8	0 to 4	1.1
Leukemias (204 to 208)	2	2.3	0 to 5	0.9	3	1.7	0 to 4	1.8
			1966 to 1977					
Liver (155)	2	0.6	0 to 2	3.3	0	0.4	0 to 2	0.0
Lymphomas (200 to 202)	0	3.2	0 to 6	0.0	4	2.5	0 to 5	1.6
Leukemias (204 to 208)	1	2.5	0 to 5	0.4	2	1.8	0 to 4	1.1
			1955 to 1977					
Liver (155)	2	1.0	0 to 3	2.0	2	0.7	0 to 2	2.9
Lymphomas (200 to 202)	3	5.6	2 to 11	0.5	6	4.3	1 to 8	1.4
Leukemias (204 to 208)	3	4.8	1 to 9	0.6	5	3.5	0 to 7	1.4

*Approximately 5 percent of the sample values fall outside these limits in a Poisson distribution with a mean equal to the stated expected value. For example, for females in the 1955 to 1965 period, the two cases of liver cancer are outside of the limits 0 to 1 and are statistically significant at the 5 percent level. This 5 percent is entirely in the upper tail when the expected value is 3.6 or less. †Ratio of observed to expected number (age standardized). ‡Numbers in parentheses are designations from the International Classification of Diseases (9th edition).

lated for each cancer site by dividing the observed number of cancer cases in the Love Canal tract by the number expected for that census tract. The expected numbers were computed by applying the annual age-, sex-, and site-specific cancer incidence rates for New York State (exclusive of New York City) to the tract population. Statistical significance was assessed by the Poisson model.

Table 1 shows the observed and expected numbers of cases of liver cancer, lymphoma, and leukemia in the census tract that includes the Love Canal. There was no evidence of an increase in lymphoma or leukemia. The SIR was statistically significant at the 5 percent level for female liver cancer in the period from 1955 to 1965. The residences of these liver cancer patients were not in close proximity to the dump site (*9*).

Table 2 shows observed and expected frequencies for the cancer groups not shown in Table 1. None show elevated rates except respiratory cancer, for which the SIR was statistically significant at the 5 percent level for both males and females.

To evaluate the findings for respiratory cancer, we calculated the SIR's for all 25 census tracts in the city of Niagara Falls. Table 3 shows that the Love Canal tract and seven other census tracts as well as the city of Niagara Falls in total have a statistically significant higher frequency of respiratory cancer among males. The Love Canal tract is also one of two tracts where SIR's are significantly higher than expected for females. Examination of the age-specific respiratory cancers shows that for both males and females 65 to 74 years old the Love Canal tract had the highest rate of the 25 tracts. However, in no other age groups was the tract ranked in the highest quintile.

Street addresses of the patients with respiratory cancer indicated that there was no tendency for cases to be located in close proximity to the dump site, nor

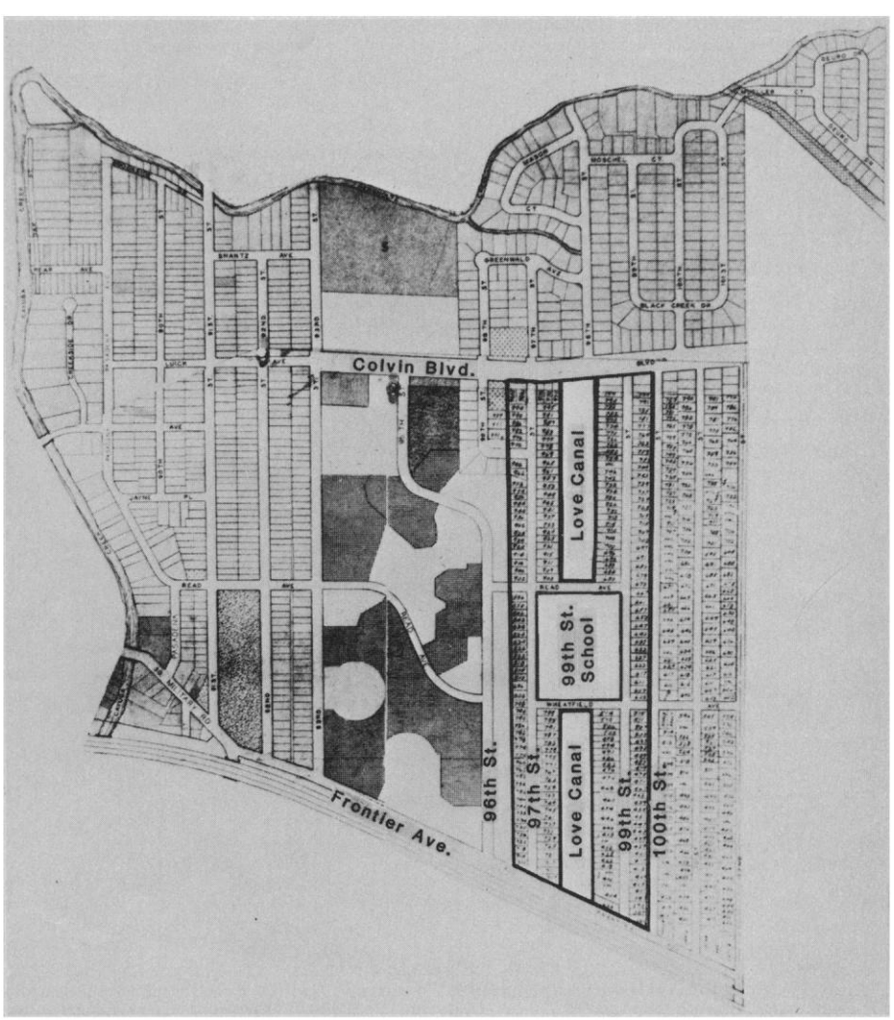

Fig. 1. Map of Love Canal census tract shows the canal dump site; the areas originally identified as rings 1 and 2 (*2*) are darkly outlined.

were they clustered or in other patterns to suggest associations between the cancers and the locations of the chemical wastes. For example, only 4 of 34 cases of respiratory cancer were located in the darkly outlined area in Fig. 1; the rest were distributed throughout the tract in geographically unremarkable manner.

Respiratory cancer rates for the residents of the Love Canal area do not show a statistically significant difference from those of other census tracts in Niagara Falls city. The SIR's for the Love Canal census tract are, however, higher than the city average, and lung cancer rates should be monitored in this area in the future. The city in general has a rate of lung cancer that is slightly above the rest of the state. The magnitude of the increased frequency is within the range of those that have been shown to be associated with environmental factors like smoking, but the explanation for this higher rate is not known (*10*).

Table 2. Comparison of observed and expected numbers of cases of selected cancers in the Love Canal census tract between 1966 and 1977.

Cancer site	Male cases				Female cases			
	Observed	Expected	5 percent confidence limits*	SIR†	Observed	Expected	5 percent confidence limits*	SIR†
Buccal cavity and pharynx (140 to 149)‡	2	2.7	0 to 6	0.7	1	1.1	0 to 3	0.9
Digestive organs (150 to 154, 156 to 159)	13	15.7	8 to 24	0.8	15	13.8	7 to 22	1.1
Respiratory system (160 to 165)	25	15.0	8 to 23	1.7	9	4.6	1 to 8	2.0
Connective tissue, bone, skin, and breast (170 to 172, 174 to 175)	2	2.1	0 to 5	1.0	27	21.2	13 to 31	1.3
Genital organs (179 to 187)	13	7.9	3 to 14	1.6	8	12.5	6 to 20	0.6
Bladder, kidney, and ureter (188 to 189)	7	6.0	2 to 11	1.2	1	2.4	0 to 5	0.4
Liver, lymphoma, and leukemia (155, 200 to 202, 204 to 208)	3	6.3	2 to 12	0.5	6	4.7	1 to 9	1.3
Others (190 to 199, 203)	6	5.1	1 to 10	1.2	4	5.1	1 to 10	0.8
All sites (140 to 172, 174 to 208)	71	60.8	46 to 77	1.2	71	65.4	50 to 82	1.1

*Approximately 5 percent of the sample values fall outside these limits in a Poisson distribution with a mean equal to the stated expected value. The 5 percent is entirely in the upper tail when the expected value is 3.6 or less. †Ratio of observed to expected number (age standardized). ‡Numbers in parentheses are designations from the International Classification of Diseases (9th edition).

Table 3. Comparison of observed and expected numbers of cases of cancer of the repiratory system (International Classification of Diseases, 9th edition, numbers 160 to 165) by census tract, Niagara Falls, New York, from 1966 to 1977.

Census tract	Male cases				Female cases			
	Observed	Expected	5 percent confidence limits*	SIR†	Observed	Expected	5 percent confidence limits*	SIR†
Love Canal	25	15.0	8 to 23	1.7	9	4.6	1 to 8	2.0
A	24	29.5	19 to 41	0.8	16	8.2	3 to 14	2.0
B	13	10.5	5 to 17	1.2	2	3.0	0 to 6	0.7
C	13	9.7	4 to 16	1.3	0	2.6	0 to 5	0.0
D	14	14.6	8 to 23	1.0	5	4.4	1 to 9	1.1
E	28	22.7	14 to 32	1.2	10	7.8	3 to 14	1.3
F	18	16.5	9 to 25	1.1	10	5.0	1 to 10	2.0
G	26	22.4	14 to 32	1.2	5	6.3	2 to 12	0.8
H	8	7.8	3 to 14	1.0	3	2.1	0 to 5	1.4
I	32	20.1	12 to 29	1.6	7	5.7	2 to 11	1.2
J	28	26.5	17 to 37	1.1	5	7.0	2 to 13	0.7
K	23	20.3	12 to 30	1.1	8	6.6	2 to 12	1.2
L	18	21.6	13 to 31	0.8	3	6.7	2 to 12	0.4
M	18	20.7	12 to 30	0.9	10	5.8	2 to 11	1.7
N	34	17.6	10 to 26	1.9	3	4.9	1 to 10	0.6
O	34	19.9	12 to 29	1.7	4	5.2	1 to 10	0.8
P	26	13.7	7 to 21	1.9	2	3.4	0 to 7	0.6
Q	28	18.5	11 to 27	1.5	5	5.3	1 to 10	0.9
R	19	14.0	7 to 22	1.4	8	3.7	1 to 8	2.2
S	15	6.2	2 to 12	2.4	2	1.6	0 to 4	1.3
T	27	16.5	9 to 25	1.6	6	4.5	1 to 9	1.3
U	19	13.7	7 to 21	1.4	1	3.4	0 to 7	0.3
V	27	25.6	16 to 36	1.1	7	7.1	2 to 13	1.0
W	17	18.2	10 to 27	0.9	9	5.4	1 to 10	1.7
X	13	10.5	5 to 17	1.2	1	2.7	0 to 6	0.4
Niagara Falls (city)	547	432.1	391 to 473	1.3	141	123.2	102 to 145	1.1

*Approximately 5 percent of the sample values fall outside these limits in a Poisson distribution with a mean equal to the stated expected value. The 5 percent is entirely in the upper tail when the expected value is 3.6 or less. †Ratio of observed to expected number (age standardized).

In interpreting these findings, it should be recognized that the data are derived from a standardized reporting system, and no new information was collected. Thus, the data do not depend on patient recall or other retrospective processes. Therefore, completeness and quality of the cancer case reports are unlikely to have been affected by events like the declaration of a health emergency at Love Canal in mid-1978. There are, however, limitations in the data. They are derived from a central registry that receives 65,000 new case reports annually from a population of 16.8 million people. The degree of completeness and the accuracy of reporting from a single census tract cannot be known precisely, but there is no reason to believe that reporting was unusual in the areas we studied. The possible effects of special risk factors such as socioeconomic status, smoking, or air pollution cannot be assessed in a study of this design. The effect on people who have migrated out of the area has not been studied, and it is important to emphasize that questions of long latency periods cannot yet be addressed.

Uncertain latency periods and the small size of the study population limit the findings of epidemiological studies of this type. The important uncertainties seem to be biological and etiological rather than statistical. However, there are few, if any, alternatives to the epidemiological approach to assessing potential human risk from toxic chemical waste dumps. Investigation of other dump sites may have even greater quantitative limitations than that of the Love Canal.

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References and Notes

1. This report is one part of the Love Canal research begun by the New York State Department of Health in the past 2 years. The full research context includes environmental studies of air, water, and soil contamination, hydrogeologic studies, biologic studies in humans and animals, epidemiologic studies of acute effects and reproductive outcomes, and long-term follow-up of residents for assessment of chronic effects.
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9. Because the diagnosis of primary liver cancer is difficult and cancers of many other anatomic sites metastasize to this organ, we included all malignant neoplasms reported as liver that were not specified as secondary. This ensured that we would not underestimate primary liver cancers. The initial report for only one of the four cases stated that the cancer was primary in the liver. Upon review of the case histories, it was determined that for both cases in females the cancers probably originated in the pancreas. For one of these cases, pancreatic cancer was confirmed by autopsy. Both of the cases in males were autopsied; one was malignant hepatoma, and the other adenocarcinoma of the pancreas.
10. New York State incidence data for 1974 to 1976 ranks Niagara County 5th for males and 36th for females for all cancers and 5th for males and 18th for females for lung cancer. New York State mortality data ranks Niagara County 17th for males and 22nd for females for all cancers and 10th for males and 12th for females for lung cancer. These ranks apply to the 57 counties outside of New York City.
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Myelination of Central Nervous System Axons in Tissue Culture by Transplanted Oligodendrocytes

Abstract. *Unmyelinated mouse cerebellar cultures in which oligodendrocyte differentiation had been suppressed by exposure to cytosine arabinoside developed axonal myelin after superimposition of kainic acid–treated cerebellar explants devoid of myelin-receptive axons. The latter explants contained differentiated oligodendrocytes. The operation of a diffusible myelin-stimulating factor was ruled out by the failure of myelination in cytosine arabinoside-exposed explants not in direct contact with oligodendrocyte-containing transplants.*

Substantial myelination is achieved by 80 percent of newborn Swiss-Webster mouse cerebellar explants after 12 days of cultivation on collagen-coated coverslips in Maximow chambers (*1*, *2*). However, if similar explants are exposed to an inhibitor of DNA synthesis, cytosine arabinoside, for the first 5 days in vitro and subsequently cultured in normal nutrient medium, myelination is rare. [Only 2 of a series of 263 cerebellar cultures initially treated with cytosine arabinoside had myelin in trace amounts after 15 days in vitro (*3*).] Although Purkinje cell axons and axon collaterals, which normally myelinate, are superabundant in such cultures (*3*), ultrastructural examination reveals a reduction in the number of oligodendrocytes and a failure of the surviving oligodendroglia to differentiate fully (*4*). Thus myelination fails because of a lack of competent myelin-forming cells.

On the other hand, if cerebellar cultures are initially exposed to kainic acid, a glutamic acid analog, all cortical neurons are destroyed except granule cells, which are selectively resistant to the neurotoxic effects of kainate, succumbing only after prolonged exposure (*5*). Such cultures also have no axonal myelination, because the only surviving axons are the parallel fibers (granule cell axons), which do not normally myelinate in mouse cerebellar cultures (*2*, *6*). However, occasional granule cells in kainate-treated cultures are observed in the living state surrounded by perisomatic myelin, which is also occasionally found in normal cerebellar explants and in cerebellum in vivo (*2*, *7*). Electron microscopic examination confirms the presence of granule cell perisomatic myelin and demonstrates normal appearing, fully differentiated oligodendrocytes in explants exposed to kainic acid (*5*).

A question can therefore be raised as to whether oligodendrocytes from explants exposed to kainic acid, in which there are no axons receptive to myelination, will, if transferred to explants treated with cytosine arabinoside, myelinate available axons that have never been myelinated because of a lack of competent oligodendroglia. The purpose of the present study was to address this question.

Parasagittally oriented cerebellar explants were prepared from newborn Swiss-Webster mice (*2*). Some explants were cultivated for the first 5 days in vitro with 5 or 10 μg of cytosine arabinoside per milliliter of nutrient medium, and subsequently with normal medium (*3*). Other explants were cultivated for the first 5 days in vitro with $10^{-4}M$ kainic acid incorporated into the nutrient medium, followed by feeding with normal medium (*5*). Still other explants served as normal medium controls. After 9 days in vitro, explants exposed to kainic acid were excised from their cover slips under a dissecting microscope, placed in a 1:1 ratio directly over explants exposed to cytosine arabinoside, and cultivated further in normal nutrient medium. Such

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