

# Incidence of Endocrine Disease among Residents of New York Areas of Concern

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There are six Areas of Concern, as identified by the International Joint Commission, located in New York State. Three are contiguous in western New York and have similar contaminants (Buffalo River, Niagara River, and 18 Mile Creek). We used the Statewide Planning and Research Cooperative System database, which records diagnoses according to the *International Classification of Disease, Ninth Revision* codes for all patients admitted to state-regulated hospital facilities, to compare incidence of selected diseases reported in hospitalized patients who reside in ZIP codes that are within 15 miles of any of these sites to those of residents of three different control populations: all residents of the rest of New York State (including New York City), all residents of ZIP codes outside New York City that do not contain any site identified as a federal or state Superfund site, and all residents of ZIP codes outside New York City that contain a federal or state Superfund site that does not have one or more persistent organic pollutants listed as a major contaminant. We found a significant elevation of disorders of the thyroid gland in women, but not in men, of all ages greater than 25 years on all three comparisons, as well as an increased incidence of morbidity from diseases of the female genital tract in women between age 25 to greater than 75 years for all comparison groups. There was also a significant elevation in incidence of endometriosis in women 25–44 years of age. All these elevations were significant at the 99% confidence level. Incidence of diseases of ovaries and testes and female infertility were not different from those in the rest of New York State. Although many factors influence incidence of thyroid and genital diseases, our results are consistent with the hypothesis that exposure to environmental contaminants through residence near polluted sites may be a factor. *Key words:* endometriosis, genital disease, hospitalization, ovaries, testes, thyroid disease. — *Environ Health Perspect* 109(suppl 6):845–851 (2001).

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Of the 42 Areas of Concern (AOCs) identified by the International Joint Commission (IJC) in 1985–1986, six are in New York State. After release of the 17 studies by Health Canada reporting disease diagnoses upon hospital discharge, incidence of birth defects, and types and incidence of cancer in Canadian AOCs compared with the rest of Ontario, Canada, the Science Advisory Board of the IJC invited the authors to attempt to obtain comparable data from New York.

In New York the Statewide Planning and Research Cooperative System (SPARCS) database records all diagnoses upon hospital discharge for all hospitals covered by Article 28 of New York State law (1). The SPARCS system, therefore, does not include patients admitted to federal or Veterans Administration hospitals or patients who are New York residents but who seek medical care out of state. The SPARCS data set includes all diagnoses of a patient, whether or not a particular disease was the cause of hospitalization, and also contains personal information such as age, sex, race, and street address. Access to this data set is controlled to prevent misuse of confidential information, but access to ZIP code of residence without any other identifying information can be obtained after a relatively rapid approval process.

We have used the SPARCS database and patient ZIP code of residence in an initial effort to obtain data comparable to the hospital diagnosis information in the 17 Canadian reports. The preliminary investigation reported here focused on combining three of the six AOCs in New York (Niagara River, 18 Mile Creek, and Buffalo River) on the basis that these three are contiguous and have similar contaminants. Detailed descriptions of these three sites are on the U.S. Environmental Protection Agency (U.S. EPA) websites (2–4). A detailed report of toxic loadings into the Niagara River has also recently been presented by the U.S. EPA and the New York State Department of Environmental Conservation (DEC) (5). These bodies of water are affected by local industries. The Buffalo River discharges into Lake Erie near the head of the Niagara River, which connects Lakes Erie and Ontario. The Niagara River enters Lake Ontario, as does 18 Mile Creek, approximately 18 miles to the east. These areas include seven federal National Priority Sites (including Love Canal and Hooker Chemical sites) plus a number of state Superfund sites.

In 1988 the U.S. EPA commissioned a study of toxic pollutant loadings into the Niagara River and identified 70 sites in the Buffalo–Niagara Falls area that they

estimated contributed 315 kg/day of toxic substances into the river (6). Beginning in 1987 the four parties with responsibility, the U.S. EPA, DEC, Environment Canada, and the Ontario Ministry of Environment, identified 18 persistent chemicals as priority toxics. These included dioxins, polychlorinated biphenyls (PCBs), four polyaromatic hydrocarbons, eight persistent pesticides, three metals, and tetrachloroethylene. For example, at the Occidental Chemical Hyde Park site, an estimated 80,000 tons of chemical wastes were deposited between 1953 and 1975, including approximately 0.7–1.6 tons of dioxin associated with 2,4,5-trichlorophenol wastes (5). The New York State Department of Health has issued advisories against eating almost all fish from both the Buffalo and Niagara Rivers on the basis of contamination with PCBs, dioxin, and mirex coming from these sites (7).

The potential sources of exposure are multiple and are not only from the bodies of water. To evaluate specific health indicators in the region, we compared all residents of ZIP codes that are totally or partly within 15 miles of one or more of these bodies of water. This distance includes all 70 sites identified near the Buffalo and Niagara Rivers, plus those near 18 Mile Creek.

We have used three different comparison populations in order to attempt to control as best one can for confounding factors other than environmental contamination. First, we compared frequency of diagnosis of endocrine disorders for residents of these three AOCs with that of the rest of New York State, except for residents within 15 miles of all six AOCs. However, this comparison includes many people who live near other contaminated sites. Therefore, we also compared frequency of diagnosis with residents of ZIP codes in New York State, excluding New York City, that do not have any state or federal Superfund sites, as well as with those of residents of ZIP codes that

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have a Superfund site but not one where the listed contaminants of concern do not include PCBs, dioxins, furans, or persistent pesticides.

There are clearly some limitations in this procedure. ZIP codes are not regular or constant in size, and residents of a ZIP code region may live at some distance from the site of contamination. Thus, residence within a ZIP code is only a crude indicator of residential proximity to a site of environmental contamination. Without personal identifiers, or at least a unique personal number, we cannot distinguish, for example, three hospitalizations by the same patient from hospitalizations of three different individuals. Furthermore, it is not possible to identify with absolute confidence a control population that is comparable in all respects other than exposure. A major limitation is that there are many causes of disease, and there may be geographic variations in the risk factors for various diseases that have nothing to do with environmental contaminants. These factors include socioeconomic status, diet, exercise patterns, genetic factors, personal habits, access to healthcare, variation in individual physician diagnostic abilities and reporting, and numerous other factors that cannot be evaluated from the use of only these databases.

However, there are also major advantages of the use of these data. Although ZIP codes provide only an approximate indication of exposure, by using all hospitalization data one has large numbers of diagnoses in the denominator (all of New York State except the study AOCs). Whereas the numerator may be small if one is dealing with an AOC with a small population, by pooling residents from urban AOCs with a relatively large population and using SPARCS data from a number of years,

we can compare hospitalization diagnoses of a significant population with those of the rest of New Yorkers, as well as more restricted New York comparison populations. Use of ZIP codes without Superfund sites serves as a control for exposure, but use of this control population is limited by the likelihood that socioeconomic status is greater in such areas. Therefore, we have used a separate comparison population living in ZIP codes with Superfund sites, but ones that do not contain the same contaminants as in the study area. If patterns of disease are found consistently over these three comparisons, then there is at least some reason for support of the hypothesis that residential proximity to sites containing persistent organics increases risk of certain diseases. In addition, use of the SPARCS data by ZIP code allows a first approach to obtaining information comparable to that in the Canadian reports on the U.S. side of the border.

## Methods

### The Study Area and Its Population

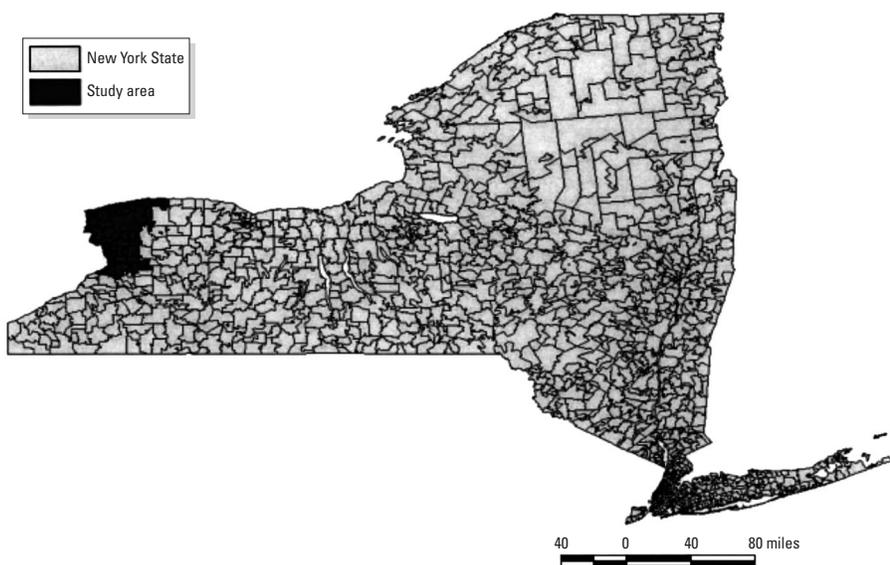
There are six AOCs in New York State: Niagara River, Buffalo River, 18 Mile Creek, Oswego River, the Rochester Embayment and Genesee River, and the St. Lawrence River near Massena. Because the initial designation was based upon these bodies of water, in an effort to define the community surrounding the waters, any ZIP code within 15 miles of the AOC was included in the study area. ZIP codes were used not only because each represents a small geographic unit, but also because they coincide with the New York State Department of Health data collection process.

This initial study focused on selected diagnoses of endocrine diseases of combined

residents of the area near the Niagara River, Buffalo River, and 18 Mile Creek. These AOCs are in geographic proximity, and in general they have the same types of contaminants. In addition, this combined area comprises a relatively populous region. ZIP codes within 15 miles of the Buffalo River are 14201, 14202, 14203, 14204, 14210, 14220, 14218, 14219, 14206, 14212, 14227, 14225, 14211, 14209, 14208, 14224, 14127, 14059, 14086, 14083, 14075, 14085, 14052, 14031, 14228, 14150, 14260, 14051, 14221, 14223, 14072, 14014, 14213, 14226, and 14059. ZIP codes for 18 Mile Creek include 14028, 14008, 14012, 14098, 14105, 14067, 14108, 14094, 14108, 14172, 14174, 14131, 14132, and 14092. ZIP codes for Niagara River are 14174, 14131, 14172, 14092, 14094, 14132, 14109, 14305, 14301, 14304, 14120, 14068, 14051, 14032, 14031, 14221, 14217, 14223, 14072, 14226, 14228, 14150, 14260, 14207, 14216, 14214, 14215, 14208, 14211, 14201, 14203, 14222, 14202, 14213, 14209, 14212, 14206, 14210, 14220, 14225, 14227, 14224, 14026, 14043, 14059, 14086, and 14303. Figure 1 shows the locations of the study area.

According to the 2000 U.S. census, the population living in ZIP codes within 15 miles of the Niagara River, Buffalo River, and 18 Mile Creek was 1,102,158. The population of New York State in 2000 was 16,224,726. Hence, the study area population represents 6.7% of the state population. However, we also excluded from consideration those persons residing within 15 miles of the other three AOCs in this comparison.

Two other comparison populations were identified. New York DEC has identified 865 state Superfund sites and lists location and major contaminants for each site. The state listing includes all federal National Priority Sites. We reviewed this list, identified all ZIP codes containing a state or federal Superfund site, then further identified those where PCBs, dioxins, furans, or persistent pesticides are listed as major contaminants. In the case of Superfund sites that are bodies of water, such as the Hudson River, we included every ZIP code that abuts the river in the region of contamination in this category. In these analyses we excluded New York City, which differs significantly from the rest of New York in many ways. We identified all ZIP codes that are not in New York City and that do not contain or abut any Superfund site. There are 1,258 such ZIP codes, with a population of 4,641,170 persons. These we call "clean" ZIP codes. Because it is likely that per capita income is higher in clean areas than in those containing Superfund sites, we also identified all ZIP codes that contain or abut a



**Figure 1.** Map of the study area in western New York State, designed to include all ZIP codes within 15 miles of the Buffalo River, Niagara River, and 18 Mile Creek.

Superfund site but that do not list PCBs, dioxins, furans, or persistent pesticides as major contaminants. Most of these have metals or volatile organics as the major contaminants. Although these contaminants may also cause health effects, they would be expected for the most part not to be identical to those induced by persistent organics. Furthermore, the per capita income in these areas is likely to be more similar to that in areas with Superfund sites containing the persistent organics. There were 1,499 such ZIP codes, with a total population of 7,772,250.

### Data Used

The disease occurrence data were obtained from the SPARCS inpatient database for 1993–1998. This data set contains the claims and discharge data for all inpatient stays in Article 28 facilities (hospitals and clinics) in New York State, with approximately 2.5 million records per year. The data include sex, age, ZIP code of residence of the patient, and the diagnosis reported by the hospital or clinic for each patient, based on the *International Classification of Disease, Ninth Revision (ICD-9)* codes (8). All diagnoses are reported for each hospitalized patient, whether or not any particular disease was the cause of hospitalization. The data were not adjusted for either multiple visits or for transfers between and within hospitals, and do not include visits to doctor's offices or outpatient departments or clinics. To increase the statistical power of the analyses and the confidence in the results obtained, data from 1993 to 1998 were considered together, giving more than 8 million hospitalizations.

The population data were extracted from Summary Tape File 3B of the U.S. 2000 Census of population and housing. The data contain 100% counts of population (by sex and by age) at the ZIP code level. The 2000 Census was used because there is no public-use data available at the ZIP code level for noncensus years 1993–1998. By using these population data we assume that the population structures kept stable from 1993 to 2000 in the study area and the comparison area.

### Data Analysis

To compare disease frequency in the two populations, we determined diagnosis of a particular disease as the annual number of diagnoses per 100,000 population. As females and males have different patterns of morbidity, we used a sex-specific approach to analyze the data. Rates were also adjusted to reflect a standard age distribution. This procedure, termed "direct age standardization," minimizes possible effects due to differences in age composition when comparing data from different populations (9).

The sex-specific U.S. population in 2000 was the standard population used in the

direct age standardization process. The direct age-standardized morbidity rates (ASMR) were calculated by the formula

$$ASMR_i = w_i(d_i/n_i) \quad [1.1]$$

where  $w_i$  is the fraction of the standard population (sex-specific) falling within age group  $i$ ,  $d_i$  is the number of hospitalizations for the period of study in age group  $i$ , and  $n_i$  is the person-years at risk for the period under study in age group  $i$ . To calculate the annual standardized rate, we divided the number of years of data analyzed by 6. Standardization was done for populations divided into 19 age groups consisting of one group of infants less than 1 year of age, a group of preschoolers 1–4 years old, 16 consecutive groups spanning 5-year age intervals, and a final group of elderly adults over 85 years of age. In some analyses, wider age groups (0–24 years, 25–44 years, 45–74 years, and  $\geq 75$  years of age) were used to be comparable to the Canadian analyses. Because a certain number of positive relationships should be found by chance, we focused on consistency of the differences between the ASMRs of the two areas over the age groups, comparing males and females, and on consistency using the three comparison populations. A summarized age-standardized morbidity rate (SASMR) was then calculated by the formula

$$SASMR_j = \sum w_i(d_i/n_i) \quad [1.2]$$

where  $j$  is an age category and  $i$  is the age group within this age category. The Z-test for the difference between the SASMRs for the study-area population and the comparison area population were then applied to determine the statistical significance of the comparison. The null hypothesis is that there is no difference between the two populations, and the corresponding research hypothesis is that there is some difference. Statistical study has shown that the distribution of an SASMR is skewed (10). To improve the normal approximation, log-transformed SASMRs were used, and standard errors were constructed for the transformed SASMRs. The formula of Z-test (11) is

$$Z = \frac{[\log_e(SASMR_a) - \log_e(SASMR_b)]}{\sqrt{\frac{\text{var}(SASMR_a)}{SASMR_a^2} + \frac{\text{var}(SASMR_b)}{SASMR_b^2}}} \rightarrow N(0,1), \quad [1.3]$$

where  $SASMR_a$  is the SASMR for the study-area population for the specified age category;  $SASMR_b$  is the SASMR for the comparison-area population for the specified age category, and

$$\text{var}(ASMR) = \frac{\sum [(N_i^2 p_i)/n_i]}{[\sum N_i]^2} \quad [1.4]$$

In formula [1.4],  $N_i$  is the person-years for the period under study in age group  $i$  of the standard population within the specified age category;  $n_i$  is the person-years at risk for the period under study in age group  $i$  of the specific population within the specified age category; and  $p_i$  is the age-specific morbidity rate for the age group  $i$  within the specified age category. All rates are expressed as annual rates. The  $p$ -value derived from this test is the probability that the actual difference in SASMRs between the study area and comparison area populations is greater than or equal to the calculated difference of Z. The only results reported are at the level of significance  $p < 0.01$ .

### Selected Health Outcomes

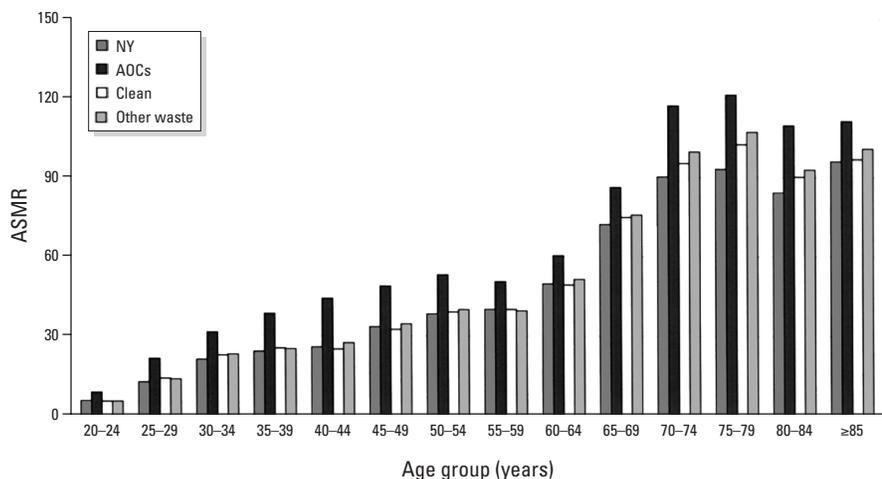
We considered only selected endocrine health outcomes for this preliminary study. These were selected on the basis of a reasonable hypothesis relating disease to exposure to environmental contaminants present in the AOCs. The selected health outcomes, with the corresponding ICD-9 codes, are as follows:

- Disorders of thyroid gland (240–246)
- Ovarian dysfunction (255)
- Testicular dysfunction (257)
- Diseases of female genital tract (617–629)
  - Endometriosis (617)
  - Infertility female (628)

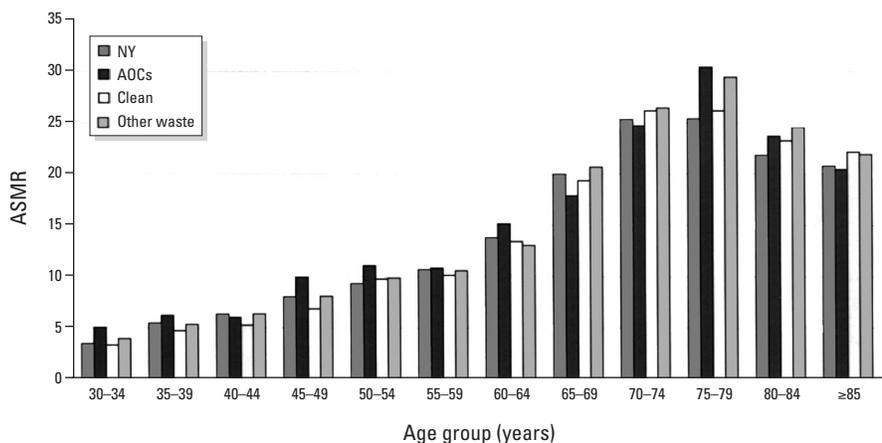
### Results

Figure 2 shows ASMR of disorders of the thyroid gland (ICD-9 240–246) for females, whereas Figure 3 shows similar results for males who reside in ZIP codes within 15 miles of the Niagara River, Buffalo River, or 18 Mile Creek (second bar from left), compared with the rest of New York State except for the six AOCs (left bar), the clean areas (second bar from right), and ZIP codes with other Superfund sites (right bar). There is a consistent elevation in incidence of thyroid disorders in women at all ages  $>24$  years in the AOCs when compared with those in all three comparison populations, whereas no such relationship is obvious for men. As expected, the ASMR for thyroid disease for females is much greater than that for males.

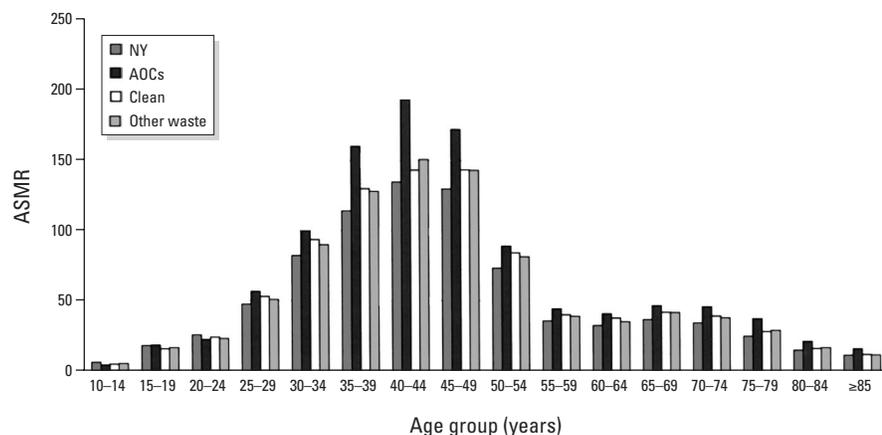
Figure 4 shows results for disorders of the female genital tract (ICD-9 codes 617–629). As for thyroid disease, there is a significant and consistent elevation in the diagnosis of female genital tract disorders in the three AOCs when compared with those in all three comparison populations at ages  $>25$  years. We examined two specific diseases in women. Infertility in females was not significantly different from the rest of the females of New



**Figure 2.** ASMR of thyroid gland disorders in females as a function of age in the study area (second bar from left) compared with the rest of New York State minus the population of all six AOCs (left bar), all clean ZIP codes outside of New York City (second bar from right), and all ZIP codes outside of New York City that have a Superfund site but do not have persistent organic pollutants as a major contaminant (right bar).



**Figure 3.** ASMR of thyroid gland disorders in males as a function of age in the study area (second bar from left) compared with the rest of New York State minus the population of all six AOCs (left bar), all clean ZIP codes excluding New York City (second bar from right), and all ZIP codes outside of New York City containing a Superfund site that does not have persistent organic pollutants. Note that the ASMR scales are different for women (Figure 2) and men.



**Figure 4.** ASMR for diseases of female genital tract as a function of age in the study area (second bar from left) compared with the rest of New York State minus the population of all six AOCs (left bar), all clean ZIP codes excluding New York City (second bar from right), and all ZIP codes outside of New York City containing a Superfund site that does not have persistent organic pollutants.

York State. Incidence of endometriosis was elevated in the study area in women for all ages >24 years (Figure 5). There was also no significant difference in diagnosis of testicular dysfunction between comparison groups.

Tables 1–3 show the Z-test sign and significance, if any, at the  $p < 0.01$  level for SASMR for all observations for these ICD-9 codes based on ages 0–24, 25–44, 45–74, and  $\geq 75$  years. Table 1 shows the results of comparison with residents of all of New York State except for the six AOCs. Table 2 shows comparison with residents of ZIP codes that do not contain any Superfund site, and Table 3 shows comparison with residents of all ZIP codes that contain a Superfund site that does not list persistent organics among the contaminants of concern. Note that there is consistency across the three comparison populations for all significant differences with the exception of endometriosis in the 45- to 75-year-old age group.

## Discussion

Several endocrine diseases appear to be more common among residents who live in ZIP codes near the three AOCs in New York State. Although there are a number of possible explanations for these differences, the diseases that are elevated are among those also elevated in some of the Canadian AOCs. These consistencies lend support for the hypothesis that exposure to environmental contaminants present in the vicinity of the Buffalo and Niagara Rivers and 18 Mile Creek may contribute to the elevated incidence of these diseases. However, we cannot rule out the possibility that the similarities result from a common set of confounders in western New York State and sites in Ontario near the Great Lakes.

The hypothesis behind these studies is that residential proximity to a hazardous waste site is a risk factor for elevated exposure to toxic substances and subsequent disease. There is only limited evidence to support this hypothesis. Yaffe and Reeder (12) did not detect elevated PCB levels in children living in an area of PCB contamination in a Toronto community compared to those in a control area. However, Stehr-Green et al. (13) reported that people living near waste sites had a higher average serum PCB level, and a greater percentage had PCB levels elevated with respect to the average U.S. level. Geschwind et al. (14) and Dolk et al. (15) have both reported elevated incidence of birth defects in individuals living near hazardous waste sites, but other studies have not seen this relationship (16).

There are a number of exposure pathways that might contribute to body burden, including consumption of local fish or other wildlife, inhalation of volatile contaminants,

and dermal absorption from swimming or wading. It is also possible that dust from contaminated sediments is ingested through a variety of routes by those living near these contaminated sites. Griffith et al. (17) have shown an association between residence near hazardous waste [National Priority List (18)] sites and incidence of various cancers. Vrijheid (19) recently reviewed residence near hazardous waste sites and various disease and concluded that various adverse health effects correlate with such residential proximity, although biases and confounders cannot be excluded as explanations for at least some of the reported relationships.

Not all Canadian AOCs show a similar pattern of disease. In fact, they appear to break down into at least two different groups on the basis of whether there are elevations in disease in general, as well as in specific diseases. For example, 14 of the 17 AOCs show elevated rates of hospitalization for both men and women, significant at the 99% confidence level. The exceptions were Wheatley, Metro Toronto, and Hamilton Harbor. These three AOCs, compared to the rest of Ontario, report a lower incidence of diagnosis of several of the diseases that one can hypothesize being related to endocrine disruption from the contaminants of concern. Other Canadian AOCs showed elevations for some, but by no means all, of the diseases under consideration. For example, hospitalizations for disease of the female genital tract were elevated in 12 AOCs, all at the 95% confidence level. The exceptions were Wheatley and Port Hope, which were not different from the rest of Ontario, and Hamilton Harbor, Metro Toronto, and Bay of Quinte, which were statistically significantly less than the rest of Ontario.

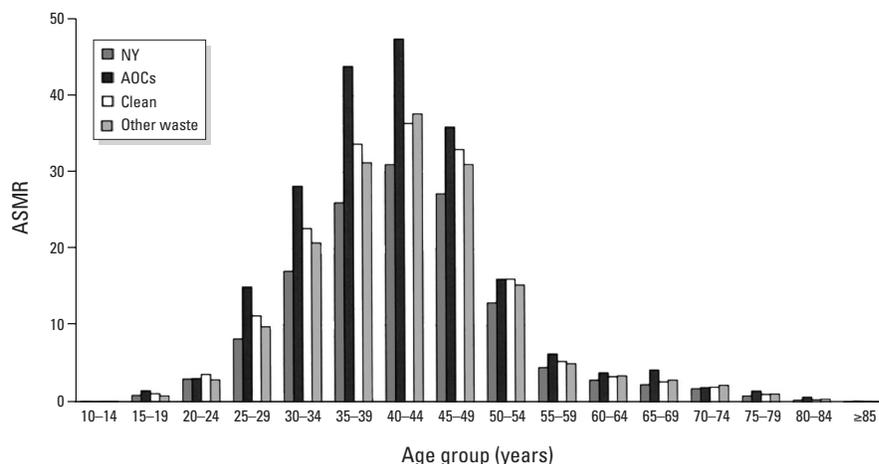
### Thyroid Disease

One of the most striking elevations in our study was that for thyroid disease in women. These ICD-9 codes include goiter, hyper- and hypothyroidism, thyroiditis, and other thyroid disorders. There was a consistent elevation in hospital diagnoses for residents of the study area compared with those of all three comparison populations, and both the incidence and the difference increased with age. This is consistent with what was found in some of the Canadian studies, where thyroid disease was elevated in women but not men from the Detroit River, St. Clair River, St. Mary's River, Collingwood, Jackfish, and Metro Toronto AOCs.

There is clear evidence from animal studies to support the hypothesis that PCBs and dioxin/furans interfere with thyroid function, probably secondary to the fact that the structures of these molecules are somewhat similar to that of thyroid hormone.

Experimental administration of PCBs results in altered thyroid structure and function. Chronic exposure to Aroclor mixtures results in an enlargement of the colloid droplets within the follicular cells and follicular cell hyperplasia (20,21). Aroclors at doses as low as 0.9 mg/kg/day for 35 days produce

changes in the thyroid gland, which implicate direct damage (22). However, different PCB congeners have very different potencies (23), and as both *ortho*-substituted and coplanar congeners alter thyroxine (T<sub>4</sub>) levels, it is unlikely that Ah-receptor activation is involved. Depending upon the dose, the



**Figure 5.** ASMR for endometriosis, a subdivision of diseases of female genital tract (Figure 4), for residents of the study area (second bar from left) compared with those of all of New York minus the six AOCs (left bar), all clean ZIP codes (second bar from right), and residents of all ZIP codes that have Superfund sites not containing the contaminants of concern.

**Table 1.** SASMR for study area compared with the rest of New York State.

Causes of hospitalization	Age categories (years)			
	0–24	25–44	45–74	≥75
Disorders of thyroid gland (female)	NS	+	+	+
Disorders of thyroid gland (male)	NS	NS	NS	NS
Other disorders of female genital tract	NS	+	+	+
Endometriosis	NS	+	+	NS
Infertility	NS	NS	NS	NS
Ovarian dysfunction	NS	NS	NS	NS
Testicular dysfunction	NS	NS	NS	NS

Abbreviations: +, sign of the Z-value with  $p < 0.01$ ; NS, SASMR not significantly different from 1.

**Table 2.** SASMR for study area compared with all clean areas.

Causes of hospitalization	Age categories (years)			
	0–24	25–44	45–74	≥75
Disorders of thyroid gland (female)	NS	+	+	+
Disorders of thyroid gland (male)	NS	NS	NS	NS
Other disorders of female genital tract	NS	+	+	+
Endometriosis	NS	+	NS	NS
Infertility	NS	+	NS	NS
Ovarian dysfunction	NS	NS	NS	NS
Testicular dysfunction	NS	NS	NS	NS

Abbreviations: +, sign of the Z-value with  $p < 0.01$ ; NS, SASMR not significantly different from 1.

**Table 3.** SASMR for study area compared with all areas with other waste sites.

Causes of hospitalization	Age categories (years)			
	0–24	25–44	45–74	≥75
Disorders of thyroid gland (female)	NS	+	+	+
Disorders of thyroid gland (male)	NS	NS	NS	NS
Other disorders of female genital tract	NS	+	+	+
Endometriosis	NS	+	NS	NS
Infertility	NS	NS	NS	NS
Ovarian dysfunction	NS	NS	NS	NS
Testicular dysfunction	NS	NS	NS	NS

Abbreviations: +, sign of the Z-value with  $p < 0.01$ ; NS, SASMR not significantly different from 1.

time of exposure, and the congeners, PCBs either decrease or mimic thyroid function (24). Both Aroclor 1254 (25) and some single congeners (26,27) have been reported upon chronic treatment to result in a decrease in serum  $T_4$ . However, one study has reported an increase in both triiodothyronine ( $T_3$ ) and  $T_4$  with either ingestion and inhalation exposure to Aroclor 1242 (28), and Desaulniers et al. (26) found that whereas chronic exposure to PCB 126 reduced both  $T_3$  and  $T_4$  in a dose-dependent fashion, PCB 153 resulted in increased  $T_4$ . Thus, different PCB congeners may have different effects. The recent paper by Zoeller et al. (29) provides particularly clear evidence that a PCB mixture, Aroclor 1254, has diverse effects on developing animals. They demonstrated that developmental exposure resulted not only in reduced  $T_4$  but also in an increased expression of genes that are stimulated by thyroid hormone.

PCBs probably interfere with thyroid function at multiple sites. PCBs bind to transport proteins and in so doing displace thyroid hormones (30). They activate glucuronidating enzymes, which further increases excretion (31). In addition they may induce direct effects on the thyroid through the inhibition of proteolysis of thyroglobulin (32). Even less is known about the actions of the various metabolites of PCBs, although it is clear that some of these also have the ability to disrupt thyroid function. Methylsulfonyl metabolites of tetra- and pentachlorinated congeners reduce  $T_3$  and  $T_4$  and cause an increase in thyroid-stimulating hormone (TSH) levels (33). Hydroxylated PCB metabolites inhibit deiodinase type 1 and  $T_2$ -sulfotransferase activity (30), and bind to transthyretin, and in so doing displace  $T_4$  (34). Cheek et al. (35) found that it was only the hydroxylated PCBs, not the parent compounds, that bound to transthyretin and thyroid-binding globulin and report that they had the same affinity for transthyretin as thyroid hormone. They may also activate uridine diphosphate-glucuronyltransferase, which then increases the biliary excretion of  $T_4$ -glucuronide (31,36). In a recent review, Brucker-Davis (37) concluded that except in the fetus the major mode of action of coplanar congeners is through increased glucuronidation, whereas the *ortho*-substituted congeners, and particularly their oxidative metabolites, act through multiple other pathways, including interference with transport proteins, direct action on the thyroid gland, and changes in the kinetics of thyroid hormone metabolism.

We previously reported a striking excess of hypothyroidism in older women from a different AOC, the Mohawk population living at Akwesasne on the St. Lawrence River at the juncture of Ontario, Canada, and New

York (38), and we are currently relating serum PCB concentration in this population to disease incidence. In Mohawk adolescents our colleagues demonstrated a significant direct relationship between serum PCB level and the levels of TSH and an inverse relationship with serum-free and total  $T_4$  (39). This relationship is particularly striking because the PCB levels are relatively low, having a geometric mean of 1.82 ppb and a maximum of 4.75 ppb in these children. These levels are not different from those found in most people in developed countries. Nevertheless, this observation of a relationship to serum PCB levels suggests that these background levels of PCBs exert significant effects on thyroid hormone levels. Emmett et al. (40) demonstrated decreased serum  $T_4$  levels in workers occupationally exposed to PCBs.

The results of the study by Schell et al. (39) are important in considering our results using the SPARCS data in that the Schell study included direct measurement of serum PCB levels. Although the adolescents in their study were not diagnosed with thyroid disease, the direct relationship between PCB levels and alterations in thyroid hormones adds support to the hypothesis that PCB levels may contribute to thyroid disease. In addition, these effects are occurring at PCB concentrations that could conceivably be influenced by residence in proximity to an AOC.

### Sex Steroids

We investigated several diagnoses related to sex steroid function. We did not detect any difference in the study area for diagnoses of ovarian or testicular dysfunction. However, there was a striking elevation in the incidence of other disorders of the female genital tract, some of which were due to an elevated incidence of endometriosis. The Canadian reports also documented an elevated incidence of female genital disease in AOCs (41).

Many of the contaminants in the AOCs have the potential to alter incidence of endocrine disease. DDT and its metabolites are estrogenic (42). Several pesticides alter estradiol metabolism (43) and increase birth defect incidence (44). Dioxin exposure results in an elevation in incidence of endometriosis in monkeys (45), and some human studies are consistent with this conclusion (46). However, a more recent publication from the same authors (47) reports that the prevalence of endometriosis in dioxin-treated animals correlated with the concentration of one coplanar PCB congener, 3,4,3',4'-tetrachlorobiphenyl (PCB 77), and not that of dioxin, although the source of PCB exposure was not known. It is not clear whether it is the dioxin exposure rather than serum levels, or the levels of PCB 77 that is related in induction of the disease.

Dioxin functions as an anti-estrogen, primarily secondary to the fact that dioxin and other dioxinlike substances (furans and coplanar PCBs) induce liver P450 enzymes that degrade estrogen (48) and/or cause a reduction in the numbers of estrogen receptors (49). However, other PCBs, and particularly the hydroxy metabolites of some PCB congeners, are estrogenic, including PCB 77 (50,51). Although the factors that promote endometriosis are not well understood, both immune and endocrine dysregulation are believed to be involved (52).

Our observations are noteworthy on several counts. We did not observe differences in fertility in women nor an elevated incidence of dysfunction of ovaries or testes. However, it is not clear that the SPARCS database is the best place for obtaining accurate diagnoses for these diseases. Most patients with fertility problems will obtain medical treatment on an outpatient basis; furthermore, infertility is not likely to be identified on records of hospitalization for other causes. The striking elevation of endometriosis is, however, consistent with exposure to dioxin and/or PCB 77. The study region near the Buffalo River, Niagara River, and 18 Mile Creek is known to have high dioxin levels at some sites. For example, a leachate from Love Canal contained 3 ppm dioxin, and that component accounted for all the adverse effects of leachate given to rats (53). The mechanism by which dioxin and/or PCBs induce endometriosis in monkeys is not known, but our observations, together with those of Pauwels et al. (46), are consistent with the hypothesis that a similar relationship exists in women. The diagnosis of endometriosis was greater in the AOCs than in the control, even at older ages, although it was much less than in the 30- to 50-year age range. It is interesting that postmenopausal endometriosis has been associated with hormone replacement therapy (54,55). Conceivably, an endocrine-disruptive xenobiotic could induce similar disease.

### Conclusions

It is entirely possible that the results reported here are unrelated to the environmental contamination of the Buffalo and Niagara Rivers and 18 Mile Creek. However, it is not obvious what other factors would result in these specific endocrine diseases being elevated compared with those in each of the three comparison groups. Certainly there are numerous risk factors for each of these diseases, and exposure to PCBs, dioxin/furans, and persistent pesticides would probably not be listed as the major risk factors by most knowledgeable professionals. Nonetheless, our observations, in conjunction with the Canadian studies detailed in this Supplement

(41,56), provide support for the hypothesis that environmental contaminants contribute to the incidence of these diseases, and that simply living near a contaminated site results in an increase in exposure, which is reflected in elevated disease diagnosis among those residents. This hypothesis must be further tested at different sites and with direct measurement of biomarkers of exposure.

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