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CHAP Studies A and C Integration: A Report to the Technical Subcommittee of the Public Liaison Committee for the City of Port Colborne

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Appendices

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1.0 Introduction

The studies reviewed here are those relating to the health of the residents, commissioned by the City of Port Colborne, to evaluate the health status of the community and to examine associations between health status and particular exposures of concern. These exposures are to cobalt, nickel, copper, and arsenic, hereafter referred to as the "chemicals of concern" (COCs). Two reports were prepared by the Ventana Clinical Research Corporation ("Ventana") for the Community Health Assessment Project (CHAP). These were a community survey, here called the CHAP A report, and an examination of hospital discharge data, the results of which are here called the CHAP C report. The purpose of the present report is to make a recommendation as to whether future studies of human health, specifically case controlled studies, are warranted by the integrated evidence of CHAP A and CHAP C. These recommendations are based upon review of the findings reported by the Ventana analysts, results of further analyses as appropriate, and a review of the literature pertaining to the COCs . The criteria, laid out in CHAP B, the Decision Document, were reviewed and conclusions regarding future studies were drawn.

2.0 Review of the Reports of the CHAP Studies A and C

CHAP A was a cross-sectional community-based survey of health conditions and symptoms, conducted in the City of Port Colborne in 2003. Extensive efforts were made to identify all households in the City, and self-administered questionnaires (one for adults, and one for children completed by their parents) were mailed to all known residents of the City in February 2003. Data were collected on items such as overall health status, sociodemographic characteristics, lifestyle and occupational exposures, length of residence in the City, and a substantial list of signs and symptoms of adverse health conditions, as well as physician-diagnosed diseases. All health data were self-reported, and there was no effort to confirm reported diagnoses through physician or hospital records. To the extent possible, the health-related questions were constructed to allow comparison to other Canada-wide, Ontario-based, or other specialized surveys.

The response of residents was substantially less than anticipated, being approximately 35% to 40% overall. The response by Geographical Study Area (GSA) was highly variable, ranging from 28% to 50%. The low response rates, along with a variation in response among GSA regions, diminish the representativeness of the achieved sample, and reduce the comparability both between GSA regions and between the City and other survey findings. In addition, the generalizability of the findings for the City as a whole is limited by the low response.

In general, the questionnaires appeared reasonably comparable to other reports, although there are some consistent differences. In particular, the Port Colborne survey examined lifetime prevalence, while surveys such as the Canadian Community Health Survey (CCHS) asked about point prevalence. This would obviously lead to over-estimation of "prevalence" in the CHAP A report, and excess "risk" when these data are compared with, say, the CCHS. Attempts were made by the investigators to adjust findings for potentially confounding variables, including sex, age, income, and tobacco exposure. Dose-response, while incompletely analyzed in the report, was assessed with the proxy measure of length of residence in the GSA 3.

CHAP C was based on hospital discharge data, and compared these for Port Colborne with data on a set of Ontario communities chosen for their similarities to Port Colborne based upon a set of sociodemographic variables. In addition, the Port Colborne discharge data were compared to Ontario

overall, and to the group of 11 other communities which comprise the Niagara peninsula. Data for this analysis were provided by the Canadian Institute for Health Information (CIHI), and covered the period 1980 to 2000. Some adjustment of the hospital discharge rates was possible, for such potential confounding variables as sex and age (available at the individual level), and mean income, education level, smoking, and availability of physicians (ecological variables).

A number of factors limit the conclusions that can be made from the hospital discharge comparison. The discharge database does not represent individual patients, but individual hospitalizations. To the extent that some individuals are hospitalized for the same condition more than once in a given year, the hospital discharge rates for that condition will be overestimates. Aside from differences in disease frequency and severity, discharges can vary between communities due to different hospitalization patterns of the treating physicians and differential access to hospital beds. Adjustment for the potentially confounding ecological variables is probably less than complete, so that residual confounding cannot be ruled out. Finally, air pollution - a probable confounding factor for a number of the discharge diagnoses - was not measured or accounted for.

The principal findings from CHAP A need to be considered in two parts. First is the comparison to Ontario data; this indicates that Port Colborne residents were more likely to report a number of signs and symptoms of diseases of various systems, including cardiovascular (hypertension, heart attack, angina, congestive heart failure), digestive (ulcers, allergies, and bowel disorders), respiratory (asthma and chronic bronchitis), and endocrine (thyroid). On the other hand, given the difficulties with direct comparison to data that were collected using different survey methods and different wording of some questions, one would expect that the lifetime prevalence reported by Port Colborne residents would be higher than the current prevalence reported in the comparison survey, since lifetime prevalence would include current prevalence of signs and symptoms of diseases, as well as any signs or symptoms of diseases which might have occurred in the past but are now resolved.

The more robust comparisons are those internal to Port Colborne, particularly a comparison of data from the GSA's with those of long-term residents of GSA 3. In this regard, GSA 3 was higher than the other GSA's for only a few conditions: peripheral neuropathy, ulcers, and symptoms associated with hypothyroidism, and symptoms associated with chronic fatigue syndrome. Estimates show that GSA 3 residents had lower risk of food allergies than the residents of the other GSA's.

A larger number of significant elevations appeared in the comparison between long-term GSA residents and those Port Colborne residents who never lived in GSA 3. These centred around the endocrine and musculoskeletal systems [thyroid (both hyper- and hypothyroid conditions), chronic fatigue syndrome and the complex of symptom ascribed to it, multiple chemical sensitivities, arthritis and rheumatism], but also included diabetes, high blood pressure, stomach or intestinal ulcers, migraine headaches, and peripheral neuropathy. It is telling that there was no dose-response for any of these conditions or symptoms evident in the data. Dose-response is one of the features of association between exposure and disease that is used to support a conclusion of causation. (Other features include consistency of findings across studies, biological plausibility, and high relative risk.) It is supposed that the greater the dose of exposure, the greater the likelihood of an effect due to that exposure. Without evidence of a dose-response, it may be as likely that the association between exposure and disease is simply a coincidence, or that some other exposure is associated with, and causal of, the effect.

The principal findings from CHAP C relating to the Ontario comparison indicated higher hospital discharge rates for many of the discharge diagnoses evaluated. As with CHAP A, however, this comparison is less valuable than those which use the Niagara communities as the comparator, since the

Ontario comparison could not be adjusted for some of the important confounding variables. The comparator communities yielded indications of excess hospital discharge for Port Colborne for some conditions, namely ischemic heart disease, asthma (only in two of the four age groups and one of the two time periods), acute respiratory infection (overall, and in three of the four age groups, both sexes, and both time periods), and chronic obstructive pulmonary disease (only in the youngest age group).

The comparison with the Niagara communities was somewhat at variance with that for the other comparison communities. There was an excess of discharges in Port Colborne for ischemic heart disease (overall, and in three of the four age groups, both sexes, and both time periods), asthma (only in one of the age groups), acute respiratory infection (overall, in two of the four age groups, but only in females and only in the later time period), and chronic obstructive pulmonary disease (only in the youngest age group). On the other hand, there also were excesses for respiratory system cancers (only in the young adult age group and in the earlier time period), acute myocardial infarction (middle-aged males), cerebrovascular disease (males only), pneumonia and influenza (overall, and in one of the age groups, females, and the later time period).

Along with these excesses, what also should be clearly recognized is the very large number of decreases in hospital discharges for Port Colborne, especially in relation to the comparison communities, as well as the overwhelming number of "equivalencies" in relation to the Niagara communities.

With the limitations of comparing Port Colborne with provincial data firmly in mind (as described above), one might examine the excesses noted in CHAP A and CHAP C, to look for consistencies in the findings. With respect to CHAP A, the only partially consistent findings were for hypertension, diabetes, thyroid symptoms (particularly hypothyroid), and arthritis and rheumatism. We say "partially consistent" because, within Port Colborne, these conditions were not uniformly elevated (GSA 3 vs. other, and GSA 3 long vs. never).

With respect to CHAP C, again, only partially consistent findings (i.e., an effect is seen only in some of the subgroups defined by age group, sex, and time period) were obtained for ischemic heart disease, asthma, acute respiratory infections, and chronic obstructive pulmonary disease.

The final comparisons to be made for these two reports relate to the consistency of findings between CHAP A and CHAP C, where possible. These comparisons are limited due to the different disease/symptom classifications used in the two studies. Still, there are salient findings, for conditions identified in both reports:

- heart disease was not elevated in CHAP A, but was in CHAP C; heart attack was elevated in CHAP A (vs. Ontario only), and also in CHAP C (vs. Niagara communities);
- congestive heart failure was consistently not elevated in CHAP A, nor in CHAP C;
- cancer was elevated in CHAP A (vs. Ontario only), and respiratory malignancies were elevated in CHAP C (only in young adults, and in one time period);
- asthma was elevated in CHAP A (vs. Ontario only) and in some of the sub-analyses in CHAP C;
- while the conditions that might be classified as respiratory infections (sinusitis, rhinitis, bronchitis) were generally not elevated in CHAP A, that group of conditions was elevated in CHAP C.

The inconsistencies within and between the findings of CHAP A and CHAP C may be due to a number of factors, such as differences in terminology, differences in severity, and random variation across multiple comparisons. Some terminological differences are unavoidable: in CHAP A the focus was on self-reported symptoms and conditions, and diseases needed to be identified in the vernacular. In contrast, in CHAP C, discharge diagnoses would be dictated by the terminology and coding rules of the International Classification of Diseases, version 9 (ICD-9). Similarly, differences in severity were embedded in the methods of each of the CHAP reports: self-reported symptoms mild enough to be tolerated without need for medical advice, vs. those requiring hospitalization.

In summary, there were some elevations in symptom reporting and hospital discharges in Port Colborne that require further consideration, with respect to statistical and biological concerns. These conditions are asthma, hypothyroid symptoms, symptoms of chronic fatigue syndrome, ischemic heart disease, acute respiratory infection, and chronic obstructive pulmonary disease. (This last is an anomalous finding, since chronic obstructive pulmonary disease is highly unlikely to occur in this young age group, being rather a disorder that develops over decades of exposure to a causative factor.. Distinguishing between asthma and chronic obstructive pulmonary disease may be complex, suggesting that in the CHAP C report we are seeing a mis-diagnosis/mis-coding of asthma as chronic obstructive pulmonary disease in young people.)

3.0 Statistical Considerations and Analysis

The Executive Summary of the CHAP C report prepared by Ventana describes hospital discharge rates over the period 1980 to 2000, in Port Colborne, Ontario, and in two sets of comparator communities. In the final paragraph of the Executive Summary it is suggested that the statistically significant higher hospital discharge rates observed in Port Colborne for ischemic heart disease (IHD), acute respiratory tract infections (ARI), chronic obstructive pulmonary disease (COPD), and asthma "should be evaluated as candidates for further research".

In this section of our report, a new statistical analysis is presented that uses the same database as did Ventana, but in a version more detailed and recent than was available to Ventana when they prepared the CHAP C report. This new analysis is carried out for the four hospital discharge categories of IHD, ARI, asthma, and malignant neoplasms of the respiratory and intrathoracic organs, the latter label shortened to respiratory cancer in this report (RC). These analyses were carried out for all ages combined as well as the four age-groups used in the CHAP C report. Special attention is given to the age groups in which the excesses of hospital discharge rates in Port Colborne were the largest, and statistically significant. These included: IHD (20-44 and 65+ years of age), ARI (20+ years of age) , asthma (< 20 years of age), and RC (20-44 years of age).

The elevated hospital discharge rate in Port Colborne for RC was not listed for further consideration in the CHAP C report for several reasons. The only statistically significant increase for RC was found in the 20 to 44 year age grouping, and was only significant relative to one of the two comparison groups, while statistically significant decreases were found in the other three age groups. Nevertheless, this category is re-analyzed here because cancer was a major concern expressed by 86 percent of the respondents in a random sample of 959 residents of Port Colborne that was conducted prior to the CHAP series of studies (CHAP A Report, Page 27). Moreover, the self-reported prevalence of cancer among those who participated in the Port Colborne Health Assessment was estimated to be 3.6 times higher than Ontario residents [OR=3.59, 95% CI=3.38, -

3.82 (CHAP A Report, p. 138)]. However, as stated in that report, a self-reported measure of disease, especially one associated with high mortality, does not provide an accurate assessment of population prevalence. This larger ratio may be partially due to reporting bias as can occur, for example, when a benign tumour is incorrectly reported as a malignant tumour or when the time period implied in the question is longer than that of the reference question used in the comparison survey. The elevated ratio may also be partially due to selection bias which may arise when those members of a population with an increased awareness of the issues prompted by their ill health are often found to be more likely to volunteer to participate in a survey designed to study their illnesses.

Despite these considerations hospital discharge rates for RC were re-analyzed, in addition to a more comprehensive analysis of cancer incidence rates using data in the Ontario Cancer Registry. To evaluate the extent that selection and reporting biases influenced the results, the objectively defined outcome measures of hospital discharges, and incident cases from the provincial cancer registry were analyzed. The latter offer a distinct advantage because they capture incident rather than prevalent cases that allow for community-specific rates to be estimated at an individual rather than aggregate level.

The COPD discharge rates among those less than twenty years of age were not re-analyzed because asthma accounts for the vast majority (95%) of these discharges. As such, the excess observed in the COPD category would be driven by hospital discharges for asthma.

The first CHAP C report was released before being reviewed by the TSC of the CHAP. A number of reviewers, asked to comment on the document, raised concerns and demanded modifications that were incorporated in the final CHAP C report. They asked:

(a) Was the group of 35 communities used to compare the hospital discharge rates in Port Colborne appropriate?

(b) Was the use of all five categories of hospital discharge: acute in patient, day surgery, rehabilitation, chronic care, and "other" appropriate or should only the acute in-patient category have been used.

(c) Was the Poisson Regression model appropriate for handling data expected to exhibit very large variation? Such "over dispersion" can produce p values that are too small.

(d) In each table, many comparisons were made that gave rise to statistically significant findings. Should a p value adjusted for these multiple comparisons have been used as a criterion for statistical significance?

The authors of the CHAP C report attempted to address all concerns raised in the review process. They presented their findings in a logical manner and used the word Exhibit rather than Table throughout their report. Age standardized hospital discharge rates based on a 3-year moving average for each year between 1981 to 1999 for each of the 18 health condition categories, are presented in exhibits 4 to 21. Each graph contains 4 longitudinal plots for Port Colborne, all of Ontario, and two additional comparison groups discussed below.

The 18 statistical analyses of the comparisons of hospital discharge rates between Port Colborne and the two sets of comparison communities are presented in exhibits 22 to 39. These analyses were further stratified by: age (<20 , 20 – 44, 45 – 64, and >64 years), sex, and calendar period (1980 - 1989, 1990 - 2000).

3.1 Comparison Communities

In the CHAP C Report the hospital discharge rates for Port Colborne were compared to two different comparison groups. In the first group, called the Comparison Communities (CC) in their report, communities were selected based on a score developed using a discriminant analysis to produce a measure of the statistical distance between each eligible community and Port Colborne. The scale was a linear combination of census variables such as mean income and mean age. The thirty-five communities with smallest statistical distance to Port Colborne were selected. Communities within 50 km of Port Colborne were ineligible. As shown in Table 1 this process was moderately successful in producing a comparison group more like Port Colborne than the residents of Ontario. From Exhibit 1 on page 15 of their report, part of which is given in Table 1, the mean family income in Port Colborne is much lower than the mean family income in Ontario, but quite similar to the mean family income in the group of comparison communities. Similar shrinkages of differences between Port Colborne and the CC occurred for the proportion of the population without a high school education, the unemployment rate, and the proportion of individuals over 65 years of age. The 35 communities selected are listed in Exhibit A13. That only 35 communities were used may be because the authors decided that a comparison with a larger number of communities, while likely to benefit from a reduction in variance that a larger sample size would provide, might lead to the inclusion of communities less similar to Port Colborne. Such a variance/bias tradeoff is often considered in health studies.

Table 1 Sociodemographic Characteristics for Residents of Port Colborne, the Comparison Communities and Ontario ***

Sociodemographic Characteristic	Port Colborne	35 Comparison Communities	Ontario
Mean Population Size	18,600	17,605	12,301
Percentage of population over 65 years of age	16%	15%	11%
Mean Family Income	$37,736	$37,021	$46,688
Percentage Unemployed	11%	11%	8%
Percentage not completing high school	50%	53%	40%

*** Extracted from Exhibit 1 of the CHAP C Report; values based on averages from census data from 1981, 1986, 1991, 1996.

After the first release of the CHAP C report there was considerable discussion about the validity of the CC despite the evidence reported above. A recommendation was then made by the TSC to create a second comparison group of 11 communities located geographically close to Port Colborne in the Niagara Peninsula (NG). These communities consisted of: Fort Erie, Grimsby, Lincoln, Niagara Falls, Niagara on the Lake, Pelham, Thorold, St. Catharines, Wainfleet, Welland and West Lincoln. It is often a good strategy to identify more than one comparison group. A cornerstone of the scientific method is being able to replicate the findings of previous studies. No comparison group is perfect. The differences in the means of many important confounder variables between Port

Colborne and this first comparison group were less than those between Port Colborne and the province. The second comparison group consisted of communities geographically close to Port Colborne. These communities might provide a less biased comparison with Port Colborne because they may share unknown factors common to that region. This comparison group had only eleven communities, much less than the thirty five in the CC. This small sample size might well have reduced the power of finding elevated discharge rates in Port Colborne. However it would also substantially reduce the ability to adjust for possible confounding variables, as will be discussed below. Another strategy would have been to re-analyze the data several times with Port Colborne being replaced as the target community by neighboring communities such as Welland, Niagara Falls and Fort Erie, to determine whether any elevations in the hospital discharge rates in Port Colborne relative to the CC were unique to Port Colborne. The decision to create this second comparison group was not made by Ventana but was the result of discussions following the initial release of the CHAP C Report. The statistical power associated with this smaller group will be smaller and as discussed later in this report the Niagara peninsula group was not as similar to Port Colborne as two new groups created using statistical methods similar to those used in CHAP C.

In CHAP C, Poisson regression was used to estimate the ratio of hospital discharge rates for Port Colborne relative to each of the two comparison groups. For each comparison, two sets of rate ratios were reported. The first was adjusted only for differences in the age, sex, and calendar-year distributions between Port Colborne and the comparison groups. However, other important demographic variables such as mean community income and the proportion of individuals in a community with at least a high school education could also account for differences that might be found in the hospital discharge rates between Port Colborne and other communities. Such variables derived from the 1981, 1986, 1991 and 1996 censuses were used in addition to sex, age and calendar year in the adjustment of the second set of ratios. The addition of these sociodemographic variables of income and education, by and large, attenuated many of the difference in rate ratios between Port Colborne and the comparator communities, and the Niagara communities.

Since the release of the Study C report, a much larger comparison group of communities than the two used in CHAP C has become available to us. These data were assembled as part of a research project to look at variations in asthma discharge rates in relation to outdoor levels of air pollution. This project is being led by Dr. Villeneuve, who has provided these data for analyses but is not involved in the interpretation of subsequent findings.

Hospital discharge data between 1986 and 2002 were available at a CSD level for Ontario using the 2001 census. There was a total of 586 census subdivisions (CSDs) in Ontario for which information was collected on variables such as income, proportion of males, and mean age. However, sociodemographic information is suppressed for census areas that are not large enough, are Indian reserves, or where the data are deemed to be of poor quality. Eleven of these census subdivisions provide no hospital discharge data, leaving 575 CSDs available for the analysis. For the discharge data, the number of discharges and population estimates based on census data was provided by 5 year age groupings. Restriction to those communities with sodiodemographic characteristics left 507 CSDs for analyses.

Information on smoking status was obtained from the two Canadian Community Health Surveys (CCHS) conducted in 2001 and 2003 (Appendix 1). From these two surveys combined, responses were obtained from participants in 423 Ontario census subdivisions. After restricting to Ontario CSDs with at least 10 participants, information on the prevalence of smoking was obtained for 340 CSDs, and information on the prevalence of smoking inside a home was obtained for 343 CSDs.

Hospital discharge data from the Canadian Institute of Health Information (CIHI)'s data abstract database (DAD) were extracted at a CSD level. Hospital discharge data for each year between 1986 and 2002 were supplied by five year groupings and discriminated by sex from CIHI's DAD database.

After merging the datafiles, 339 CSDs were found to have information from the Census, CCHS, and DAD databases. With these data the discharge rates over the period 1986 to 2002 for asthma, IHD, ARI, and RC were analyzed using the comparison group of 338 CSDs (CG) as well as a comparison group of 11 communities (NG), the same as one of the two comparison groups used in the CHAP C report.

A list of some of the variables from the 2001 census and the crude unadjusted hospital discharge rates among Port Colborne, the 11 other comparison communities of NG, and the remaining 327 communities with smoking status information are presented in Table 2. These numbers should, and do differ from the corresponding numbers found in the CHAP C report because the hospital discharges are collected over different periods of time. As shown in Table 2 the unemployment rate is almost the same in Port Colborne and the comparison communities. Histograms of these confounder variables are given in Appendix 2.

TABLE 2 Socio Economic Statistics from the 2001 Census for Port Colborne, the 11 Communities in the Niagara Peninsula and the Remaining 327 Communities with Information from the Canada Health Survey

		Port Colborne	Statistical n=35*	CG 338 CSDs	NG 11 CSDs	327 CSDs
Mean Income	(MINC)	48,500	53,260	68,000	57,110	68,416
Mean Age	(MAGE)	42.0	40.6	37.5	39.9	37.4
% Unemployment	(UNEMP)	12.9%	11.1%	12.9%	11.8%	13.0%
% > High School	(GTHS)	35.1%	37.4%	43.8%	40.4%	44.0%
% Males	(MALE)	48.8%	49.6%	49.4%	49.1%	49.4%
% Current Smokers	(SMOKE)	29.3%	27.7%	22.8%	22.6%	22.8%
% Resident Smokers	(SHS)	18.3%	19.4%	19.3%	21.5%	19.2%

Unadjusted Hospital Discharge Rates between 1986 and 2002

Outcome	Age group				
Asthma	<20	6.84	3.61	4.32	3.58
IHD	20-44	1.56	0.80	0.90	0.79
IHD	65+	42.84	29.08	31.08	28.94
AR	20+	1.02	0.59	0.59	0.37
RC **	20-44	0.11	0.08	0.08	0.08

* Comparison group used in CHAP C report.

** See Appendix 19 for acronyms.

As shown in Table 3A using information from 339 Ontario communities derived from the 2001 Census we find that a community's mean income is negatively related to the hospital discharge rate for IHD in the 20 to 44 year old age group. The measure used to describe the strength of such an association is called the Pearson correlation coefficient (R). The correlation coefficient for the

association between the mean income and hospital discharge rate for ischemic heart disease among those between 20 and 44 years of age is -0.53. This means that a community with a lower mean income is expected to have a higher frequency of hospital discharge rates for IHD. The correlation coefficient between the hospital discharge rate for IHD (20–44 years of age) and the percentage of smokers in a community (SMOKE) is 0.57 meaning that communities where the percentage of smokers is high are expected to have higher discharge rates for IHD. The correlation between the mean age of the community and IHD (20-44 years of age) is 0.37. From the 2001 census the mean age of the Port Colborne residents is 42 years, about five years older than the average age of the 338 communities (CG). The percentage of smokers is 29.3%, 6.5 percentage points higher than the CG and the mean income in Port Colborne is $48,500 much lower than the mean income of $68,000 in the CG. Therefore, it is important when observing an increase in a hospital discharge rate for Port Colborne such as IHD, to determine what part of that increase may be normal and in the expected range for a city with an elevated mean age, an elevated percentage of smokers and a lower mean income. In this context the mean age, mean income and percentage of smokers in a community are called confounder variables and are used in the Study C report and our report to reduce the bias in all comparisons between Port Colborne and the comparison communities. The difference in the percentage of homes with a regular smoker (SHS) in Port Colborne (18.3%) and the CG (19.3%) is very small and, not surprisingly, was not found to have a confounding effect in any of our analyses.

Table 3 Weighted (*) Pearson Correlation Coefficients Between Census Covariates and Hospital Discharge Rates

Table 3A Comparison Group (CG) n = 339

RATE	MINC	UNEM	GTHS	MAGE	MALES	SMOKER	SHS
ASTHMA <20	-0.37	0.29	-0.26	0.20	-0.31	0.38	0.35
IHD 20-44	-0.53	0.42	-0.57	0.37	-0.02	0.57	0.64
IHD 65+	-0.48	0.35	-0.58	0.32	-0.06	0.49	0.55
ARI 20+	-0.50	0.17	-0.60	0.34	0.04	0.40	0.52
ARI 20-44	-0.48	0.29	-0.57	0.18	0.04	0.42	0.50
ARI 45-64	-0.48	0.19	-0.58	0.30	0.04	0.43	0.51
ARI 65+	-0.40	0.22	-0.60	0.24	0.12	0.33	0.45
RRC 20-44	-0.26	0.23	-0.22	0.21	-0.11	0.22	0.31

Table 3B Comparison Group (NG) Niagara Peninsula n = 12

	MINC	UNEM	GTHS	MAGE	MALES	SMOKER	SHS
ASTHMA <20	-0.81	0.64	-0.53	0.45	-0.80	0.70	0.40
IHD 20-44	-0.74	0.31	-0.77	0.11	-0.39	0.81	0.46
IHD 65+	-0.31	0.04	-0.54	-0.21	-0.10	0.27	-0.12
ARI 20+	-0.38	0.43	-0.10	-0.42	-0.24	0.23	0.19
ARI 20-44	-0.44	-0.10	-0.56	0.13	-0.23	0.31	0.22
ARI 45-64	-0.50	0.03	-0.50	0.37	-0.31	0.31	0.28
ARI 65+	-0.25	-0.21	-0.35	0.41	-0.10	0.15	0.16
RRC 20-44	0.02	0.14	-0.08	-0.28	0.16	-0.10	-0.18

The two comparison groups used in our analyses were these two groups with Port Colborne removed.

* A weighted correlation coefficient gives more weight to rates from communities in which more individuals of a given age group lived over the follow-up period 1988 to 2001.

3.2 Use of Inpatient Hospital Discharge Data

After the first release of the CHAP C report concern was raised over the use of all categories of hospital discharge data: inpatient, day surgery, rehabilitation and chronic care and other. The recommendation was that inpatient days would be more reliably coded than those based on outpatient data. However using only inpatient discharge data might be problematic in instances where the total of inpatient and outpatient discharges were similar across CSDs but the inpatient discharge rates differed simply because of differences in the mix of inpatient and outpatient discharges across hospitals.

To address these concerns, the authors reported their analyses of the differences between the hospital discharge rates of Port Colborne and Ontario in Exhibits 40 to 57 using inpatient discharges only, as well as using a combination of inpatient, day surgery, rehabilitation and chronic care and other discharge categories. A review of these 18 exhibits indicates that the ratios of the discharge rates in Port Colborne relative to Ontario were similar or slightly increased for the analyses that included all four types of hospital discharges. In Exhibits 58 and 59 of their report the comparisons using Inpatient Only and All discharges is summarized for the comparisons to the CC and NG comparison communities. These analyses are not broken down by age, sex, and calendar period as was done for Exhibits 22 to 39.

As shown in Table 4 for all discharge categories except RC very little extra information, as measured by the percentage increase, was provided by using all hospital discharge categories instead of the Inpatient Only category. Differences in the estimated discharge ratios based on these two approaches are almost identical. The 20% discrepancy in the total number of discharge cases for cancer of the respiratory tract raises the issue of incomplete ascertainment of cancer cases that might occur from using hospital discharge data and supports our decision to reanalyze the cancer rates using the database of Cancer Care Ontario. In our re-analysis of the hospital discharge data only inpatient discharge data were used.

Table 4 Use of Inpatient Only Data in the Analysis

	Number of Types of Hospital Discharges			Ratio of Hospital Discharge Rates in Port Colborne Relative to Ontario	
	Inpatient Only	All Four* Discharges	Percentage Increase	Inpatient Only	All Discharges
IHD	4631	4900	5.5	1.40	1.38
ARI	1218	1224	0.5	1.78	1.75
COLD	1832	1843	0.6	1.18	1.17
Asthma	1130	1131	0.1	1.52	1.51
RC	530	662	19.9	0.96	1.04

* Inpatient acute care, day surgery, rehabilitation and chronic care.

** Extracted from Exhibits 41 to 57 of CHAP C.

3.3 Multiple Comparisons

In Exhibit 37 of the CHAP C Report results from the analysis of the hospital discharge rates for asthma are summarized for three categories: age, gender, and calendar time. The five age categories used were all ages, <20, 20-44, 45-64, ≥ 65 years of age and the two duration periods are 1980 to 1989 and 1990 to 2000. The two largest significant ratios of hospital discharge rates, occurring among those less than 20 years of age, are 1.49 for the comparison of Port Colborne to the CC comparison group and 1.38 for the comparison to the NG group. Of the remaining sixteen ratios of hospital discharge comparisons reported in the last column of Exhibit 37 all are smaller and only two are statistically significant. One of these smaller but significantly elevated ratios was for the 65+ years of age category. Should the statistical significance of the under age 20 comparison be devalued because it is just one of eighteen CC comparisons?

The multiple comparisons problem in statistics is supported by the intuitive notion that data subdivided and analyzed in many different ways will increase the probability of a statistically significant result due to chance alone. That is, an uncontrolled increase in the number of possible statistical tests will increase the number of false positive findings. However, in the case of asthma, the accumulated scientific evidence suggests that potential environmental stressors are more likely to be important among vulnerable groups such as the young and the elderly. As shown in Table 5, using data from the 339 communities, asthma hospital discharge rates are highest among the young. Although an adjustment would normally be made for such multiple comparisons, we practiced caution and permitted the a priori evidence of such an association to play a role in the evaluation of the evidence.

Table 5 Mean Asthma Hospital Discharge Rates (/ 1000)

Age Category	Sex	Cases	Mean	Min	Max
< 15	Male	104,349	5.34	0	22.3
	Female	56,112	3.01	0	14.1
15 - 64	Male	29,891	0.57	0	2.3
	Female	67,282	1.42	0	6.2
>= 65	Male	11,234	1.52	0	12.6
	Female	23,610	2.16	0	11.5

3.4 Heterogeneity of Data

The Ventana authors point out that for some diseases such as asthma, an individual who is sick is more likely to return to the hospital for the same condition, thus producing overdispersion in the data. Ignoring over-dispersion in the analysis will result in an increase of the frequency of spurious statistically significant findings. Repeat hospital discharges are not likely to play a large role in the over-dispersion that was found in their data. It is more likely to arise from the large variation across communities in the many variables associated with hospital discharge rates such as the proportion of current smokers in a community (SMOKER) and mean household income (MINC). The authors included such variables in their analyses to reduce bias in their comparisons. The inclusion of a Deviance scale factor to adjust the standard errors of their estimated hospital discharge ratios was done to make their analyses more reflective of the true variation in their data.

However, there may be some residual heterogeneity not accounted for in their analysis. For example, in the first column of their summary table (Exhibit 2, page 45), statistically significant differences ($p < 0.05$) between the Port Colborne hospital discharge rates and those of the comparison communities were found for fourteen of the eighteen diagnostic discharge categories. This would have been a calamitous result if these significant findings had all been due to elevated hospital discharge rates in Port Colborne. In fact, 12 of the 14 significant findings were associated with lower discharge rates in Port Colborne relative to the comparison communities. Such a large number of significant negative and positive findings would be expected if the estimated variation used in the statistical model was less than the actual variation in the data.

Therefore, there may be some residual heterogeneity not accounted for in their analysis. As an example of this possibility, a review of Exhibit 37 on page 90 shows that the 95% confidence interval of the ratio of the hospital asthma discharge rates between Port Colborne and the 35 CC for those under 20 years of age is (1.37, 1.62). These confidence limits were adjusted for the eight confounding variables age, sex, calendar period, mean community income, mean proportion of residents without high school education, regional prevalence of non-smoking, and the population-to-physician ratio of each community, the same set of eight variables used in all of their Poisson regression analyses reported in exhibits 22 to 39.

As shown in Appendix 3, the 95% confidence interval of the ratio of the hospital asthma discharge rates for Port Colborne compared to the 35 comparison communities of (1.37, 1.62) can be used to demonstrate that the Gaussian Z ratio for determining the p value of the test of significance is 9.3 (Appendix 3) with an associated p value of 1.137×10^{-20}, a p-value smaller than would ever be seen in health or environmental research especially one that is associated with such a small elevated ratio of hospital discharges rates. The authors of the CHAP C report stated that they used the square root of the deviance scale factor to adjust the standard error of the hospital discharge rate ratios. However, the large number of significant findings, both positive and negative, as well as some extremely small p values, might indicate that the heterogeneity in the data was not adequately accounted for. As shown below many of the estimated ratios in our analysis, while being very similar to those reported in the Study C report, lose their statistical significance as would be expected if a more robust estimate of the standard error is used in the analysis.

3.5 Analysis of More Detailed Hospital Discharge Data

The hospital discharge rates for the following eight disease categories were re-analyzed using two different comparison groups. The first comparison group consisted of 338 communities with information from the 2001 census on five socioeconomic variables: mean age, mean income, percentage of unemployed, percentage of persons with more than a high school education, and the percentage of males. Estimates of the percentage of smokers in the community (SMOKE) and the percentage of households with at least one regular smoker (SHS) were obtained from the 2001 and 2003 Canadian Community Health Surveys (CCHS). The second comparison group consisted of the same eleven communities in the Niagara Peninsula used in the CHAP C report. In each of the four hospital discharge categories the analysis was done for all ages combined and for each of the four age categories used in the Study C Report.

As shown in Table 6, the seven ecological confounder variables are correlated with each other. Not surprisingly, communities having a large percentage of residents with more than a high school education (%GTHS) tend to have a higher mean income (MEAN INCOME). The correlation coefficient is $R = 0.60$. Communities with a lower mean income will tend to have a higher percentage of residents unemployed ($R = -0.45$).

Table 6 Weighted Correlation Coefficients (*) between Covariates (N=339)

	MINC	UNEM	GTHS	MAGE	%MALE	%SMOK	SHS
MEAN INCOME	1.00	-0.45	0.60	-0.63	0.23	-0.57	-0.65
% UNEMPLOYED	-0.45	1.00	-0.10	0.32	-0.27	0.35	0.34
% >HIGH SCHOOL	0.60	-0.10	1.00	-0.20	-0.29	-0.57	-0.66
MEAN AGE	-0.63	0.32	-0.20	1.00	-0.29	0.19	0.34
% MALES	0.23	-0.27	-0.29	-0.29	1.00	0.02	0.14
% SMOKERS	-0.57	0.35	-0.57	0.19	0.02	1.00	0.79
% RESIDENT SMOKER	-0.65	0.34	-0.66	0.34	0.14	0.79	1.00

* The weights used in the calculation are the population sizes of the communities. See Table 3 and Appendix Table 1B.

Because communities with a lower mean income tend to have higher hospital discharge rates and because the mean income in Port Colborne is much lower than that of the 338 comparator communities any comparison between Port Colborne and the 338 communities must include an adjustment so that the comparison is with communities of the same mean income. This is done statistically (graphically) by finding (a) the line that relates income to discharge rate and comparing the distance between the discharge rate in Port Colborne to the point on the line representing the same income as Port Colborne. The graphical display of the relation between the discharge rate for asthma (<20 years) and the seven potential confounders is given in Appendix 4. The seventh covariate SHS was not a confounder in any of our analyses. The two parallel lines above the straight line fitted through the data are the 95% prediction limits. A discharge rate for a community with a given income that is above or below these two lines is declared significantly different from that expected for a community with the same income.

Because these seven confounding variables are measured on a sample of the population they have an associated sampling error. What effect might such error have on our analysis? It is known that when only one variable, such as mean income, is used to reduce bias in the comparison of Port Colborne with a particular comparator group of communities, that the effectiveness of the adjustment is reduced by the sampling error. An insignificant difference may, under such circumstances, be erroneously declared to be statistically significant. In other words, our analysis has an increased risk of declaring an insignificant risk as significant. The term used to describe this situation is called residual confounding. A non-significant result may be viewed with more confidence, providing comfort to residents of Port Colborne.

In our analysis of the data we adopted the strategy of first deriving a ratio of rates in Port Colborne relative to the 338 comparison communities without an adjustment for any of the seven covariates. The next analysis included the important INCOME variable. In all cases the income adjusted ratio was smaller than the unadjusted ratio. It would be inappropriate to analyze all 256 possible models in search of a "favourable" result. For the larger comparison group of 338 communities our strategy

was to carry out only one additional analysis in which all covariates were included in the model. With one exception this additional analysis using seven covariates was not done when the much smaller comparison group of 11 communities in the Niagara Peninsula was used. The exception was the analysis of the IHD variable in which a strong quadratic effect between income and discharge rate ratios was observed for several of the age categories. Only in this situation was an extra variable added to the model when the comparison group consisted of the 11 Niagara Peninsula communities. The extra variable was the square of the income variable.

Two statistical models were used in these analyses. The first involved weighted multiple linear regression using as weights the denominator of the rate, that is, the number of individuals in each particular age category followed over the period 1988 to 2001. Linear regression analyses were supported by a re-analysis using the Poisson regression model with an adjustment for over dispersion. Detailed results associated with the age categories in which statistically significantly elevated hospital discharge rates were reported as significant in the CHAP C report are given in Appendices 5 and 6. It should not be surprising that these two models gave similar results. In both models the response variable is the hospital discharge rate and in both cases more weight is given to communities with rates based on larger denominators. (For more details see Appendix table 1B).

3.5.1 Respiratory Cancer

Table 7 contains estimates of the ratio of hospital discharge rates for Respiratory Cancer, their 95% confidence intervals and the corresponding estimates given in the CHAP C report. In Table 7a the estimated ratios based on the 338 communities used in our report are compared with the estimated ratios based on the 35 communities used in the CHAP C report. In Table 7b both analyses compared the hospital discharge rates among residents of Port Colborne to the group of eleven Niagara Peninsula communities. In our re-analysis of the data none of the ten estimated ratios of discharge rates were statistically significant, with p values ranging from 0.38 to 0.89.

Nevertheless, given the elevation in self-report of cancers in the CHAP A report in comparison with the Province of Ontario, and the findings in the CHAP C report, it seemed prudent to explore the cancer occurrence in Port Colborne through the use of the data in the Ontario Cancer Registry.

Standardized Incidence Ratios (SIRs) were estimated for Port Colborne for the period 1999-2003, with standardization to the 2001 population of Ontario. The SIRs were estimated separately for males and females, and for specific cancer sites as well as for overall cancer occurrence. Table 8 displays the SIRs and 95% Confidence Intervals (CIs). The geographical coding of residence in the Cancer Registry does not allow for such fine detail as GSAs within the city, so only Port Colborne in total could be examined here. It is clear that, while there are some increased SIRs (that is, SIRs greater than 1.00), none of these increases is very large, and all of the confidence intervals include 1.00.

Table 7 Hospital Discharge Rates for RC

Table 7a

	Our Analysis Using 338 Communities (CG)							CHAP C Using 35 Communities		
Age Group	CG Rate	PC Rate	Unadj Ratio	Adj * Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	0.91	1.12	1.23	0.79	0.47	1.33	0.38	0.81	0.69	0.95
< 20	0.023	0.013	0.55	0.35	0.01	20.08	0.61	----	----	----
20 =< 44	0.076	0.107	1.41	1.31	0.42	4.08	0.64	1.23	0.80	1.91
45 =< 64	1.58	1.66	1.05	0.82	0.38	1.41	0.35	0.65	0.56	0.75
65+	4.54	3.84	0.84	0.78	0.45	1.35	0.38	0.65	0.58	0.74

* Adjusted for all 7 predictor variables.

Table 7b 11 Niagara Peninsula Communities (NG)

	Our Analysis Using							CHAP C using		
Age Group	NG Rate	PC Rate	Unadj Ratio	Adj ** Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	0.94	1.12	1.19	1.03	0.67	1.58	0.89	1.12	0.95	1.32
< 20	0.027	0.013	0.47	0.37	0.01	13.90	0.59	----	----	----
20 =< 44	0.083	0.107	1.30	1.33	0.50	3.52	0.57	1.66	1.06	2.59
45 =< 64	1.42	1.66	1.17	0.97	0.67	1.40	0.89	0.95	0.82	1.10
65+	3.93	3.84	0.98	0.89	0.61	1.31	0.56	0.89	0.79	1.01

** Adjusted for income alone

Table 8 SIR's and 95% Confidence Intervals for Cancer Incidence in Port Colborne, by Cancer Site and Sex

Cancer Site	Sex	SIR	95% CI
All Sites	Male	1.02	0.92 - 1.14
	Female	0.87	0.77 - 0.99
	All	0.95	0.88 - 1.03
Breast	Female	0.80	0.61 - 1.03
Prostate	Male	0.85	0.67 - 1.07
Lung	Male	1.17	0.88 - 1.52
	Female	0.97	0.68 - 1.35
	All	1.08	0.87 - 1.33
Colorectal	Male	1.13	0.83 - 1.50
	Female	1.00	0.71 - 1.37
	All	1.07	0.86 - 1.32
Non-Hodgkin's	Male	0.94	0.50 - 1.61
Lymphoma	Female	1.16	0.63 - 1.94
	All	1.04	0.69 - 1.52

3.5.2 Acute Respiratory Infection

None of the ten estimated ratios of hospital discharges for acute respiratory infection was significantly elevated. In Table 9a it is interesting to note that for the age categories < 20 years and 65+ years of age the estimated ratios obtained using our CG comparison group were almost identical to those based on the CC comparison group in Exhibit 33 in the CHAP C report. However, the p values from our analysis were very large, p = 0.74 and p = 0.24. There also were no significant results from our analysis using the NG comparison group.

Table 9 Hospital Discharge Rates for ARI

Table 9a

	Our Analysis Using 338 Communities (CG)							CHAP C Using 35 Communities		
Age Group	CG Rate	PC Rate	Unadj Ratio	Adj * Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	1.48	2.66	1.79	1.13	0.54	2.36	0.74	1.38	1.24	1.52
< 20	4.50	7.75	1.72	1.08	0.49	2.39	0.85	1.08	1.00	1.17
20 =< 44	0.23	0.44	1.93	1.09	0.47	2.52	0.84	1.46	1.11	1.91
45 =< 64	0.27	0.65	2.45	1.31	0.57	3.02	0.53	1.51	1.18	1.94
65+	1.09	2.62	2.41	1.54	0.75	3.15	0.24	1.50	1.29	1.75

Table 9b

	Our Analysis Using 11 Niagara Peninsula Communities (NG)							CHAP C Using		
Age Group	NG Rate	PC Rate	Unadj Ratio	Adj ** Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	2.52	2.66	1.06	0.82	0.43	1.56	0.54	1.19	1.07	1.32
< 20	7.98	7.75	0.97	0.71	0.34	1.47	0.35	0.81	0.75	0.87
20 =< 44	0.31	0.44	1.43	1.20	0.49	2.95	0.69	1.24	0.94	1.63
45 =< 64	0.40	0.65	1.64	1.32	0.53	3.28	0.55	1.47	1.14	1.89
65+	1.59	2.62	1.64	1.53	0.68	3.46	0.30	1.37	1.17	1.60

* The ratio of the hospital discharge rates that uses the larger comparison group of 338 communities includes all seven of the predictor variables in the adjustment.

** The ratio of hospital discharge rates that uses the much smaller comparison group of 11 Niagara Peninsula communities includes only income in the adjustment.

3.5.3 Ischemic Heart Disease

In Table 10a using the CG comparison group, none of the five estimated ratios of hospital discharge rates for IHD was significant. However, in Table 10b where the comparison was with the 11 Niagara Peninsula communities three of the elevated ratios were significant for the three age categories: 20–44 years old, 65+ years old, and all ages.

How should these elevated ratios be interpreted? In Figure 3.5.3A a straight line is fitted though mean income and IHD ratio for the all ages variable. The eye immediately picks up what appears to be a non linear departure from the straight line. A quadratic curve, fitted through the same data and shown in Figure 3.5.3B, not only increased the adjusted R^2 from 0.55 to 0.62 but reduced the estimated ratio of hospital discharge rates. Detailed analyses of the IHD discharge rate are given in Appendix Tables 8 to 12.

Table 10 Poisson Regression Analysis of Hospital Discharge Rates for IHD

Hospital Discharge Rates for IHD

Table 10a

	Our Analysis Using 338 Communities (CG)							CHAP C Using 35 Communities		
Age Group	CG Rate	PC Rate	Unadj Ratio	Adj * Ratio	95% CI		P Value	Adj * Ratio	95% CI	
All Ages	6.11	11.80	1.93	1.16	0.86	1.60	0.38	**1.18**	1.09	1.27
< 20	0.06	0.15	2.36	1.70	0.69	4.22	0.25	----	----	----
20 =< 44	0.80	1.56	1.95	1.29	0.74	2.23	0.37	1.37	1.11	1.69
45 =< 64	11.03	15.06	1.37	1.05	0.68	1.60	0.83	1.04	0.97	1.11
65+	29.04	42.84	1.48	1.24	0.92	1.67	0.16	1.15	1.09	1.20

Table 10b

	Our Analysis Using 11 Niagara Peninsula Communities (NG)							CHAP C Using		
Age Group	NG Rate	PC Rate	Unadj Ratio	Adj ** Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	7.78	11.79	1.52	1.39	1.12	1.74	**0.004**	1.34	1.24	1.44
< 20	0.08	0.15	1.92	1.63	0.47	3.45	0.21	----	----	----
20 =< 44	0.90	1.56	1.72	1.47	1.23	2.58	**0.005**	1.54	1.25	1.91
45 =< 64	12.46	15.06	1.21	1.07	0.84	1.36	0.59	1.18	1.10	1.26
65+	31.08	42.84	1.38	1.34	1.01	1.78	**0.04**	1.31	1.25	1.38

* The adjustment in our analysis includes all 7 predictor variables.
** The adjustment in our analysis includes only the mean income variable.

FIGURE 3.5.3A

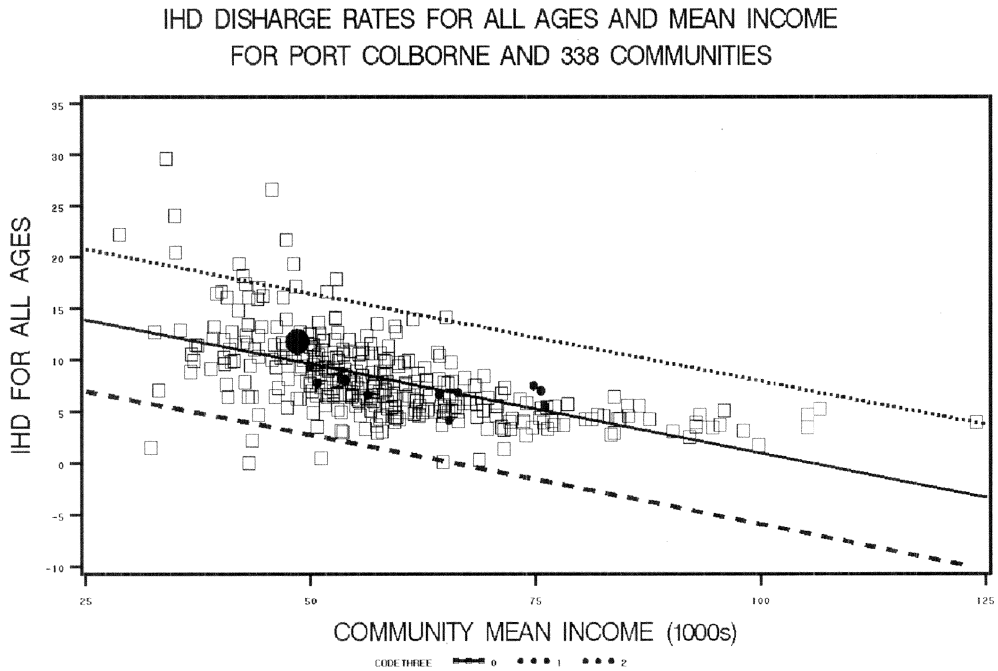
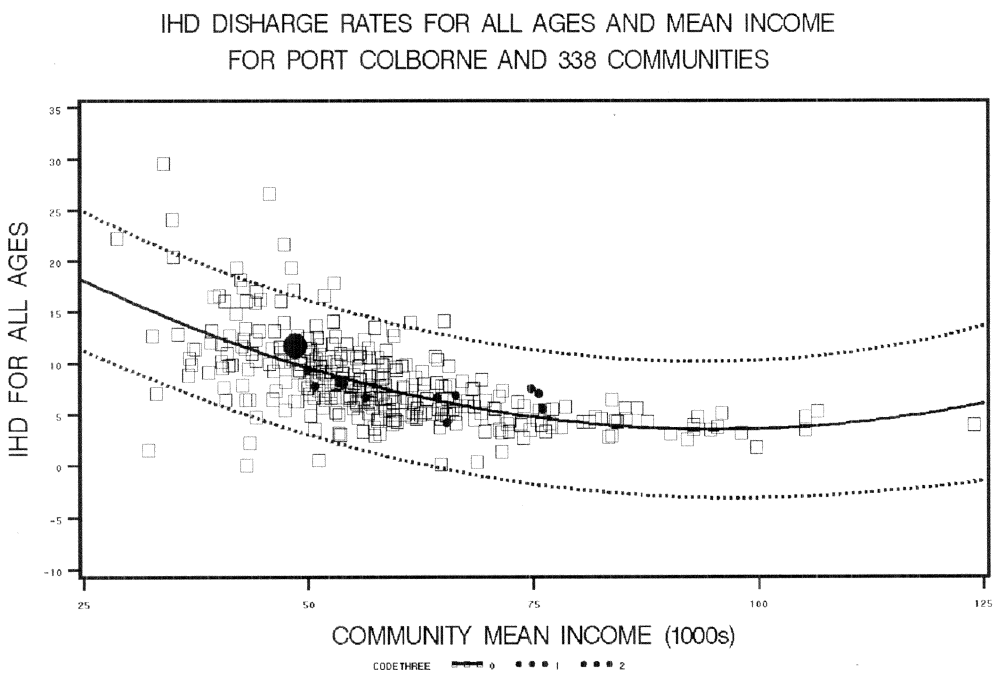


FIGURE 3.5.3B



The large dot is Port Colborne and the eleven small dots are communities within the Niagara peninsula and the squares represent the remaining 327 communities

In Table 11, a comparison is made between the two estimated ratios that used the CG and NG comparisons groups. The large number of 338 communities in the CG group permitted the use of all seven covariates in the adjustment process. To make the comparison with the NG estimates fair

only the mean community income variable was used in the bias adjustment when the small group of eleven Niagara Peninsula communities was used.

For the three age categories, all ages, 20-44 and 65+ years, a strong and statistically significant non-linear relation between the IHD discharge rate and mean income was found when the CG comparison group was used. In each of these categories using the quadratic curve adjustment reduced the estimated ratio and increased the p value. It is revealing that only in the three age categories where a strong quadratic effect was found in the CG group was there also found a strong statistically significant elevation in the hospital discharge ratio when the NG comparison group was used. The small number of communities precluded the use of the quadratic term in the adjustment process. Therefore in the three age groups where the quadratic term would have been useful in controlling for bias it could not be effectively used.

TABLE 11 Comparing Hospital IHD Discharge Ratios based on the CG AND NG Comparison Groups Using Only Income in the Adjustment

		n = 338		n = 11		
Age groups (years)		RATIO	P	RATIO	P	QUADRATIC EFFECT
All Ages	Linear	1.33	0.20	1.39	0.004	YES
	Quadratic	1.21	0.32	1.29	0.06	
< 20	Linear	1.58	0.34	1.63	0.21	NO
	Quadratic	1.74	0.25	1.14	0.76	
20-44	Linear	1.33	0.42	1.47	0.01	YES
	Quadratic	1.15	0.66	1.44	0.03	
45-64	Linear	1.02	0.93	1.07	0.59	NO
	Quadratic	0.93	0.77	1.08	0.62	
65+	Linear	1.26	0.19	1.34	0.04	YES
	Quadratic	1.30	9.21	1.34	0.11	

3.5.4. Asthma

None of the ratios presented in Table 12 are statistically significant. To assist understanding of these results consider the hospital discharge rate for asthma among persons younger than twenty years of age. The hospital discharge rate for Port Colborne is 6.84 per thousand among the population under twenty years of age compared to 3.61 for the 338 comparison communities. The ratio of these two rates is 1.89. This ratio is expected to be equal to 1.0 if there were absolutely no difference between Port Colborne and the comparison communities. However, a community sampled from the 338 communities may have an elevated hospital discharge rate simply due to the variation of possible outcomes associated with the sampling process as well as due to differences between it and the comparison group in the levels of important confounder variables. The ratio drops to 1.65 when the analysis is adjusted for the difference in mean income between Port Colborne and the comparison group of 338 communities. This ratio of 1.65 is not statistically significant from 1.0 ($p = 0.08$). This means that after making Port Colborne more like the comparison communities with respect to mean income that even if there were no true difference between Port Colborne and the 338 communities the chance of getting a ratio this large just by

chance is 0.08. For the other seven hospital discharge categories the p values are very large, indicating no statistical significance.

What is the implication in these elevated ratios? Let us use as an example the largest statistically significant ratio of 1.47 found among residents 20 to 44 years of age. There are approximately 6,600 persons in Port Colborne between 20 and 44 years of age. In the worse case scenario the elevated hospital discharge rate of 1.47 for Port Colborne is believed to be due to factors intrinsic to Port Colborne. If all such factors were eliminated from Port Colborne there would be an expected 56 fewer hospital discharges per year for IHD among those between 20 and 44 years of age. That is, among the 6,600 persons 20 to 44 years of age fewer than 5 such hospital discharges per month would be expected.

In the re-analysis of the data none of the ten comparisons were statistically significant (Table 12). Although the elevated hospital discharge rate for asthma in Port Colborne was not statistically significantly higher than that in the group of comparison communities ($p > 0.05$) it is still useful to understand the practical implication of such an elevation. From the 2001 census the number of children less than twenty years of age in Port Colborne is about 4,300. On average there are about 30 hospital discharges per year for asthma among persons less than twenty years of age. If the increase in the adjusted hospital discharge ratio of 1.65 given in Table 12A were entirely due to factors associated with Port Colborne then if all of these factors could be eliminated from Port Colborne we could expect an annual decrease in hospital discharges of about 12. That is, under the worse case scenario where all of the excess is assumed to be due to factors unique to Port Colborne the excess of hospital discharges among the 4,300 persons under twenty years of age is one hospital discharge per month.

Table 12 Poisson Regression Analysis of Hospital Discharge Rates for Asthma

Hospital Discharge Rates for Asthma / 1000

Table 12a

	Our Analysis Using 338 Communities (CG)							CHAP C Using 34 Communities		
Age Group	CG Rate	PC Rate	Unadj Ratio	Adj ** Ratio	95% CI		P Value	Adj ** Ratio	95% CI	
All Ages	1.61	2.78	1.73	1.36	0.82	2.26	0.23	1.07	0.98	1.17
< 20	3.61	6.84	1.89	**1.65**	**0.94**	**2.90**	0.08	**1.49**	**1.37**	**1.62**
20 =< 44	0.64	1.03	1.59	1.14	0.53	2.42	0.74	0.84	0.67	1.06
45 =< 64	0.92	1.25	1.36	0.87	0.43	1.74	0.68	0.85	0.70	1.04
65+	1.61	2.63	1.63	**1.20**	**0.65**	**2.22**	0.56	**1.23**	**1.05**	**1.44**

Table 12 Poisson Regression Analysis of Hospital Discharge Rates for Asthma

Hospital Discharge Rates for Asthma / 1000

Table 12b Our Analysis Using CHAP C Analysis Using

11 Niagara Peninsula Communities (NG)

Age Group	NG Rate	PC Rate	Unadj Ratio	Adj Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	2.04	2.78	1.36	0.99	0.66	1.47	0.96	1.02	0.93	1.12
< 20	4.32	6.84	1.58	**1.09**	**0.59**	**1.99**	0.79	**1.38**	**1.27**	**1.50**
20 =< 44	0.91	1.03	1.13	0.85	0.56	1.30	0.47	0.84	0.67	1.06
45 =< 64	1.19	1.25	1.05	0.75	0.41	1.36	0.34	0.84	0.69	1.03
65+	2.12	2.63	1.24	0.98	0.64	1.52	0.94	1.12	0.95	1.31

** The adjustment in our analysis includes all 7 predictor variables

In Table 13 and Figure 3.5.4A we see that Port Colborne is one of a cluster of four Niagara peninsula communities that are very similar in their hospital discharge rates for asthma and their mean income. The hospital discharge rates for asthma in this cluster of four cities were compared as a group to the remaining communities. The hospital discharge rate for asthma among those less than 20 years of age was significantly higher in this cluster of four communities both when compared to the other eight communities in the Niagara Peninsula as well as when compared to the other 335 communities. The previous statement is *ad hoc* - the statistical significance cannot be treated at face value because these four communities were not randomly selected for the comparison, but were identified because of their elevated asthma discharge rates. Nevertheless, the proximity of these four communities to each other is suggestive of an elevation in asthma rate not unique to Port Colborne, rather to the area. The reason for elevated asthma could be environmental, but the observation could as well be explained by differences in some of the socioeconomic characteristics of the residents of these four cities.

TABLE 13 Hospital Discharge Rates for Port Colborne and each of the Other 11 Communities in the Niagara Peninsula Comparison Group

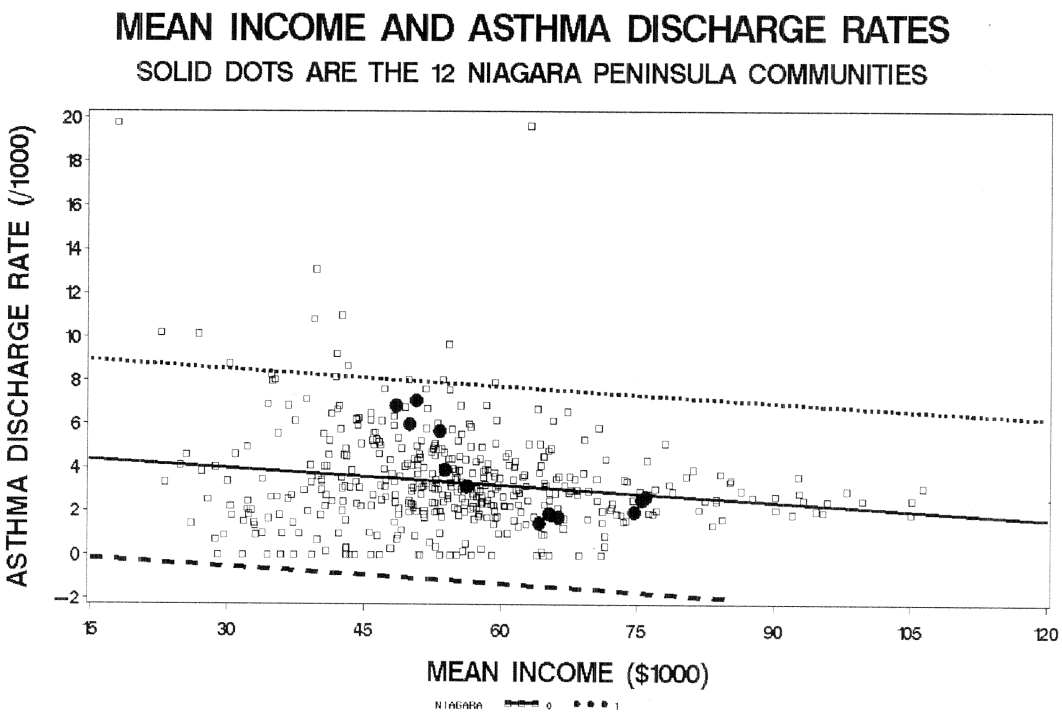
NAME	POP*	INCOME*	ASTH	ARI	IHD	RC
Welland	48.4	50.7	7.09	0.44	1.02	0.09
Port Colborne	18.5	48.5	6.84	1.02	1.56	0.11
Fort Erie	28.1	45.0	5.99	1.12	1.02	0.11
Niagara Falls	78.8	53.3	5.68	0.80	1.08	0.06
St. Catharines	129.2	53.9	3.91	0.53	0.85	0.09
Thorold	18.0	56.3	3.15	0.47	1.09	0.07
Pelham	15.3	76.0	2.66	0.18	0.64	0.09
Niagara-on-the-Lake	13.8	75.5	2.52	0.89	0.48	0.06
Grimsby	21.3	74.7	1.97	0.51	0.68	0.12
Wainfleet	6.3	65.3	1.89	0.34	0.61	0.05
Lincoln	20.6	66.3	1.73	0.31	0.66	0.03
West Lincoln	12.3	64.2	1.45	0.37	0.80	0.19

* x 1000

Hospital discharge rates per 1000 persons in the population age group.
ASTH - asthma - <=20 and <=15 years old
ARI - acute respiratory infection 20+ years old
IHD - ischemic heart disease - 20 - 44 years old
RC - respiratory cancer - 20 - 44 years old.

See Appendix table 13 for a detailed list of all predictor variables.

FIGURE 3.5.4



Although the p value of 0.08 for the comparison of hospital discharge rates for asthma in the < 20 age group did not achieve the commonly accepted requirement of a p of 0.05 needed to declare a result statistically significant, the asthma data were nevertheless analyzed further in relation to the other communities in the Niagara Peninsula.

A benefit of having identified this list of twelve communities is that one could select one of them and carry out the same statistical analysis that was carried out for Port Colborne. The purpose of such an exercise would be to determine whether any effect found in Port Colborne was unique to Port Colborne, or rather due to factors found in common in all of the communities.

For example, the ratio of the hospital discharge rate for asthma in Welland compared to the other 338 communities was equal to 1.52, significantly larger than 1.0 after adjustment for the confounding covariates ($p = 0.01$). The hospital discharge rate for asthma in the cluster of four communities located close to each other - Fort Erie, Niagara Falls, Welland and Port Colborne relative to the 334 remaining communities is 1.5 ($p = 0.0001$). This p value must be treated with some caution because the group of four communities was not part of a planned comparison identified before the data were collected. The small distances between these four communities were only noted after their elevated asthma discharge rates became apparent. The number of possible ways of randomly selecting such a cluster is very large and leads to a very small adjusted p value. Such a correction totally obliterates any formal statistical significance. Furthermore, the elevated ratio of hospital discharge rates for the 12 Niagara peninsula communities relative to the remaining 326 communities was only 1.18 ($p = 0.04$). It is interesting to compare the mean concentration of three air pollutants among the 12 Niagara peninsula communities and the remaining communities that have proximate air monitoring stations. As shown in Table 14, the mean concentrations of total

suspended particulates, NO_2 and SO_2 are only slightly higher among the 12 Niagara Peninsula communities compared to the rest of the monitoring stations in the province.

Table 14 Mean Concentration of Four Air Pollutants in the Niagara Peninsula and Remaining Air Quality Monitoring Stations

		N	Niagara Peninsula	N	Remaining Communities
TSP	(ug/m3)	12	55.3	207	49.3
OZONE	(ppb)	9	25.0	116	27.4
NO2	(ppb)	7	17.9	73	16.0
SO2	(ppb)	5	4.3	64	3.6

TSP = Total Suspended Particulates
N = Number of Monitoring Stations

3.7 Creating a Comparison Group Statistically Similar to Port Colborne

The main comparison group used in Ventana's CHAP C report consisted of 35 communities that were more similar to Port Colborne with respect to many socioeconomic variables than was the entire population of Ontario. Summary variables for each community, such as mean income, proportion of smokers, and mean age, were used in its creation. Their statistical model was used to identify and rank communities according to their similarity to Port Colborne with respect to these variables. Because of boundary changes and community amalgamations we could not carry out a statistical analysis using the same 35 communities as used in their report. Instead, we used multiple linear regression to rank order the 35 communities by their probability of predicting Port Colborne. Regression analysis was performed, either unweighted, or weighted by the population size of each community. The following seven covariates were used in the model.

(a) Mean income (b) Mean age (c) % Unemployment (d) % HighSchool
(e) % Males (f) % Smokers (g) % Resident Smokers

The communities identified by our analysis are given in Appendix 16a where it is seen that the two comparison groups had 85 % (29/35) of the communities in common. As shown in Appendix 16b1 and 16b2, the process proved successful and the means of the seven covariates in the two comparison groups were much more similar to those of Port Colborne than was the case for the large comparison group of 338 communities also used in our report. Note also that the Niagara peninsula comparison group was not as similar to Port Colborne as were the two statistically derived comparison groups.

The two new groups were used once again to compare hospital discharge rates for asthma, ischemic heart disease and acute respiratory infection. As seen in Tables 16c to 16e of Appendix 16, the findings using these two new comparison groups were very similar to those obtained with the much larger group of 338 communities, and the findings resulted in the same conclusions.

3.8 Conclusions

In the CHAP C report, the main results of the tests of the null hypotheses - that the observed elevated ratios of hospital discharges in Port Colborne relative to two different comparison groups are simply due to sampling variation - were reported in Exhibits 22 to 39. These results are summarized in Exhibits 2 and 3.

In Exhibit 2, the comparison group CC consisted of the 35 communities that were considered statistically similar to Port Colborne. Among the 158 ratios, 86 were reported as being significantly less than 1.0 and 19 significantly greater than 1.0. These estimated ratios were adjusted for several socioeconomic variables such as the mean income of a community and the percentage of residents without a high school education. This adjustment reduced the potential bias in the comparison between Port Colborne and the 35 communities. A ratio less than 1.0 indicates that the percentage of Port Colborne residents who are discharged from a hospital is less than the percentage of residents from the comparison group. If the residents of Port Colborne were facing excess health risks due to their exposure to chemicals of concern (COCs), one would anticipate that they would be hospitalized for various diseases more frequently than residents not facing such exposures. That is, we would expect the ratios of hospital discharge rates to be greater than 1.0. Surprisingly, a much larger percentage of the significant ratios were negative. Even more surprising was the very large proportion of significant results (105 out of 158).

In Exhibit 3 of the CHAP C report, the comparison group NG consists of the 11 communities in the Niagara Peninsula. Among the 158 ratios, 19 were reported as being significantly less than 1.0 and 29 significantly greater than 1.0. If the null hypotheses were true, we would have expected about 8 significant findings (158 x 0.05 = 7.9). Not only did we find many more (48) but again the significant ratios were both greater than 1.0 (29) and less than 1.0 (19). This surprisingly large percentage of significant findings in both directions suggests that heterogeneity was not adequately accounted for in the analysis.

A dataset consisting of 338 CSDs (CG) became available to us. Because we were aware of the importance of these findings to Port Colborne residents we chose to re-analyze the hospital discharge data for cancer, acute respiratory infection, ischemic heart disease and asthma for the all age categories and for the four age categories used in the CHAP C report.

There were no significantly elevated ratios for respiratory cancer using either the comparison group of 338 communities or the comparison group of 11 communities. These results were corroborated by the analysis of cancer incidence rates using the Ontario cancer registry data. No statistically significant elevated discharge rates in Port Colborne relative to the mean discharge rates in the 338 comparison communities were found after adjustment for confounders. Not only was the asthma discharge rate in Port Colborne not significantly elevated relative to the CG, but the practical implication of the elevation would have been less than one extra hospital discharge per month in a population of over 4000 persons under 20 years of age.

There were no significant elevated ratios in Port Colborne IHD discharge rates when compared to CG. However, significant increases in the hospital discharge rate for IHD among persons in Port Colborne were found for residents 22-44 years of age, 65+ years of age, and people of all ages, when compared to the 11 communities in the Niagara Peninsula.

Hospital discharge rate ratios reported in Table 15 for Disease of the Circulatory System, extracted from Exhibits 28 to 29 in CHAP C, remind us that the ratio is not greater than 1.0 for the combined

category Diseases of the Circulatory System nor are they significantly elevated for any of the sub categories except IHD.

TABLE 15 Adjusted Discharge Rate Ratios Reported in CHAP C for Different Categorizations Parts of the Circulatory Disease System Category

		CHAP C	
		CC	NG
Hospital Discharge Categories		(n=35)	(n=11)
Diseases of Circulatory System	390-459	0.88 *	0.99
Ischemic Heart Disease	410-414	1.18 *	1.34 *
Acute Myocardial Infarction	410	0.98	1.11
Heart Failure	428	0.88	1.01
Cerebrovascular Disease	430-438	0.84 *	1.09

This phenomenon is not unusual in the health field. A drug or dietary intervention may show no benefit in reducing total mortality while at the same time be associated with increased mortality from one disease and a reduction in mortality for another. Sometimes this may be explained by misclassification of categories within a combined category.

Welland was found to have a statistically significant elevated hospital discharge rate for asthma compared to the comparison group (CG), reminding us that even if the evidence had more strongly indicated an elevated ratio for hospital asthma discharges in Port Colborne, it still would not have been a result unique to Port Colborne.

The four highest asthma discharge rates among the 12 Niagara Peninsula communities occurred in Welland, Port Colborne, Niagara Falls, and Fort Erie. These four communities have a significantly higher percentage of smokers [27% vs 20% ($p = 0.02$)], a significantly lower percentage of post-high school education [37% vs 42%, ($p = 0.005$)], and a much lower mean income [$51,500 vs $60,500 per annum ($p = 0.06$)].

Table 16 contains the analysis of the ratios of hospital discharge rates for Port Colborne relative to the comparison groups CC and CG and relative to the NG comparison group. In summary, there were no statistically significant elevations in hospital discharge rates for any of the discharge categories when compared to the comparison group of 338 CSDs. The lack of an elevated hospital discharge rate for respiratory cancer was corroborated by an analysis of cancer incidence rates using the Ontario Cancer Registry. This lack of statistically significant results were corroborated by two further analyses, with two new comparison datasets created using regression methods, so as to be more similar to Port Colborne than the comparison group of 338 communities.

An intriguing elevation of the hospital discharge rate for asthma in the four neighbouring cities of Welland, Port Colborne, Niagara Falls, and Fort Erie is suggestive of an environmental effect. However, these four communities differed from another eight Niagara Peninsula communities in having a significantly higher percentage of smokers, a significantly lower percentage of persons with post high school education, and a much lower mean income. These large differences in three socioeconomic variables may provide a better explanation for their higher hospital discharge rates for asthma than does an air pollution hypothesis.

Table 16 Comparison of Adjusted Ratios (*) of Hospital Discharge Rates

Table 16A Port Colborne and the other Communities

Discharge category	Our Regression (338 CG)				CHAP C (35 CC)		
	Adj Ratio	95% CI		P	Adj Ratio	95% CI	
Asthma	1.65	0.94	2.90	0.08	1.49	1.37	1.62
IHD 20-44	1.29	0.74	2.23	0.37	1.37	1.11	1.69
IHD65+	1.24	0.92	1.67	0.16	1.15	1.09	1.20
ARI 20+	1.35	0.67	2.73	0.40	-	-	-
20-44	**1.09**	0.47	2.52	0.84	**1.46**	1.11	1.91
45-64	1.31	0.57	3.02	0.53	1.51	1.18	1.94
65+	1.54	0.75	3.15	0.24	1.50	1.29	1.75
RC	1.31	0.42	4.08	0.64	1.23	0.80	1.91

16B Port Colborne and the Eleven Niagara Peninsula Communities

Discharge Category	Our Regression (NG)				CHAP C (NG)		
	Adj Ratio	95% CI		P	Adj Ratio	95% CI	
Asthma	1.09	0.59	1.99	0.79	1.38	1.27	1.50
IHD 20-44	**1.47**	1.12	1.92	0.01	**1.54**	1.25	1.91
IHD65+	1.27	0.96	1.67	0.10	1.31	1.25	1.38
ARI 20+	1.50	0.63	3.56	0.36	-	-	-
20-44	1.20	0.49	2.95	0.69	1.24	0.94	1.63
45-64	1.32	0.53	3.28	0.55	1.47	1.14	1.89
65+	1.53	0.68	4.36	0.30	1.37	1.17	1.60
RC	1.09	0.59	1.99	0.79	1.66	1.06	2.59

NG and CC are the two comparison groups used in the CHAP C report
NG = 11 Niagara Peninsula Communities CC = 35 Comparator Communities

* The adjustment in our analysis includes all 7 predictor variables.

| RC | 1.66 | 1.06 | 2.59 | 1.09 | 0.59 | 1.99 | 0.79 |

NG and CC are the two comparison groups used in the CHAP C report
NG = 11 Niagara Peninsula Communities CC = 35 Comparator Communities

* The adjustment in our analysis includes all 7 predictor variables.

4.0 Sample Size Considerations

In Exhibit 114 of the CHAP A report, the estimates of the pool of potential cases available for a case-control study are reported for 18 conditions. A case-control study, even if deemed necessary based on scientific considerations, would not be carried out if the available pool of cases was too small. Therefore it is important to estimate the sample size required so that the probability of identifying a health effect of a specified size is sufficiently large. This probability is called power and conventionally set at 0.80. In our sample size estimation the size of the health effect is measured by the size of the statistically significant odds ratios reported in Exhibit 114. The sample size must also be large enough so that an observed odds ratio is not declared significant when there is no effect. This probability is called a Type I error rate and conventionally set at 0.05. The last three pieces of information required for the sample size calculation are (1) the estimate of the probability of the disease or condition, P(Disease) , (2) the estimate of the conditional probability of the disease or condition among exposed individuals, (Disease | Exposed), and (3) an estimate of the probability of being exposed, P(Exposed). The details of how these three estimates were obtained from tables in the CHAP A report are given in Appendix 17. In Exhibit 114 the odds ratios were obtained from three different analyses, each based on a comparison that involved a different exposure group. The three comparisons and associated exposure groups reported in Exhibit 114 are:

(a) Respondents who are residents of GSA3 compared to respondents from GSAs 1, 2 and 5 (COMP1).

(b) Respondents who have lived in GSA3 for at least 20 years compared to respondents who have never lived in GSA3 (COMP 2).

(c) Respondents who live in Port Colborne compared to a survey representative of residents of the Province of Ontario.

Our sample size estimates were calculated and reported only for the two internal comparisons involving GSA 3 because the estimated sample sizes required, based on the comparison of Port Colborne to the Province of Ontario, were in the many thousands.

The three conditions for which the estimated number of cases available was sufficient to carry out a case-control study were:

(a) High Blood pressure (b) Stomach or Intestinal Ulcers (c) Arthritis and Rheumatism

In section 2.0 a clear argument was made as to why the results of CHAPs A and C do not provide strong evidence of a causal link between the COCs and the various conditions and symptoms in the CHAP A report and the selected hospital discharge categories in the CHAP C report. These arguments are reinforced here for the above three conditions.

For only one of the four internal comparison groups was there a significant elevation of blood pressure reported in Exhibits 99 and 101 of the CHAP A report. Because of the well known association between high blood pressure and cerebrovascular disease (CVD) and between high blood pressure and ischemic heart disease we reviewed the hospital discharge data for these two conditions in CHAP C. In Exhibit 11 of the CHAP C report we see that the age sex standardized hospital discharge rates for CVD in Port Colborne and in the province of Ontario have been steadily declining over the 20 year period from 1980 to 2000 and in Port Colborne have declined by almost 40 percent. There is no strong evidence of an elevated hospital discharge rate for cerebrovascular

disease in Port Colborne relative to the two comparison groups used in CHAP C (Exhibit 29). In fact, of the 16 analyses conducted across different categories, five involved statistically significant lower relative discharge rates for CVD among Port Colborne residents compared to only one in which there was a significant elevation. Furthermore there was no overall elevated hospital discharge rate for ischemic heart disease for any age group in our re-analyses of the CHAP C report (Chapter 3) nor was there an elevation of heart disease or heart attack conditions in the eight analyses reported in Exhibits 99 and 101 of the CHAP A report.

To help us understand the elevated reporting of stomach and intestinal ulcers we reviewed the hospital discharges rates for diseases of the digestive system reported in Exhibits 12 and 30 of the CHAP C report. Over the twenty year period covered in the CHAP C study there was an increase in hospital discharges in Port Colborne as well as in the province of Ontario for the category Diseases of the Digestive System (Exhibit 12). However in nine of the 18 categories in Exhibit 30 there were statistically significant lower hospital discharge rates among Port Colborne residents compared to the two comparison groups used in CHAP C, and only one case where there was a significant elevation.

As discussed in more detail in Appendix 19, there may be significant over reporting of ulcers. Not only might Ventana's estimate of available cases be too high, but the estimated sample size required to carry out a case-control study will be underestimated.

There was no reported elevation of the condition Arthritis and Rheumatism for the comparison that involved residents of GSA3 (COMP1), nor for the comparison that involved residents of GSA4 (Exhibit 93). Although there was an elevated "prevalence" of cases for the two comparisons that involved the twenty year residency (COMP2), there was no exposure response (Exhibit 96).

In summary, a statistically significant elevation in the reported frequency of a condition was reported for eight of the eighteen conditions in Exhibit 114 when the comparison group consisted of residents who had lived in GSA3 for 20 years or more (COMP2). Of these, three had a pool of cases that might be sufficient to carry out a case-control study. For high blood pressure and stomach or intestinal ulcers there are strong reasons to doubt any causal relation. For the condition arthritis and rheumatism the data from the CHAP A report are inconsistent across the two types of internal comparisons and display no exposure response effect. These are strong reasons against carrying out a case-control study for any of the conditions listed in Exhibit 106 of the CHAP A report.

5.0 Review of the Literature

The purpose of this section of the report is to provide information relevant to deciding the plausibility of linking any one of the COCs – cobalt (Co), nickel (Ni), copper (Cu), and arsenic (As) – to a possible health effect emerging from CHAP Reports A and C. We provide a general discussion of issues and background relevant to a consideration of the health risks of the COCs and then review briefly the toxicology of each of the four COCs, with emphasis on what is known about environmental exposure. Then we will present in some detail what is established regarding involvement of the COCs in carcinogenicity and immunosensitization, including asthma. We will also discuss the potential for exposure by various routes to species of the COCs that may be present in the Port Colborne environment. Only for Ni have speciation studies been carried out.

We will define key terms such as speciation and bio-availability, as they arise, and unless otherwise noted these refer to usage as accepted by the International Union of Pure and Applied Chemistry (IUPAC) [1]. Some selected **definitions** are provided in Appendix 16.

5.1 Background and general considerations

In 1991, the Ontario Ministry of the Environment (MOE) conducted soil tests in the Port Colborne vicinity with concern for phytotoxicity. Subsequent additional studies produced soil contours in the vicinity of the INCO refinery of 50 - 150 μg/g for Co, 200-3000 μg/g for Ni, 200-400 μg/g for Cu, and 25-55 μg/g for As. For comparison, upper limits of soil concentrations of the COCs at "Generic site conditions in a potable groundwater condition" (MOE 2004 guidelines) are as shown in Table 16 (values in μg/g, ranges arise from different soil types).

Table 17 - Guidelines and measurements in Port Colborne of COCs in soil.

	MOE-guidelines		Port Colborne Soil Contours (MOE)
	Agricultural soil	Other uses	
Co	40-50	40-50	50-150
Ni	150-200	150-200	200-3000
Cu	150-200	225-300	200-400
As	20-25	20-25	25-55

In 1998 the MOE reported results of estimated daily intake studies for Co, Ni, and Cu in Port Colborne [2]. Cobalt intake of 333 μg/day and 375 μg/day for children and adults, respectively, were compared with estimates of intake from food of 300-1800 μg/day to conclude that no adverse effects were anticipated from exposure to Co in Port Colborne soils. For Ni, they estimated a lifetime averaged chronic daily intake (CDI) of up to 18.5 μg/kg/day, which is below the United States Environmental Protection Agency (USEPA) lifetime averaged exposure reference dose of 20 μg/kg/day. Noting that the USEPA value incorporates a large safety factor, it was concluded that exposure to Ni in soil in Port Colborne was unlikely to result in adverse health effects in children or adults. Likewise, estimates for Cu intake (2084 μg/day for adults) fell well below the World Health Organization (WHO) acceptable maximum daily intake (500 μg/kg/day) and were in keeping with the National Academy of Sciences (NAS) adequate daily dietary intake level (2000-3000 μg/day for adults); again the soils of Port Colborne were not expected to pose an appreciable risk. Although the value accepted at the time has been revised down to about 150 μg/kg/day in some recommendations, the estimated intake of 18.5 μg/kg/day is still well within a safe range.

Here we present an overview of the concepts that are relevant to the potential for environmental exposure to the COCs to cause health effects in humans. We will consider (i) the environmental source and route of exposure, (ii) bio-availability and factors affecting bio-availability, (iii) the importance of speciation, (iv) acute *versus* chronic toxicity, and (v) a distinction between environmental and occupational studies of toxicity.

5.1.1 Route and source of exposure

A substance may be toxic by one route of exposure, and relatively harmless by another. Nickel is a good example. Inhalation of aerosols containing soluble nickel salts has been associated with respiratory cancers, while ingestion of nickel compounds is not considered to carry any carcinogenic risk [3]. (This example is considered in more detail below.) Thus, it is important to clarify the source of the COC (air, food, drinking water) and the consequent route of intake (inhalation, ingestion, dermal absorption). In the Port Colborne environment, exposure to each of the COCs is likely restricted to inhalation, dermal contact, or ingestion of particles attached to soil or dust, incorporation of the element into food, or dissolution of soluble species of the element into water. Exposure is a critical concept in toxicology, and not as straightforward as it seems at first. It can be defined in one sense at least as a process by which a substance becomes available for absorption by the target population or organism. So, before we can start to talk about exposure, it is recognized that we must consider the environmental source and the subsequent mechanism, and the following issues arise.

5.1.2 Bio-accessibility and bio-availability

Most elements are absorbed by living organisms from aqueous solution, whether it is from fresh water, soil water, aerosols, or dietary intake to the gut [4]. A substance is bio-accessible if it is possible for it to come into contact with a living organism, which may then absorb it. For example, any substance trapped inside an insoluble particle will not be bio-accessible, although substances on the surface of the same particle will be accessible and may also be bio-available. However, even surface-bound substances may not be accessible to organisms that can only incorporate the substance if it is in solution. Thus, bio-accessibility is a function of both chemical speciation and biological properties. In some cases, bio-accessibility will be the limiting factor determining uptake, and this is particularly true of metallic elements and sedimented particles in soils, and other particulate matter by which humans are exposed to the COCs.

Substances are biologically available if they can be taken up by living cells and organisms and can interact with target molecules. Substances that are not bio-available may still cause physical damage and immunological responses, or may alter the availability of other substances. The bio-availability of an element depends upon its chemical speciation. Elements occur in the soil in either the solid phase or an aqueous soil solution. In the solid phase, ions can be bound to organic and inorganic soil components in various ways, including ion exchange and surface complexation, or they can exist in minerals or be co-precipitated with other minerals in the soil. In the soil solution, the elements can exist either as free ions or as complexes with organic groups, such as amino, carboxyl, and phenolic groups, or inorganic groups, such as carbonate, chloride, hydroxide, nitrate, and sulfate. Ions in solution are generally bio-accessible, and ions in the solid phase of the soil may become accessible if environmental conditions change (e.g., pH, presence of complexing agents, occurrence of biotransformation). This is true of each of the COCs.

A main concern in the Port Colborne environment is with deposition of the COCs in soil. Analyses have shown that less than 5 % of the nickel in the Port Colborne soil is soluble and available to plants

(see section **VI**). Most solutions of metals in soil are not saturated. Therefore, dissolution from the solid phase tends to occur. The rate at which this occurs depends on the solubility of the metal in the solid phase, and is one of the determinants of bio-accessibility. Sorption of ions, compounds, and complexes of metals onto soil particles also limits their bio-accessibility. Thus, the nature of the metal-containing particles that were emitted and then deposited in soil is a primary determinant of their availability. The fate and accessibility of a COC ion depends on the nature of the soil in a given environment. For example, ion exchange occurs at sites where there is a permanent electrical charge on clay minerals. Soils high in clay typically have the highest metal ion exchange capacity. Ion exchange is affected by the speciation of elements as reflected in their oxidation state, as this also affects the net charge on their ions or on other electrically charged derivatives. Soil conditions that cause precipitation or sorption of elements reduce their soil mobility and bio-accessibility. The metal ions that tend to be the most mobile and bio-accessible are those that form weak bonds with organic or inorganic soil components or those that complex with ligands in solution and that are not adsorbed to soil particles. This would include cobalt and nickel. When considering a very localized environment like the city of Port Colborne, these concepts should be kept in mind.

Even if there is high bio-accessibility, a number of additional factors determine bio-availabilty, some of which are mentioned here.

a) Elemental species are often transported into cells by specialized protein carriers [5] or by organic ligands, such as chelating agents or ionophores. Some may diffuse passively through the phospholipid bilayer of the cell membrane [6].

b) The physical form is important in addition to chemical speciation. For example, inhalation of an insoluble species as a dust or aerosol will localize the effect to the lung.

c) The inorganic complexation of many ionic species in water, including Co(II) and Ni(II), is often negligible, and the inorganic speciation is then dominated by the uncomplexed aquated ions. However, Cu(I) is strongly complexed by chloride ions, and its inorganic complexation varies widely with sodium chloride concentration. Further details are given in Section **VI** below.

5.1.3 Speciation

The terms "species" and "speciation" have become widely used in the chemical and toxicological literature, and it is now well established that the occurrence of an element in different compounds and forms is often crucial to understanding the environmental and occupational toxicity of that element. A number of definitions of chemical speciation can be found in the literature. In the past, the term "speciation" has been used to refer to "reaction specificity" (rarely); in geochemistry and environmental chemistry, to changes taking place during natural cycles of an element (species transformation); to the analytical activity of measuring the distribution of an element among species in a sample (speciation analysis); and to the distribution itself of an element among different species in a sample (species distribution). After a series of International Symposia on Speciation of Elements in Toxicology and in Environmental and Biological Sciences, the organizers formulated the definition "Speciation is the occurrence of an element in separate, identifiable forms (i.e., chemical, physical or morphological state)". The aim was to include determinants of reactivity, and produced a definition that goes well beyond speciation in a chemical sense and would include different phases of a pure substance, and even different-sized particles of a single compound. This selection of definitions illustrates the circularity in defining a species in terms of an entity, form, or compound and indicates the lack of prior consensus in use of the term speciation. To attempt to harmonize the field and offer at least partial solutions to the ambiguities present in some of the earlier definitions, IUPAC formulated and adopted the following explanations:

Chemical species refers to specific forms of an element defined as to isotopic composition, electronic or oxidation state, and/or complex or molecular structure. Speciation analysis is the analytical activity of identifying and/or measuring the quantities of one or more individual chemical species in a sample, and speciation of an element denotes the distribution of an element amongst defined chemical species in a system. At the lowest level two distinct species may differ only in their isotopic composition. In terms of human health and risk assessment, though, some structural aspects of speciation are more important than others. Of great importance in metal toxicology are differences in electronic or oxidation state. Also critical for understanding toxicity are differences in the molecular structures and complexes in which the element participates. Macromolecular species are excluded from the definition unless a macromolecular ligand is specifically defined. For example, a metal ion bound to two isoforms of a protein with defined amino acid sequences could be considered two species, but an ion bound to a poly-electrolyte in soil such as humic acid would not be defined in terms of multiple species representing individual molecules in the heterogeneous and polydisperse population. In this case, it is advisable to refer to a fraction. "Fractionation" can be defined as the process of classification of an element according to physical (e.g. size, solubility) or chemical (e.g. bonding, reactivity) properties. In this context, "speciation" is defined as the distribution of an element among defined chemical "species" in a system, and "speciation analysis" is the analytical activity of identifying and/or measuring the quantities of one or more individual chemical species in a sample.

Several recent discussions of speciation outline its importance in understanding toxicity [4, 7-11]. In addition, the European Virtual Institute for Speciation Analysis (EVISTA) maintains a website at http://www.speciation.net/index.html that includes data bases of speciation analyses and toxicity studies for individual metals as well as ongoing dialogue within the speciation community and occurrences of the incorporation of speciation data in legislation on a continent-by-continent basis.

5.1.4 Acute vs. chronic toxicity

Acute and chronic exposures to harmful substances typically have different patterns of effects. In toxicology acute studies generally refer to single exposure and a study duration of less than two weeks, and acute effects usually occur within the first 24 hours, or up to two weeks following a single exposure. Chronic refers to mammalian studies lasting considerably more than 90 days or to studies occupying a large part of the lifetime of an organism. A chronic effect is one that develops slowly and/or has a long lasting course, or the term may be applied to an effect that develops rapidly but is long lasting. In the context of environmental exposures in Port Colborne, we are looking for chronic effects, and many of the toxicological studies with the COCs that have been carried out with animals may be of diminished relevance.

Chronic toxicity testing is expensive and labour-intensive, and a particular problem arises when the exposure is low or the effect develops a very long time after exposure. It becomes difficult to attribute a cause to the delayed effect, and to test substances for such effects. Cancer is an example. In humans it may take up to 40 years to develop cancer after exposure to a carcinogen. Our normal test rodents have life spans of about 2 years or less. In order to cause malignant tumours within such a short time, very large doses of test compounds must be applied, and these may overwhelm defence mechanisms that work well within likely human exposure ranges. For these reasons, this report focuses on the environmental toxicology of the COCs, including the problem of low exposures over prolonged periods.

5.1.5 Environmental vs. occupational exposure

It should be clear from the above that risks from exposures to a particular COC are highly dependent on the species, route, and extent (level and duration) of exposure. Thus, we need to consider these factors carefully when assessing an environmental risk. Standards set in one scenario are not generally applied to the other.

As an example, exposure to radioactive substances is one of the most tightly regulated and monitored exposures in our society. The natural exposure to Canadians (from cosmic rays, naturally occurring isotopes such as ^{40}K, etc.) is 2-3 mSv/yr. Among the general public, including scientists using radioisotopes in research, the allowed exposure dose limit is 1 mSv/yr above the natural exposure. This is the same as allowed for the general public. However, for workers at nuclear power plants, the limit is set at 100 mSv over 5 yrs with a maximum of 50 mSv in any given year. This is considered a safe level that will protect the workers, yet let them engage in productive employment while increasing their risk of an adverse effect from radiation exposure by an acceptable amount. (While stochastic effects of radiation exposure can occur at any level, the first deterministic effects are minor blood changes seen at 250 mSv.) Thus, standards for exposure to any potentially hazardous substance in the general public are often set well below those for individuals dealing with the substance on a daily basis and out of occupational necessity. While the workers are still considered to be at an acceptable level of risk, the guidelines for the public often follow the precautionary principle by further reducing exposure levels. This example, quite different from the COCs, illustrates the point well. In general, we don't have direct comnparison guidelines for the COCs where, e.g., Ni iin air if regulated in the workplace but the guideline is for Ni in tapwater in the home.

The point here is that standards are set differently for occupational and environmental exposure, and so they should be. An exposure that increased an annual risk by 1×10^{-6} for a specialized occupation that employed 100 people would not be expected to produce an adverse effect in their lifetime. The same exposure applied to 32 million Canadians might be of concern. Since data on effects of environmental exposures are sparingly available, much of the toxicology that we have to rely upon for the COCs is based upon occupational studies,. The COCs are important metals in occupational health, and the medical data we have are generally based upon exposures at or near the occupational limit values. When using findings from occupational medicine as a basis for assessing health effects, one has to keep in mind that environmental exposures at Port Colborne are much lower.

In sections **5.2 - 5.5** the COCs are discussed in the order in which they appear in the periodic table. Information on the relevance of speciation of the COCs to toxicokinetics is adapted from [4]. The role of the COCs in asthma is complex. Certain metals can give rise to immune-mediated responses leading typically to anaphylactic (Type I) or contact (Type IV) allergic reactions, or autoimmune disease [12]. The immunosensitizing properties of cobalt, copper and nickel are considered here, arsenic not generally displaying this phenomenon. Biomonitoring (as defined above) of cobalt and nickel is discussed in some detail here to provide some background to the relevance and approaches that might be applied to environmental exposures. With the exception of arsenic in areas of known high exposures through drinking water, biomonitoring of exposure to the COCs is mainly conducted in occupational settings.

5.2 Cobalt

5.2.1 Environmental toxicology

The Agency for Toxic Substances and Disease Registry (ATSDR) of the U.S. Department of Health and Human Services produced a summary of exposures and health effects of cobalt in 2004 [13]. It notes

that cobalt in soils is variable at 1 - 40 µg/g (ave. 7 µg/g), whereas surface and groundwater (U.S.) generally contains 1 – 10 µg/g. The main source of cobalt intake is food, with the average North American diet giving 11 µg/day. Cobalt is an essential element for human life, being a component of cyanocobalamin (vitamin B12). Cobalamin is required for fatty acid metabolism and synthesis of the amino acid methionine and typically accounts for 10-20% of cobalt in the body [14]. Recommended daily intake and recommended daily allowance for vitamin B12 are respectively 6 µg and 2.4 µg, the latter corresponding to about 0.1 µg of cobalt entering the body. Cobalt deficiency is rare in humans. On the other hand, because cobalt is generally excreted very efficiently in the urine (see information on biomonitoring below), cobalt intoxication is also extremely rare. To put the toxicity into perspective, it is often noted that cobalt is cardiotoxic, and indeed deaths from cardiomyopathy have been reported. One of the last cases of iatrogenic disease from the therapeutic use of cobalt salts to treat anemia was described in 1978 [15]. A 17-year-old anephric girl with severe, persistent anemia was given 25 mg $CoCl_2$ twice daily for nine months before dying in biventricular failure. The addition of cobalt salts to beer in several breweries in the 1960's was associated with death from cardiomyopathy of some workers in those breweries who drank heavily throughout the day, and took in up to 10 mg cobalt/day. Hypothyroidism has been found in chronic animal studies of exposure to cobalt salts, and thyroid changes were noted in some patients with the excessive exposures leading to cardiomyopathy. Cumulative high exposures in a cobalt production plant was associated with echocardiographic changes indicating altered left ventricular function, but no clinical cardiac dysfunction was found [16]. ATSDR found no studies on reproductive effects in humans, or carcinogenic effects in humans or other animals after oral exposure [13]. Respiratory disorders associated with occupational exposures to cobalt include bronchial asthma, chronic bronchitis, and an interstitial fibrosing alveolitis that is associated with mixed exposure to cobalt and metal carbides [17]. (Cobalt is used as a binder in cementing tungsten carbides and other metal carbides, referred to as hard metals, used in the fabrication of grinding and drilling tools.) Immunological effects following dermal (dermatitis) and inhalational (interstitial lung disease) are discussed below.

Summing up, the ATSDR report decides a minimal risk level (MRL) at 0.01 mg/kg body weight/day for intermediate duration oral exposure. This is based on a lowest-observed-adverse-effect level (LOAEL) of 1 mg/kg/day with an endpoint of (transient) polycythemia as the most sensitive endpoint in human exposure. With the highest Port Colborne soil contour at 100 µg/g of soil, the LOAEL would represent chronic ingestion of 10 g of soil/kg body weight/day, or 700 g of soil for a 70 kg adult, if the cobalt were all bio-accessible and bio-available. The corresponding MRL would be 7 g/day for the same adult or a daily uptake of 1 g of soil for a child of 10 kg body weight. Of course the bioavailabilty is low, and even such an intake would probably not significantly add to the normal dietary intake.

The International Agency for Research on Cancer (IARC) finds that cobalt metal, soluble cobalt salts, and cobalt oxide are carcinogenic to animals but insufficient evidence in humans and conclude these compounds are possibly carcinogenic to humans (Group 2B) [18]. They find limited evidence for the human carcinogenicity of hard metal dust, which is classified as probably carcinogenic (Group 2A). The American Conference of Governmental Industrial Hygienists (ACGIH) considers cobalt a confirmed animal carcinogen with unknown relevance for humans (Level A3) [19].

5.2.2 Speciation and toxicokinetics

Complexation of Co(II) with compounds such as histidine, lysine, glycine, caseine, and the chelator EDTA reduce its uptake in the gastrointestinal tact. In animal studies, there was no difference in absorption between cobalt(II) chloride ($CoCl_2$) and cobalt(III) chloride ($CoCl_3$), but Co(II) complexed with glycine was better absorbed than Co(III) from its glycine complex. Little is known about the respiratory absorption of cobalt in humans, although animal studies suggest that approximately 30% of

the cobalt in an inhaled dose of cobalt(II/III) oxide is absorbed by the lung. Sweat can oxidize metallic cobalt to Co^{2+} ions, which can then penetrate the skin.

5.2.3 Immunosensitization

Hard metal production and use in drilling and machining are important sources of exposure to cobalt as mixed metal carbide dusts. Respiratory disease and skin sensitivity are associated with chronic exposure and provide us with much of the information on cobalt sensitization.

Respiratory pathology in hard metal workers takes the form both of obstructive disease (occupational asthma or work-related wheezing) and interstitial lung disease (fibrosing alveolitis). A cross-sectional study of more than 1000 tungsten carbide workers at 22 sites identified work-related wheezing in 10.9% and a profusion of opacities on chest radiograms in 2.6% [20]. The relative odds of work-related wheeze was 2.1 when those with current workplace cobalt exposure exceeding 50 $\mu g/m^3$ were compared with those exposed to lower ambient concentrations. Studies by Lison and Lauwerys [21-23] cast some doubt on the exclusive role of cobalt, suggesting that synergy between cobalt and tungsten carbide dust is responsible for disease. However, diamond polishers exposed to cobalt have developed a pattern of occupational asthma and fibrosing alveolitis termed "cobalt lung" [24, 25]. These similarities have strengthened the argument for cobalt as an etiologic agent in hard metal dust.

A small percentage of exposed workers develop interstitial lung disease and true occupational asthma, focusing debate on the distinction between the sensitizing effects of cobalt and its direct cytotoxicity. An immunological basis for cobalt-related interstitial disease is controversial. Evidence for the importance of sensitization has come from Japan where eight cases of confirmed occupational asthma related to hard metal dust were positive in inhalational provocation tests with nebulized aqueous $CoCl_2$ [26]. Specific IgE antibodies to a complex of cobalt with human serum albumin were found in serum samples from four of these patients, but not in samples from 60 unexposed asthmatics or 25 non-asthmatic coworkers. Type I hypersensitivity mediated by IgE is suggested. Of 700 workers producing hard metal tools, 2.0% had cobalt-specific IgE antibodies and symptoms of asthma [27]. However, when the same investigators subjected eight patients with hard metal asthma to bronchial provocation challenge with $NiSO_4$ [26], seven responded with a drop > 20% in forced expiratory volume (FEV_1, an indicator of lung function), and antibodies to nickel-conjugated albumin were present in four, suggesting that nickel may also have played a role in their asthma. Alternative nonimmune mechanisms may involve susceptibility of macrophages to activation by cobalt or reactivity of target cells to macrophage-derived mediators [28]. It must be stressed that while these studies provide clear evidence of respiratory symptoms upon chronic occupational exposure to cobalt-containing dusts, there is no evidence of such effects from environmental exposures.

Consistent with immunologic effects of cobalt, allergic dermatitis has been reported in workers in numerous cobalt-related industries, including those in hard metal and cobalt alloy, paint, cement, and rubber industries [29, 30]. An allergic dermatitis has been observed in Finnish potters handling cobalt clay [29] and is strongly associated with a history of eczema [31]. Many patients with Ni^{2+} sensitivity also have Co^{2+} sensitivity, but this may reflect concomitant sensitization rather than cross reactivity; cross reactivity of Ni^{2+}-reactive T-cell clones is seen with Cu^{2+}, but not with Co^{2+} [32, 33].

5.2.4 Biomonitoring

In contrast to copper, occupational exposures to cobalt and nickel are routinely monitored in industries where these metals are mined of refined, and we present here abbreviated guidelines from the WHO [34, 35] that might be adapted to environmental exposures, bearing in mind the generally much lower levels

of exposure encountered in the community than in the workplaces that have been studied. Measurements of total cobalt in urine, blood, plasma, or serum can be useful for monitoring occupational exposure. In individuals not occupationally exposed to cobalt, concentrations in blood and urine may be higher than in serum or plasma. Because cobalt is rapidly eliminated in urine and readily exchanges with body stores, levels in all these body fluids best reflect most recent exposures; non-invasive procedures for monitoring long-term cobalt exposures are not available [35]. Concentrations of cobalt in urine and blood are strongly correlated during exposure in the work environment [36, 37]. However, because concentrations in urine are much higher than in blood, and the latter are near the reliable detection limit by common analytical methods, urine sampling is most useful. Typically, start- and end-of-shift samples (daily or weekly) are collected [35].

5.3 Nickel

5.3.1 Environmental toxicology

Humans are exposed to nickel through air, water, and diet. Dietary intake of nickel is usually about 100 µg/day [38]. Nickel is not generally believed to be essential for higher organisms, but is a cofactor in several enzymes of plants and microorganisms, and thus vegetarian diets may be higher in nickel content; diets rich in nuts and soy products may lead to intakes of nearly 1 mg/day [39]. Urban atmospheres in the U.S. have been reported to contain nickel at about 25 ng/m^3 and urban dwellers inhale 0.2 - 1.0 µg nickel/day [34, 39]. Values of about 150 ng/m^3 have been recorded in polluted areas, particularly where fossil fuels are burned. Nickel in cigarette smoke increases intake by as much as 4 µg/pack in smokers. Other non-occupational exposures arise from handling metal objects such as jewelry and coins, and from implantation of medical prostheses made from nickel-containing alloys. These exposures are primarily of interest for immunosensitization (see below).

Nickel inhaled from fumes and dusts, including that from occupational exposure to welding fumes, is mainly deposited as particulates in the nasal sinuses, upper airways, and lungs, depending on the aerodynamic size distribution of the particles. Aerosolized nickel compounds encountered in some occupations are absorbed and result in immediate increases in blood nickel levels [34]. Transdermal absorption of nickel is low, but binding of nickel as a hapten to ligands in the skin can result in antigen presentation and contact dermatitis [12, 38]. Oral absorption of nickel contained in food is low, but increases to about 30% when soluble nickel salts are given in water to fasting persons [40, 41].

The acute toxicity of ingested soluble nickel is low [42, 43]; accidental ingestion of gram quantities have been tolerated with minimal side effects. The main concern is for the carcinogenic potential of chronic exposure. Certain nickel compounds are potent carcinogens in animals and there is now sufficient evidence for carcinogenicity in humans. The Doll Committee [44] concluded that increased risks of respiratory cancers are primarily related to exposures to less soluble nickel oxides and sulfides at concentrations in excess of 10 mg/m^3 and to soluble nickel compounds at concentrations above 1 mg/m^3.

IARC reviewed the Doll and other data [3] and concluded that nickel compounds are carcinogenic to humans (Group 1), whereas metallic nickel is possibly carcinogenic to humans (Group 2B). There is no significant evidence linking purely environmental nickel exposure to cancer. The major occupational studies (summarized from IARC) were conducted at INCO Ontario, MONDO/INCO South Wales, and Falconbridge Norway. Among the Ontario workers no nasal cancer was observed among sintering workers with more than five years of exposure to sulfidic nickel, but the standardized mortality ratio (SMR) for lung cancer was 492. In another group of sinter workers with additional exposure to nickel oxides and soluble nickel, this value rose to 789 and nasal cancers were also observed (SMR ~ 13,000).

Comparable results were observed in leaching and calcining workers with similar exposures, whereas among electrolysis workers with lower exposures to all classes of nickel compounds no excess cancers at any site were found.

In Wales, exposures of five or more years duration to nickel oxides, sulfides, salts, or metal in a variety of occupations associated with nickel production were associated with SMRs of 300-1200 for lung cancer and 1,000-78,000 for nasal cancer. In the Norwegian study, electrolysis workers with low exposure to sulfidic nickel had an increased SMR for lung cancer compared to workers in other regions of the plant who had not been significantly exposed to nickel salts (SMR = 476 *vs.* 254).

It is important to stress that these positive cancer statistics are based on inhalation only, in occupational settings where exposures had been far above those encountered in the general atmosphere, whatever the level of local soil contamination. It should also be pointed out that the proven associations with human lung and nasal cancers are for nickel sulfates, and mixtures of nickel oxides and sulfides encountered in the nickel refining industry. Even these associations are weak, and tend to ignore confounders such as concomitant exposure to sulfuric acid, itself associated with lung cancer in industrial settings, or sulfur dioxide. Production of human tumours by other nickel species or at other sites remains unconfirmed.

A question was raised by the community about the role of nickel in colonization of the stomach with *Helicobacter pylori*. *H. pylori* requires the Ni for a urease enzyme needed to help regulate pH and allow adhesion [45]. However, the nickel intake in a normal diet should be sufficient. An increase in Ni activates pumps that efflux nickel and regulate the nickel content in the bacterium [46]. Furthermore, increasing nickel to 100 μM represses expression of the nickel permease NixA, making nickel less available to the organism [47]. The authors note "NixA presumably should be able to ensure nickel uptake with minimal external concentrations. ... the reduced synthesis of NixA is a protective measure against the toxic effect of an increased intracellular nickel content."

5.3.2 Speciation and toxicokinetics

Soluble nickel salts dissociate and release Ni^{2+} ions in aqueous media. Oral nickel absorption in rats is greater with more soluble compounds, for example 34% for nickel(II) nitrate ($NiNO_3$), 11% for $NiSO_4$, 10% for $NiCl_2$, 0.5% for Ni_3S_2, 0.09% for metallic nickel, 0.04% for black nickel oxide, and 0.01% for green nickel oxide [4]. Absorption is reduced by binding to amino acids such as cysteine and histidine. Oral absorption of $NiSO_4$ given in drinking water to fasting human subjects was (27 ± 17)% (mean ± s.d.) but was only 0.7 ± 0.4% when the $NiSO_4$ was given in food [40]. The water solubility of nickel compounds correlates well with the rate of absorption of Ni^{2+} into the blood from nickel-containing particles that reach the alveolar level in the lung. When soluble $NiCl_2$ was deposited in the lungs of rats by intratracheal instillation, 75% per cent was absorbed within 3–4 days, whereas 80% of deposited NiO aerosol still remained in hamster lungs after 10 days [4]. The half-lives of nickel in rat lungs following inhalation of nickel(II) sulfate ($NiSO_4$), nickel(II) subsulfide (Ni_3S_2), and nickel(II) oxide (NiO) were about 30 h, 4–6 days, and 120 days, respectively [4]. The depth of penetration into the skin of nickel from Ni(II) salts is a function of the counterion (acetate > nitrate > sulfate > chloride. Using excised human skin under occlusion, penetration of Ni^{2+} from $NiCl_2$ through the skin was about 0.23% of the applied dose after 6 days and 40–50 times quicker than from $NiSO_4$. Without occlusion, the permeation of $NiCl_2$ was reduced by more than 90%, and no absorption was detectable using $NiSO_4$ [4].

5.3.3 Immunosensitization

Nickel can well be considered the prototype for understanding metal sensitization. Occupational exposures to nickel are widespread and occur in mining and refining of nickel ores, and production of

alloys. Electroplating with nickel, stainless steel welding, and use of nickel alloys in the electronics industry are also important sources of exposure. Further exposures occur in nickel-cadmium battery manufacture, the chemical, pigment, and ceramics industries, and manufacture of nickel-based catalysts for industrial hydrogenation reactions. Some nickel platers, refiners, and welders have developed occupational asthma, chronic bronchitis, and pneumoconiosis. While nickel may be an etiological agent in these cases, IARC [3]was unable to determine its causal significance.

Non-occupational exposures arise from handling metallic objects such as jewelry and coins. A high rate of nickel allergy is associated with ear piercing and subsequent wearing of nickel alloy jewelry [48]. Interestingly, comparing the lower incidence of nickel allergy in those who wore nickel-releasing dental braces before ear piercing, with the higher incidence in those who wore them only after or not at all, provides evidence for the development of tolerance to nickel [49, 50]. Dietary intake of nickel is at least 100 µg/day [38], and diets naturally high in nickel can exacerbate dermatitis in nickel-sensitized individuals [51]. Dermal exposure to nickel is primarily related to contact dermatitis that begins as an erythematous lesion, usually on the hands and forearms, eventually becoming eczematous [52]. Asthma, conjunctivitis, and local inflammation associated with prosthetic devices have also been reported [52]. Sensitivity can also be manifest as asthma, and rare instances of anaphylaxis have been reported following parenteral injections of nickel-contaminated medications [52]. Much is known about the mechanisms of nickel sensitization, including specific metal-protein interactions, activation of subsets of T cells, and activation of various cytokines [12, 53].

Cross-reactivity is an important issue in nickel allergy, as nickel exposure often occurs in the context of multiple metal exposures, and positive patch tests to other metals (e.g., cobalt and chromium) are common. However, some nickel-specific T-cell clones cross-react *in vitro* with copper, but not with cobalt [54], indicating that cross-reactivity can occur at the clonal level. Another study [33] confirms clonal cross-reactivity with either copper, but not cobalt, in $CD4^+$ clones from eight patients.

5.3.4 Biomonitoring

Absorbed nickel is cleared rapidly in the urine. Thus, serum and urine nickel concentrations are correlated after exposure to soluble nickel compounds and both are indicative of recent exposure [34]. Nickel does not accumulate in the body with common levels of non-occupational exposure. However, insoluble and particulate forms can accumulate in the upper airways and the lungs, and can serve as an internal source of exposure at a much later time. Therefore, whereas changes in nickel concentration in serum and urine are good indicators of exposure to bio-available nickel over the preceding 1-2 days, increases in the nickel content of these fluids will also reflect long-term exposure from these insoluble sources, and on-going, long-term monitoring is implemented in occupational health.

The nickel concentration in urine is a good indicator of current exposure to bio-available nickel, and is useful for end-of-shift monitoring in the occupational setting [42, 55]. Spot urines are collected at the beginning and end of the workday. Nickel in serum or plasma correlates with urinary levels in acute absorption, and is more reliable for long-term monitoring of insoluble nickel compounds [42, 55-57]. Biopsies of the nasal mucosa yield information on the long-term inhalation of poorly soluble nickel compounds [58]. This invasive procedure is not feasible for screening populations.

5.4 Copper

5.4.1 Environmental toxicology

Copper is an essential element and its plasma level is homeostatically regulated at about 1 μg/ml through controlled biliary excretion. Exposure is ubiquitous as copper is widely used in electrical wiring, gas and water pipes, coinage, printing, electroplating, and more. The copper-based contraceptive intra-uterine device exposed many women to copper chronically through a mucosal surface (at about 80 μg/day [59]) without apparent adverse effects. Copper released to soils is strongly adsorbed to clays, carbonates, and organic compounds and remains in the upper few centimeters [59]. Concentrations in US soils generally range up to 50-150 μg/g, with "various soils" listed as 3-300 μg/g [60], compared to Port Colborne contours of 200-400 μg/g.

The median intake of copper from food in the U.S. is ~1 mg/day [60], ranging from 0.9 - 2.2 mg [59]. This is hard to reconcile with the ATSDR's own suggested MRL of 0.01 mg/kg/day, or 0.7 mg/day in a 70 kg adult, for acute oral exposure. The main source of what is considered to be excessive copper exposure in the Western World is tap water that sits overnight in copper pipes. The WHO notes an acceptable range for oral intake is likely about 2-3 mg/day, noting this is based on gastrointestinal effects of copper in drinking water [59].

The main effects of excessive copper exposure are irritant [60]. Copper is not known to cause cancer, and both IARC and the EPA deem it unclassifiable as to human carcinogenicity (Group 3 and Group D, respectively). Patients suffering from Wilson disease give us an insight into chronic copper overload. Unable to excrete copper in the bile due to a genetic defect in copper transport, they accumulate copper to levels exceeding by orders of magnitude any that occur from environmental exposure. Over several decades of life, they develop hepatotoxicity and neurological disorders. Nevertheless, the WHO considers there is some need to develop better science on bio-availability and speciation of environmental copper [59].

5.4.2 Speciation and toxicokinetics

Approximately 30% of copper from copper(II) sulfate ($CuSO_4$) is absorbed from the gastrointestinal tract in humans [4]. Increasing pH decreases absorption, probably due to the decreased aqueous solubility of hydrolysis products such as $Cu(OH)_2$. Copper in complexes in food, such as copper methionine, is more readily absorbed than copper in inorganic salts, such as $CuSO_4$. Amino acid copper chelates may be absorbed by specific transporters, although cysteine and ascorbic acid decrease copper bio-availability, probably by reducing Cu(II) to Cu(I) [4]. Absorption of copper was studied in cattle and followed the order copper(II) carbonate ($CuCO_3$) > copper(II) nitrate [$Cu(NO_3)_2$] > $CuSO_4$ > copper(II) chloride ($CuCl_2$) > copper(I) and copper(II) oxides (Cu_2O and CuO) [61].

After oral absorption, copper is initially bound mainly to albumin, with about 5% of plasma Cu(II) bound in low molecular mass amino acid complexes [62]. After entering hepatocytes, copper is bound to caeruloplasmin and re-enters the circulation. About 65% of circulating copper is irreversibly bound to caeruloplasmin, and approximately 15% is bound to the *N*-terminus of albumin. Excessive copper is stored in the liver bound to metallothionein [62].

5.4.3 Immunosensitization

Copper sensitization is widely recognized to occur, although it has not been thoroughly investigated and is generally assumed to be rare [12]. In one study [63], six of 354 subjects reacted to a copper patch test; all were women with hand eczema, but none had apparent occupational exposure to copper, and none wore a contraceptive intra-uterine device. Cross-reactivity with copper, of nickel-selective T-cell clones, is noteworthy [33].

5.4.4 Biomonitoring

As noted above, copper is an essential element that is homeostatically regulated mainly through biliary excretion to maintain blood levels at about 1 μg/ml. The mechanism regulating copper uptake in the gut is not well understood, but absorption of available dietary copper can vary from more than 50% on low-copper diets to less than 20% with increased intake [64, 65]. While massive copper overload occurring in the genetic Wilson Disease is diagnosed by liver biopsy or trial administration of chelating agents, these approaches are uncalled for in a scenario of environmental exposure.

5.5 Arsenic

5.5.1 Environmental toxicology

Arsenic occurs in the natural environment, arising from both natural and anthropogenic sources. It is considered by some to be an essential element for life, in trace quantities; small amounts (10-50 ppb) occur in the normal diet [66]. In humans there is some detoxification of inorganic arsenic by methylation in the liver. The average intake in Europe is reported to be 10-20 μg/day, mainly through foods of plant origin [67]. In contrast to the other COCs, where most information relates to occupational exposure, there is a considerable amount of information on environmental exposure to arsenic given that it occurs in very high levels in some groundwaters that serve as sources of drinking water for significant numbers of people. Thus, the WHO has set a guideline of 10 μg/ml arsenic in drinking water. This represents a 6×10^{-4} excess risk of skin cancer, which is 60 times above generally accepted risk, but reflects the practical detection limits for measurement by most laboratories; a health-based guideline has been proposed to be 0.17 μg/L [67]. To put this in perspective, 10% of the groundwater in the U.S. exceeds the 10 μg/L guideline, and groundwaters in some areas of Bangladesh, Bengal, China, Taiwan, Thailand, Chile, Argentina, and Mexico have up to several mg/L [67].

IARC considers there is sufficient evidence to consider arsenic a carcinogen in humans, causing cancers of skin, bladder and lung, with insufficient evidence for other sites [68, 69]. In 1999, the National Research Council of the NAS published a report on arsenic in drinking water, recognizing this as the most important route of environmental exposure [70]. The Safe Drinking Water Act (U.S.) directs the Environmental Protection Agency (EPA) to establish standards for contaminants in public drinking water. The standards are to be set at concentrations at which no adverse effects are expected to occur and which provide an acceptable margin of safety for humans. However, in keeping with the recognition of practical detection limits noted in WHO guidelines above, enforceable standards are not to exceed those which can be achieved using the best technology available at the time. Bearing this in mind, the EPA set an interim maximum contaminant level (MCL) for arsenic in drinking water at 50 μg/L. The Council report noted, however, "At present [1999], the practical quantitation limit for arsenic in water in most commercial and water utility laboratories is 4 μg/L. [This] is adequate for regulatory purposes." They noted, however, that there have been no studies of "sufficient statistical power or scope" to determine whether consumption of arsenic at the current MCL (50 μg/L) causes adverse cancerous effects, and the shape of the dose-response curve is not known. The overall

assessment was that the MCL of 50 μg/L in drinking water does not achieve a sufficient safety margin for protection of the public health and should be revised downward, in agreement with the opinion of the WHO that a health-based guideline would be lower than the practical guideline, and with the ATSDR MCL drinking water standard of 10 μg/L.

The National Research Council's report also considered speciation, noting inorganic arsenic - found in ground water, surface water, and foods - is most toxic. This is not particularly helpful, as a variety of organic and inorganic species exist, with differing toxicities. Adverse effects are well established from exposure to inorganic arsenic through drinking water. These are skin cancer and to a lesser extent internal cancers, as well as peripheral vascular (Blackfoot disease) and neurological (paraethesia) effects. In considering epidemiological studies from Taiwan, Chile, and Argentina, the National Research Council concludes there is sufficient evidence that chronic ingestion of inorganic arsenic causes cancers of bladder, lung, and skin (mainly basal cell carcinoma). These studies were based on populations using drinking water with several hundred μg/L arsenic.

After these considerations had had general public scrutiny, the NAS updated the evidence in 2001 [71]. Several hundred new articles on arsenic had appeared since the 1999 report. Of four major epidemiological studies since 1999, three from Taiwan and Chile confirmed an association with lung and/or bladder cancer, while one from Utah did not. Comparison of two Taiwanese studies did not support an effect of life style. Together with the many earlier studies considered in the 1999 report, we can accept a firmly established association between chronic exposure to arsenic in drinking water and cancer of the lung and bladder.

There was also increased evidence for association between arsenic in drinking water and development of high blood pressure and diabetes, but there are inadequate data for any dose-response assessment. The NAS concluded that more studies are needed, noting that dose-response curves are still not generally known, and there is no reason to suppose they would be similar for different adverse effects of arsenic. This is really an acknowledgment that mechanisms are not known. In particular, the Academy concluded there is no "biological basis for either a linear or non-linear extrapolation." Cellular effects can occur at concentrations below those found in urine of people who drank water with [arsenic] as low as 10 μg/L.

The committee of the Academy estimated an ED_{01} value (estimated dose for a 1% response in the study population) of between 5-95 μg/L for lung cancer, and between 100-400 μg/L for bladder cancer, varying depending on the study and methods of statistical modeling. They also concluded that the database on the carcinogenic effects of arsenic is adequate for risk assessment and continued risk assessment for lung and bladder cancer should be the basis for regulatory decision making.

There are no experimental data to determine the threshold at which a risk might be present, and therefore the ED_{01} value should be used to extrapolate from concentrations of concern. Excess lifetime estimates of risk from arsenic in drinking water are shown in Table 18 [70].

Table 18 - Excess lifetime estimates of cancer risk from arsenic in drinking water

	Bladder		Lung	
µg/L	(per 10,000)			
	women	men	women	men
3	4	7	5	4
5	6	11	9	7
10	12	23	18	14
20	24	45	36	27

However, even at the highest risk estimate, it is concluded that excess risk of bladder cancer in males would be hard to detect in the U.S. population, as 45/10,000 would represent only 13 % of the total risk of bladder cancer from all causes. It would be even harder to demonstrate an association with lung cancer. Nevertheless, these estimates reinforce the idea of a risk below the MCL an 10 µg/L. Arsenic exposure by inhalation has been linked with lung and liver cancer, but only in cases of occupational exposure such as those related to smeltering or arsenical pesticide use [72].

Regarding non-cancerous effects of arsenic, targeting to mitochondria, and especially effects on hepatic cellular respiration may be important. Oxidative stress is likely a factor. Of the non-cancerous effects of chronic ingestion, cutaneous manifestations have been documented most widely, and include hyper- and hypopigmentation, palmoplantar keratoses, and ulceration [73]. There is no evidence of developmental or reproductive effects of chronic ingestion of inorganic arsenic in humans [70], although arsenic crosses the placenta and parenteral arsenic is teratogenic in a number of animal species.

It is generally accepted that methylation of arsenic is detoxifying, and organic species such as arsenobetaine found in seafood are virtually non-toxic [4]. There is a variation in urinary methylated species within a population having a uniform exposure; that is, there is inter-individual variation in detoxification capacity. The species of arsenic to which an individual is exposed are also probably important in determining the extent of metabolism. The National Research Council study [70] concluded the influence of dose, nutrition (through S-adenosyl methionine, choline, or total protein levels), and disease on arsenic methylation are not well known, and more human studies are needed. The extent to which variation in methylation affects toxicity and carcinogenicity are not known. Dimethylarsinate (DMA) may be a promoter but not an initiator of cancer.

5.5.2 Speciation and toxicokinetics

This section summarizes data presented in [4]. The extent of absorption of inorganic arsenic compounds from the lungs of hamsters after intratracheal instillation correlates with their water solubility. Retention of elemental arsenic 3 days after an intratracheal instillation (2 mg/kg body wt.) of sodium arsenite ($NaAsO_2$), sodium arsenate (Na_2HAsO_4), arsenic(III) trisulfide (As_2S_3), and lead arsenate ($PbHAsO_4$) were, respectively, 0.06%, 0.02%, 1.3%, and 45.5% of the dose. In another study, sodium arsenate and sodium arsenite (5 mg/kg body wt.) were 10-fold more bio-available than sparingly soluble gallium arsenide (GaAs). In humans, sodium arsenate is better absorbed than the highly insoluble arsenic(III) trisulfide. Arsenic(III) trioxide (As_2O_3) is cleared much more quickly from the lungs than arsenic(III) trisulfide or calcium arsenate [$Ca_3(AsO_4)_2$], reflecting the greater solubility of As_2O_3.

Water-soluble forms of inorganic arsenic are almost completely absorbed from the gastrointestinal tract of humans, e.g. at least 95% of an oral dose of arsenite. Fifty-five % – 80% of daily oral doses of soluble arsenate or arsenite have been recovered in the urine of human volunteers. Methylarsonic acid (MMA), dimethylarsinic acid (DMA), and trimethylated arsenic species are also well absorbed (at least 75–85%) in the gut, and arsenobetaine is rapidly and almost completely absorbed. Dermal exposure to environmental arsenicals is considered to be a minor route of exposure compared to oral or inhalational exposure.

Inorganic arsenic is rapidly cleared from the blood in humans and widely distributed in almost all tissues. The tissue retention of arsenite tends to be higher than arsenate, with the exception of the skeleton. The main route of excretion of arsenic after exposure to either inorganic or organic arsenic species is urine, excretion being more rapid after exposure to arsenate than to arsenite.

Unlike the other COCs, arsenic undergoes extensive biotransformation in the body. This involves methylation and resulting in the formation and excretion of monomethylated and dimethylated compounds (MMA and DMA, respectively). The liver is the major site of arsenic methylation following ingestion. Arsenite is taken up by hepatocytes much more readily than the ionized arsenate. In most mammals, only trivalent arsenic species are methylated and reduction of pentavalent arsenic precedes methylation. Thus, a major part of As(V) absorbed as arsenate is rapidly reduced to As(III) arsenite in the blood. Because arsenite is more toxic than arsenate, this initial step represents bio-activation. Genetic polymorphism in the regulation of enzymes responsible for arsenic methylation gives rise to variations in arsenic metabolism in the general population. Nevertheless, the distribution of arsenic species in urine is fairly constant across human populations independent of the source and extent of exposure, representing about 10–30% inorganic arsenic, 10–20% MMA, and 60–70% DMA.

5.5.3 Biomonitoring

Biomonitoring of exposure to arsenic may be useful both in occupational and environmental exposures. Occupational exposure to arsenic requires monitoring with the following general guidelines [70, 74, 75]. The concentration of inorganic arsenic (As^{3+} and As^{5+}, occurring as the anions arsenite and arsenate) in urine is a useful marker of both recent and on-going exposure. In the occupational setting it is measured in a spot sample at the end of the workday. Total arsenic in blood is less useful, and hair and nails are unreliable. Because organic arsenic compounds are virtually non-toxic, measurement of total arsenic in urine is not very useful. However, because inorganic arsenic is metabolized to MMA and DMA, inorganic arsenic in urine is a small and variable fraction of total exposure, and it is most appropriate to measure the sum of (inorganic arsenic + MMA + DMA), which is not the same as total arsenic. This sum correlates well with level of exposure to airborne arsenic in the workplace [75].

5.6 COC speciation and exposure in Port Colborne

To our knowledge, speciation analyses of cobalt, copper and arsenic have not been undertaken in the Port Colborne environment. Several studies have been carried out on nickel in Port Colborne soils, using combinations of scanning electron microscopy and X-ray absorption spectroscopy. These were summarized and augmented by Jaques Whitford Ltd. (Whitford), and reported in [76]. INCO undertook analysis of four soil samples provided by the MOE from the higher concentration areas and found a nickel concentration of about 10 mg/g, which was nickel metal or nickel oxides with or without traces of Fe, cobalt and copper. Subsequent analysis of two samples reported 90 to 100% nickel oxide. Further independent analyses obtained by the MOE found average total nickel of 7.4, 8.2, and 11.4 mg/g, with one lab reporting 11% nickel metal, 8% nickel sulfide, 0.4% soluble nickel, and the remainder nickel oxide, while another lab found 89% nickel oxides and no other species identified. Additional sampling of agricultural soils downwind of the refinery found primarily nickel hydroxides and sorption complexes with Fe that were attributed to weathering of the soils.

In a more detailed sampling protocol, Whitford identified 90-95% nickel oxide in samples close to the refinery and 92-97% nickel hydroxides two-to-three kilometers away, in keeping with the previous MOE reports. Furthermore, no nickel sulfide or subsulfide was identified, and differential extraction showed that less than 5% of nickel was soluble and available to plants. Previous studies on nickel in outdoor ambient air, collected on filters, were inconclusive because of the low levels of nickel present. Whitford identified nickel oxide/hydroxide (80%) in particles above 2.5 μm and Ni-Cu-Fe oxide (71%) in particles less than 2.5 μm. Metallic nickel was found (up to 12%) in the >2.5 μm fraction. No nickel sulfide or subsulfides were found in the air filters. Thus, most of the nickel in Port Colborne soils is in insoluble, poorly available forms, and the nickel collected on air filters reflects the speciation profile of that in soil.

Some additional useful information on cobalt, nickel, and copper may be extrapolated from the literature:

Cobalt: Analysis of soil and dust from the vicinity of a hard metal grinding factory revealed cobalt present in composites with tungsten, calcium, titanium and iron [77]. Less cobalt was found in particles further from the plant, suggesting mobilization of cobalt. The authors note that while metal and oxide forms of cobalt are ionsoluble in water, dissolution will take place in acidic soils, where association with manganes and iron oxides, clay minerals, and organic ligands is then likely. Dissociation is less likely in alkaline soils. When organic pollutants in water are at a high level, most cobalt will be complexed; otherwise, aquated Co^{2+} will predominate with the major minor species being the carbonate, bicarbonate, sulfate and humate, both as predicted and as measured in fresh water [13].

Nickel: In natural waters below pH 9, nickel occurs predominantly as the hexaaquo ion $Ni(H_2O)_6^{2+}$, with the hydroxide, sulfate, carbonate, and chloride as only minor species [78, 79]. Humic acids will temporarily mobilize nickel from soil water before its conversion into insoluble species [79].

Copper: Copper commonly exists in the Cu(I) or Cu(II) oxidation states. In aqueous environments, Cu(I) is rapidly oxidized to Cu(II) by oxidants, or by disproportionation. As a relatively hard ion, Cu^{2+} is then bound by water, hydroxide, carbonate, sulfate, etc., and often exists in natural waters in organic species bound to phenolics and carboxylates [59]. These species are quite water-soluble and bioavailable. The aquated species is usually relatively low, and, depending on the composition of the aqueous environment, humic and fulvic acid species can predominate [59].

6.0 Conclusions and Recommendations

In this review, we have evaluated the findings of the CHAP A and C reports, conducted additional analyses of the original and augmented administrative data, considered sample size issues, and reviewed the literature on the
potential health effects of the COC's. We conclude that there is no justification for recommending case-control studies of the population of Port Colborne, for a number of reasons.

While it is true that there are some elevated risk estimates cited in both of the study reports, there is substantial inconsistency in the findings between the two studies. For instance, heart disease appeared elevated in the CHAP A, but not in the CHAP C, report; respiratory infections appeared elevated in the CHAP C, but not in the CHAP A, report. Nevertheless, we deemed it prudent to explore these disease categories, as well as the occurrence of cancer, in Port Colborne.

Anomalous findings occur in the results of both reports. For example, respiratory cancers were elevated only in young adults, an estimate which could very possibly be diagnostic coding error and/or based on very few events. COPD in the young is another example of an unlikely condition, since it's a logical impossibility to make this chronic disease diagnosis in children. These anomalies make it difficult to cleave to a strict interpretation of the statistical findings.

Our statistical analysis places Port Colborne in the context of the complete set of Ontario communities, a much large comparison group than the 35 used in the CHAP C report. No statistically significant elevations were found. Issues raised in the re-analysis include the choices of comparison communities; multiple comparisons (age, sex, time period, and diagnostic subgroups); the interpretation of the substantial number of Port Colborne deficits for many of the disease categories; and residual heterogeneity of the data.

Even assuming the truth of the few statistically significant elevations of disease rates, given the small population and the only slightly elevated risk ratios, these elevations would translate into an excess on the order of a handful of events in a year. This has the practical effect of making it impossible for future (e.g., case-control) studies to achieve the statistical power necessary to rule in any associations. In any case, there is a growing body of literature (80-83) supporting the hypothesis that ischemic heart disease and asthma are associated with particulate matter in the air. Therefore although we find no strong evidence to support a hypothesis that residents of Port Colborne are discharged from hospitals for asthma and IHD at a greater rate than residents of the several comparison groups, what small evidence there is might be explained by a relationship between these specific disease categories and air pollution.

Our review of the literature supports the conclusion that no further study is necessary, based on the lack of evidence that the particular species of the COC's, and their distribution and potential for exposure in Port Colborne, are unlikely in the extreme to be related to the specific disease excesses noted in the CHAP A and C reports. In particular, exposures to nickel in Port Colborne are not to the highly carcinogenic forms, nor are they the mixed inhalational exposures that have been associated with increased nasal cancers in chronic occupational settings. Very significant exposures to arsenic through drinking water are notably associated with skin cancers following other obvious dermal manifestations of exposure; these are not evident in Port Colborne. Nickel and cobalt are immune sensitizers, but this toxicity is manifest as contact dermatitis. In the case of cobalt, an interstitial lung disease and occupational asthma develop after prolonged occupational exposure to cobalt and cobalt-containing dusts. There is no evidence that environmental exposure to either metal

is causal of childhood asthma. While ingestion of high levels of cobalt has been associated with cardiomyopathy in rare cases, this has never resulted from environmental exposures and, in any event, is unrelated to ischemic heart disease.

In the end, it is important to assess the potential for causation of any health effects, with respect to living in Port Colborne (or specific neighbourhoods within the city). The criteria for assessing causation include the strength of the observed associations; the consistency of the associations across different studies and within a study in different subgroups; the presence of a dose-response; and biological plausibility. On all of these grounds, the analyses we have presented here fail to support a link between exposure to COC's in Port Colborne and the disease and symptom outcomes measured in the CHAP A and C studies.

The CHAP B Decision Document identifies four decision points, which can be addressed as follows:

1. Are there statistically significant increased risk estimates in the CHAP A and C reports? Yes, but not with a degree of consistency across age groups or regions, or between CHAP A and C.

2. Is the number of available cases in Port Colborne sufficient to provide adequate statistical power for detecting associations of the magnitude identified in point #1? Yes, for a few, but for these conditions we argue that such studies would be uninformative.

3. Is there evidence of an association between the observed health effects and exposure to the COC's? No, environmental exposures to the COCs have not been linked to any of the disorders showing increased risk in Port Colborne.

4. Is there justification for any additional studies of health effects in Port Colborne (either case-control or other study designs)? No, on the basis of points 2 and 3 above.

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Appendix 1

Explanation of Databases used in these Analysis

Hospital discharge data from the Canadian Institute of Health Information (CIHI)'s data abstract database (DAD) were extracted at a census subdivision level. Before the 2001 Canadian census there was little information available from smoking surveys administered to Ontario residents to give reasonable estimates of smoking prevalence at a census subdivision level. Such information is now available in the 2001 Canadian Census.

The 2001 Canadian Census

We first examined census population estimates made available to Health Canada by Statistics Canada. In 2001, there were 586 census subdivision areas in the province of Ontario. Seventeen of these were aboriginal communities and have no census data. Another 25 census subdivisions had census data suppressed because their populations were too small (<10). Data were available for 544 CSDs with population sizes ranging considerably between 10 and 2,481,494.

Sociodemographic characteristics of the census subdivisions were extracted from a Statistics Canada database (Statistics Canada Catalogue Number: 95F0495XCB01001). CSDs level characteristics that were extracted from this file included: unemployment rate, household income level, average dwelling price, 1996 population estimate, and educational attainment. In this file, there were a total of 557 observations for Ontario but these included one observation that was an overall summary for Ontario, 49 that were for census divisions, and 507 census subdivision observations. Note, the census divisions contain several census subdivisions, and were dropped from the analysis. The population estimates for these CSDs ranged from 46 to 2,481,494. A request has been made to Statistics Canada to explain the reasons for the exclusion of the 79 CSDs. Some were not in the file because of small sample sizes, and aboriginal communities. However, this does not explain in full, why 79 CSDs do not appear in file.

Cigarette Smoking Information

Information on the prevalence of current smokers was ascertained from the 2001 and 2003 Canadian Community Health Surveys (CCHS). There were 37,681 and 40,507 Ontario residents who supplied smoking data in the 2001 and 2003 surveys. For these analyses the data were combined by CSD. This assumes that the data are independent (i.e., individuals were did not participate twice, which is likely given the sampling methods employed by Statistics Canada in doing these survey). The variable P_SMOKER represent the prevalence of current smokers among CCHS participants who lived in a given census subdivision and SHS represents the proportion of homes in which someone smoked inside the home on a regular basis. These questions were asked in the both surveys. No information is available from CSDs with a total number of respondents less than 10 across the two surveys. SHS was available for a total of 340 CSDs, and P_SMOKER for a total of 343 CSDs.

CIHI Discharge data

Hospital discharge data between 1986 and 2002 were supplied from CIHI's DAD database. Discharge counts were supplied by five year age groupings, by sex, for each year. Population estimates were made available with the CIHI database and are based on population counts estimated from Canadian censuses, and interpolation of these data (by age and sex) in non-census years. It should be noted that given the length of the period (1986-2002) some noteworthy changes in discharge counts were observed over the years. For example, the number of asthma discharges decreased from approximately 22,000 in 1986 to 8,325 in 2002. Such changes warrant some consideration in analyses. There are a smaller number of CSDs based on 2001 geography than those used in the original CHAP C report. However, the defined boundary for Port Colborne has not changed.

Appendix 1B Regression Analysis

The two statistical analyses used in this report are weighted linear regression analysis and Poisson regression analysis.

(a) Weighted Regression Analysis

In this analysis we assume that there is a linear relation between the hospital discharge rate and the predictor variables. For example the following formula can be used to determine whether there is a relation between the asthma rate for persons under twenty years of age and whether you are resident of Port Colborne, and the predictor variables mean income and the mean age of the Jth community

$$HDR_J = \frac{ND_J}{NL_J} = \beta_0 + \beta_1 PortColborne + \beta_2 MeanIncome_J + \beta_3 MeanAge_J + Error_J$$

The hospital discharge rate HDR_J is equal to the number of hospital discharges ND_J in the under 20 year age category in the jth community over the period 1986 to 2001 divided by the total number of persons NL_J living in that same age category in that same community over that same period. The Port Colborne variable is equal to 1 for a hospital discharge of a Port Colborne resident and 0 otherwise. The mean income and mean age is of the community from which the discharged patient lives..

A larger positive (negative) regression coefficient β_1 implies a larger (smaller) expected hospital discharge rate for residents of Port Colborne compared to the comparison communities. A larger positive (negative) regression coefficient β_2 implies that the hospital discharge rate is expected to be larger (smaller) for larger (smaller) values of a community's mean income. A larger positive (negative) regression coefficient β_3 implies that the hospital discharge rate is expected to be larger (smaller) for larger (smaller) values of a community's mean age.

In the analysis more weight is given to rates based on a larger number of exposed individuals. In this case it means that communities with a larger population in the under 20 year age category over the 1986 to 2001 exposure window will be given more weight. The weighted regression analysis was carried out using the SAS procedure REG. This regression analyses produces estimates of the unknown parameters β_1, β_2 *and* β_3 along with their standard errors. With an estimate and its standard error a confidence interval and a p value can be calculated to determine whether a departure of these estimates

from zero is likely due to chance. The estimate of the parameter β_1 is an estimate of the size of the difference in hospital discharge rates between Port Colborne and the comparison communities. If a variable such as mean income is a confounder then the size of this estimate will change depending on whether mean income is or is not included in the analysis.

(b) Poisson Regression

The probability of K hospital discharges over the period 1988 to 2001 in the Jth community that has a hospital discharge rate of HDR_J and a total number of NL_J living individuals over the follow-up period is

$$P(X_J = K) = \frac{(HDR_J \times DL_J)^K e^{-HDR_J \times DL_J}}{K!}$$

This model assumes that hospital discharges are distributed randomly across communities, an assumption rarely satisfied in practice unless account is taken of the various predictor variables that are likely the cause of variation in excess of that predicted by the Poisson model. The equation used to link the hospital discharge rate to predictor variables is

$$log(HDR_J) = \beta_0 + \beta_1 PortColborne + \beta_2 MeanIncome_J + \beta_3 MeanAge_J + Error_J$$

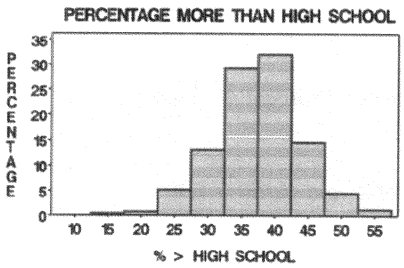
Therefore in this model it is the log of the hospital discharge rate rather than the rate itself that is linked to the predictor variables. If excess variation still exists even after several variables have been added to the model an adjustment must be made in the standard errors of the estimates otherwise the p values associated with testing various hypotheses will be too small.

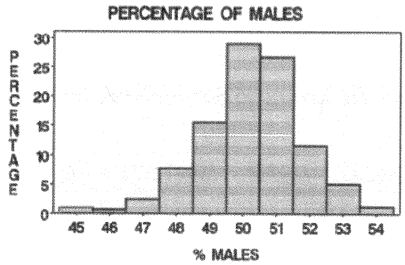
One advantage of this model is that the hospital discharge ratios are directly related to the unknown parameters in the model β_1, β_2 *and* β_3. For example the ratio of the hospital discharge rate for Port Colborne relative to the comparison communities is equal to e^{β_1}. If $\beta_1 = 0$ then the hospital discharge rate ratio is equal to 1.0. Therefore we can report ratios and confidence intervals of ratios. The Poisson regression analysis was carried out using the SAS procedure GENMOD.

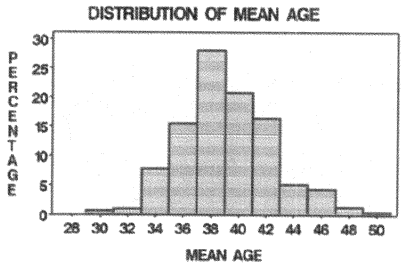
Often in data analysis the variation among sampling units is in excess of that explained by the Poisson probability model. Ignoring such excess variation will produce p values that are too small. Often it is the variability of predictor variables and confounders such as mean income that cause such excess variation. When added to the model the size of the over dispersion is often reduced. However, the excess that often remains can be accounted for by multiplying the standard error of all estimates by the square root of the over dispersion ratio. The over dispersion ratio is the ratio of the variance among sampling units in which no model assumptions are made to the variance based on the Poisson model. This adjustment was made in all of the Poisson regression analyses.

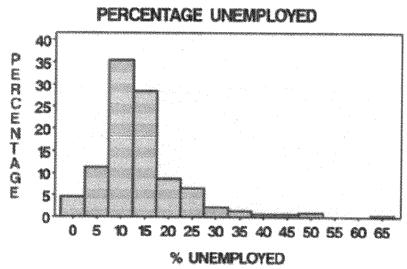
Appendix 2

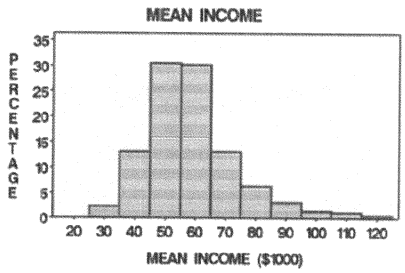
Histograms of the seven Potentially Confounding Variables for the 339 Communities used in the First Reanalysis of the Hospital Discharge Data

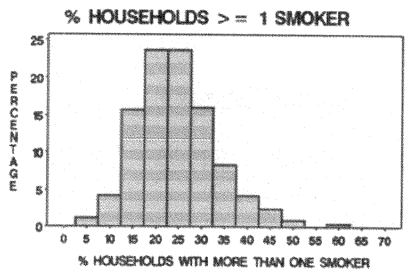


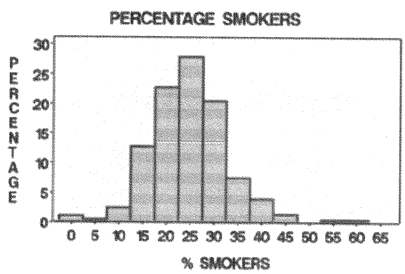












Appendix 3 Calculation of P Values Associated with the 95% Confidence Intervals given in the CHAP C Report

$$95\%\ CONFIDENCE\ INTERVAL\ OF\ THE\ \log(RATE\ RATIO)$$

$$= (logRatio - 1.96 \times SE_{logRatio} ,\ logRatio + 1.96 \times SE_{logRatio}) = (logHI , logLO)$$

where LO and HI are the 95% confidence limits reported in the Protocol C Report

$$logRatio = \frac{logLO + logHI}{2} = \frac{log(1.37) + log(1.62)}{2} = 0.39862 \ \ and \ \ Ratio = 1.49$$

$$and\ SE_{\log Ratio} = \frac{logHI - logLO}{2 \times 1.96} = 0.04276 \quad Z = \frac{0.39862}{0.04276} = 9.322 \ \ p = 1.163 \times 10^{-20}$$

Examples of the Relation Between
Reported WALD 95% Confidence Limits and P Value

EXHIBIT 23 Malignant Neoplasms Chest 20-44 Years vs NG Group

LOWERCL	UPPERCL	LOGRATE	RATE	SE	ZWALD	WALDCHI	P
1.06	2.59	0.50496	1.66	0.2279	2.22	4.91	0.02671

EXHIBIT 26 Ischemic Heart Disease 20-44 Years vs NG Group

LOWERCL	UPPERCL	LOGRATE	RATE	SE	ZWALD	WALDCHI	P
1.25	1.91	0.43512	1.55	0.1083	4.02	16.19	0.00006

EXHIBIT 33 Acute Respiratory 65+ Years vs CC Group

LOWERCL	UPPERCL	LOGRATE	RATE	SE	ZWALD	WALDCHI	P
1.18	1.94	0.41410	1.51	0.1268	3.27	10.66	0.00109

EXHIBIT 36 Chronic Obstructive Lung Disease < 20 Years vs CC Group

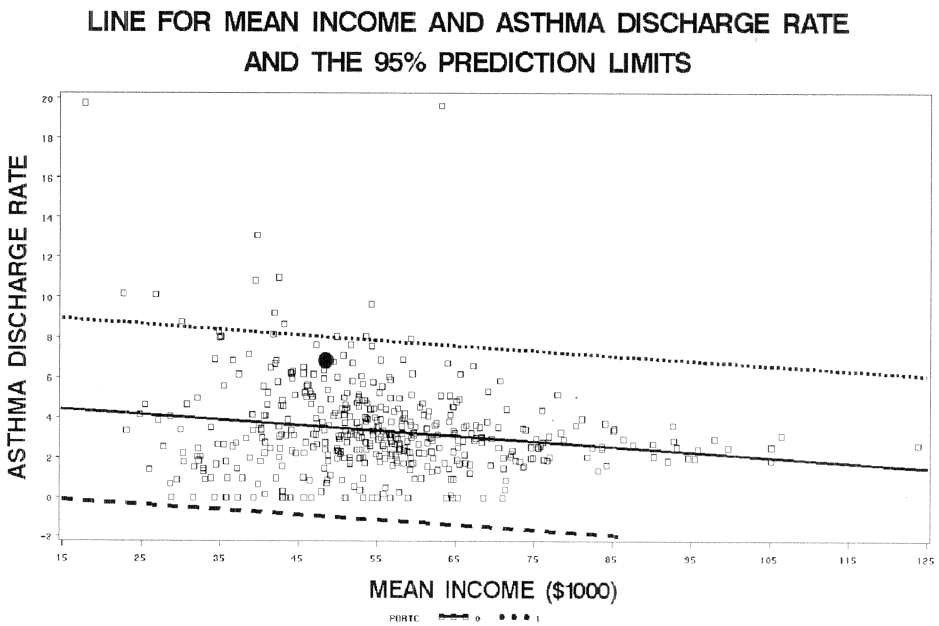
LOWERCL	UPPERCL	LOGRATE	RATE	SE	ZWALD	WALDCHI	P
1.20	1.46	0.28038	1.32	0.0500	5.60	31.41	2.091E-8

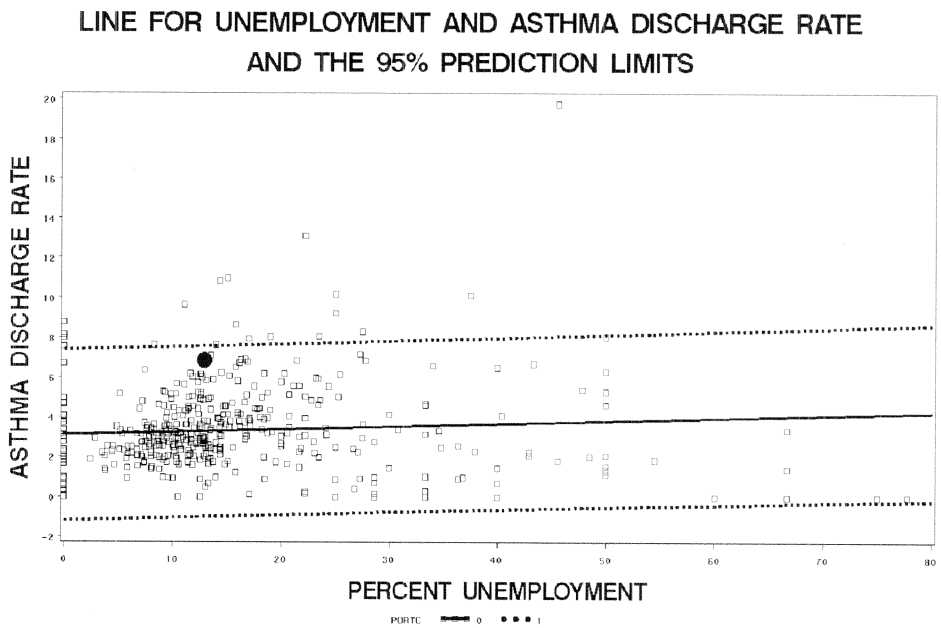
EXHIBIT 37 Asthma < 20 Years vs CC Group

LOWERCL	UPPERCL	LOGRATE	RATE	SE	ZWALD	WALDCHI	P
1.37	1.62	0.39862	1.49	0.0428	9.32	86.91	1.137E-20

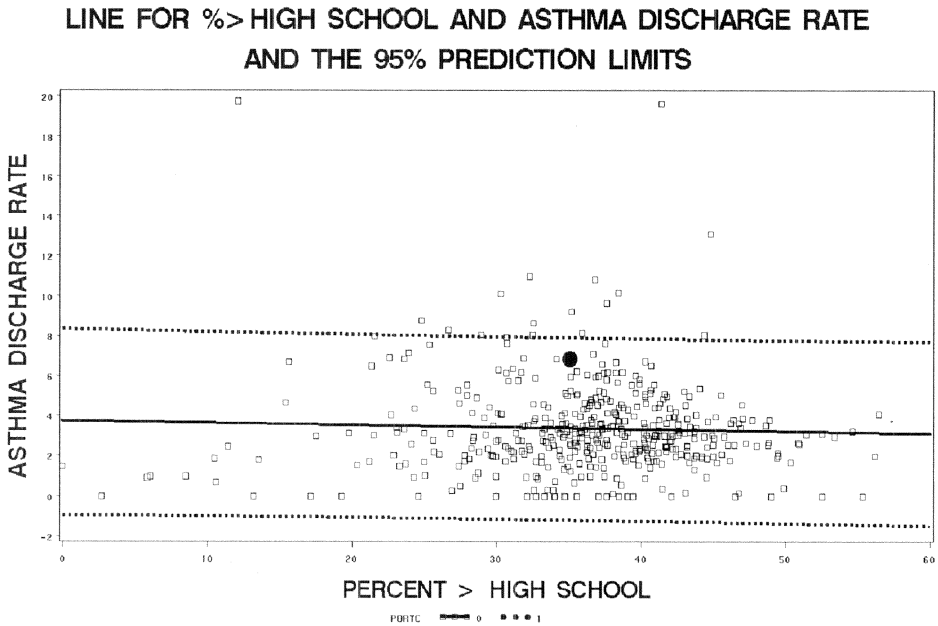
NOTE: Exhibit numbers refer to tables in the CHAP Report.

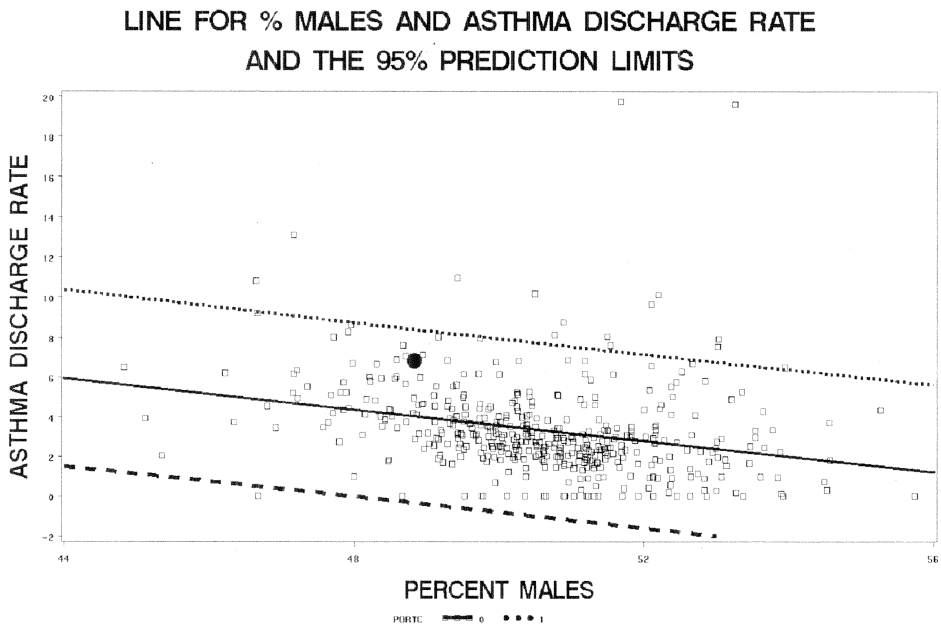
Appendix 4 Relation Between the Seven Potential Confounders used in the Statistical Analyses and the Hospital Discharge Rates for Asthma among those Under Twenty Years of Age



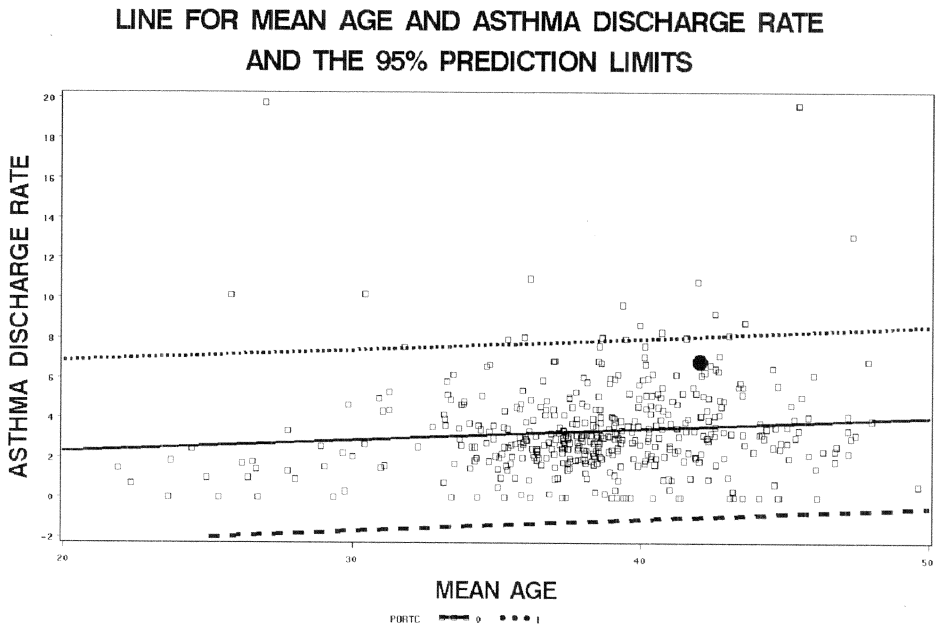


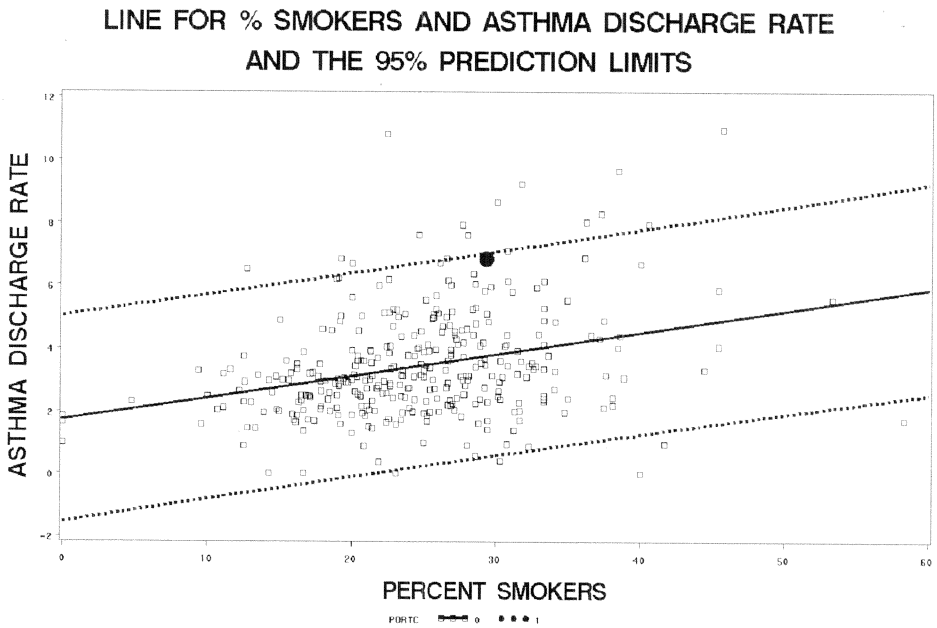
Appendix 4 Relation Between the Seven Potential Confounders used in the Statistical Analyses and the Hospital Discharge Rates for Asthma among those Under Twenty Years of Age (continued)



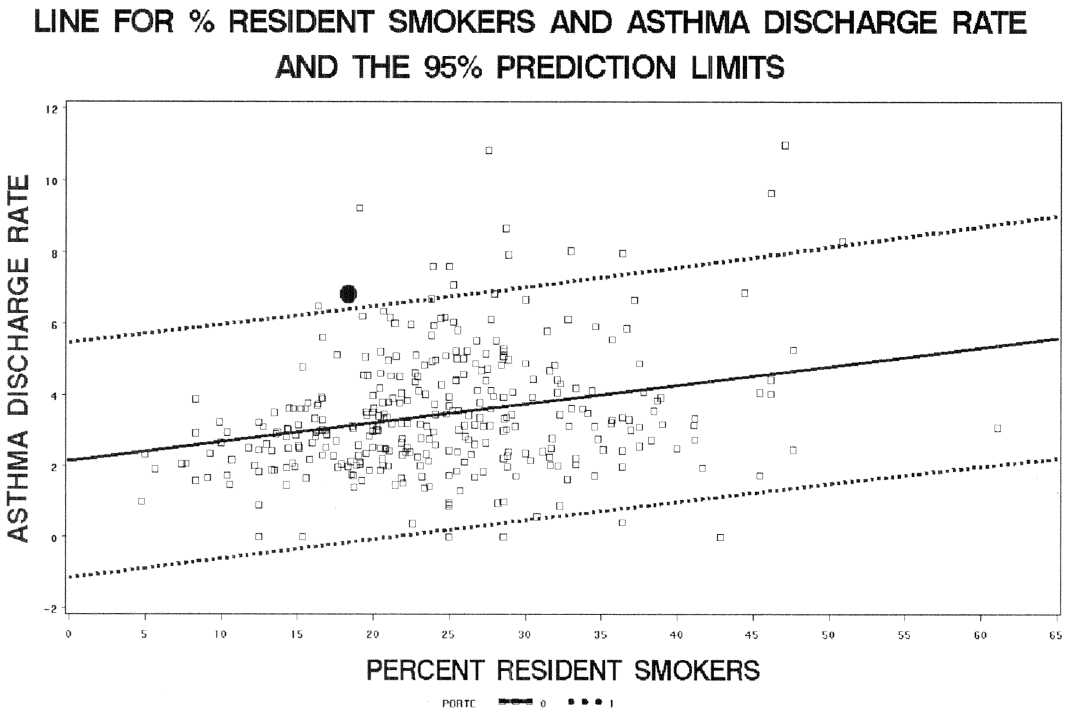


Appendix 4 Relation Between the Seven Potential Confounders used in the Statistical Analyses and the Hospital Discharge Rates for Asthma among those Under Twenty Years of Age (continued)





Appendix 4 Relation Between the Seven Potential Confounders used in the Statistical Analyses and the Hospital Discharge Rates for Asthma among those Under Twenty Years of Age (continued)



Appendix 5 Weighted Regression Analyses of Ratio of Hospital Discharge Rates in Port Colborne Relative to Comparison Group (n=338)

Appendix 5A Asthma Rates < 20 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	3.23	1.53	0.04	0.01	1.90	0.65	0.06
INCOME	2.58	1.59	0.11	0.14	1.58	0.49	0.14
ALL	2.60	1.47	0.08	0.30	1.65	0.47	0.08

Appendix 5B IHD Rates 20-44 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.76	0.54	0.16	0.01	1.95	0.94	0.17
INCOME	0.01	0.07	0.86	0.07	1.33	0.48	0.42
ALL	0.03	0.06	0.70	0.14	1.29	0.36	0.37

Appendix 5C IHD Rates 65+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	13.80	7.43	0.06	0.01	1.48	0.31	0.07
INCOME	9.32	6.54	0.16	0.24	1.26	0.23	0.19
ALL	8.44	5.56	0.13	0.48	1.24	0.19	0.16

Appendix 5D Acute Respiratory Infection Rates 20+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.64	0.35	0.07	0.01	2.71	1.53	0.08
INCOME	0.44	0.30	0.14	0.27	1.58	0.67	0.28
ALL	0.32	0.26	0.22	0.47	1.35	0.48	0.40

Appendix 5E Acute Respiratory Infection Rates 20-44 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.21	0.20	0.29	0.00	1.93	1.23	0.30
INCOME	0.11	0.18	0.54	0.23	1.23	0.60	0.68
ALL	0.06	0.16	0.71	0.38	1.09	0.47	0.84

Appendix 5 (continued) Weighted Regression Analyses of Ratio of Hospital Discharge Rates in Port Colborne Relative to Comparison Group (n=338)

Appendix 5F Acute Respiratory Infection Rates 45-64 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.39	0.26	0.14	0.01	2.45	1.55	0.16
INCOME	0.24	0.23	0.30	0.23	1.44	0.70	0.46
ALL	0.18	0.21	0.39	0.39	1.31	0.56	0.53

Appendix 5G Acute Respiratory Infection Rates 65+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	1.53	0.84	0.07	0.01	2.41	1.20	0.08
INCOME	1.11	0.77	0.15	0.17	1.64	0.70	0.25
ALL	0.98	0.68	0.15	0.39	1.54	0.56	0.24

Appendix 5H Respiratory Cancer Rates 40-65 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.031	0.068	0.65	0.001	1.41	1.05	0.65
INCOME	0.012	0.065	0.86	0.07	1.10	0.71	0.89
ALL	0.025	0.064	0.70	0.14	1.31	0.76	0.64

Appendix 6 Weighted Regression Analyses of Ratio of Hospital Discharge Rates in Port Colborne Relative to Comparison Group 3 - Niagara Peninsula(n=11)

Appendix 6A Asthma Rates < 20 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	2.52	2.59	0.35	0.09	1.59	0.77	0.34
INCOME	1.10	1.79	0.55	0.63	1.09	0.34	0.79

Appendix 6B IHD Rates 20-44 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.65	0.24	0.02	0.42	1.72	0.36	0.009
INCOME	0.51	0.16	0.01	0.79	1.47	0.20	0.005
GTHS	0.44	0.17	0.03	0.76	1.35	0.21	0.051

Appendix 6C IHD Rates 65+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	11.76	4.78	0.03	0.38	1.38	0.18	0.02
INCOME	10.97	5.07	0.06	0.41	1.34	0.19	0.04
GTHS	9.13	4.96	0.10	0.49	1.27	0.18	0.10

Appendix 6D Acute Respiratory Infection Rates 65+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.43	0.32	0.21	0.15	1.72	0.72	0.20
INCOME	0.35	0.33	0.31	0.24	1.50	0.66	0.36

Appendix 6E Acute Respiratory Infection 20-44 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.13	0.17	0.46	0.05	1.43	0.67	0.45
INCOME	0.08	0.17	0.64	0.21	1.20	0.55	0.69
GTHS	0.03	0.16	0.87	0.32	1.01	0.44	0.98

Appendix 6 Weighted Regression Analyses of Ratio of Hospital (continued) Discharge Rates in Port Colborne Relative to Comparison Group 2 Niagara Peninsula (n=11)

Appendix 6F Acute Respiratory Infection Rates 45 - 64 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.26	0.24	0.31	0.10	1.64	0.78	0.29
INCOME	0.17	0.23	0.46	0.30	1.32	0.61	0.55
GTHS	0.13	0.24	0.60	0.28	1.20	0.57	0.71

Appendix 6G Acute Respiratory Infection Rates 65+ Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	1.02	0.76	0.21	0.15	1.64	0.62	0.19
INCOME	0.92	0.81	0.29	0.18	1.53	0.64	0.30
GTHS	0.77	0.79	0.35	0.25	1.41	0.57	0.39

Appendix 6H Respiratory Cancer Rates 40-65 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.03	0.04	0.58	0.03	1.30	0.60	0.57
INCOME	0.03	0.05	0.58	0.04	1.33	0.66	0.57

Appendix 7 Weighted Regression Analyses of Ratio of Hospital Discharge Rates Welland Compared to the 338 Other Communities

Appendix 7A Asthma Rates < 20 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	3.50	0.92	0.0002	0.03	1.97	0.40	0.0008
INCOME	2.93	0.96	0.003	0.16	1.69	0.31	0.005
ALL	2.46	0.89	0.006	0.31	1.52	0.26	0.014

Appendix 7B IHD Rates 65+

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	-1.92	12.96	0.88	0.0001	1.08	0.18	0.65
INCOME	-1.60	4.45	0.72	0.23	0.94	0.13	0.69
ALL	-4.14	3.74	0.27	0.48	0.88	0.10	0.29

Appendix 8 Weighted Regression Analyses of Ratio of Hospital Discharge Rates for IHD in Port Colborne Relative to Comparison Group (n=338)

Appendix 8A All Ages

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	5.68	2.99	0.06	0.01	1.93	0.68	0.06
INCOME	3.40	2.18	0.12	0.48	1.33	0.30	0.20
QUADRATIC	2.19	1.86	0.24	0.63	----	----	----
ALL	2.03	1.61	0.21	0.73	1.16	0.19	0.38

Appendix 8B < 20 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.088	0.057	0.012	0.01	2.36	1.35	0.13
INCOME	0.062	0.051	0.23	0.20	1.58	0.76	0.34
ALL	0.062	0.047	0.19	0.35	1.70	0.79	0.25

Appendix 8C 20 - 44 Year of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.76	0.54	0.16	0.01	1.95	0.94	0.17
INCOME	0.45	0.46	0.32	0.29	1.33	0.48	0.42
QUADRATIC	0.22	0.40	0.59	0.45	1.15	0.36	0.66
ALL	0.38	0.32	0.31	0.55	1.29	0.36	0.37

Appendix 8D 45 - 64 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	4.03	4.76	0.40	0.00	1.37	0.51	0.40
INCOME	0.84	3.87	0.83	0.34	1.02	0.28	0.93
QUADRATIC	-1.00	3.47	0.77	0.48	0.93	0.23	0.77
ALL	0.70	3.15	0.82	0.59	1.05	0.23	0.83

Appendix 8E 65+

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	13.80	7.43	0.06	0.01	2.03	0.71	0.04
INCOME	9.32	6.54	0.16	0.24	1.36	0.30	0.16
QUADRATIC	6.78	6.09	0.27	0.34	1.30	0.27	0.21
ALL	8.44	5.56	0.13	0.48	1.17	0.20	0.36

Appendix 9 Weighted Regression Analyses of Ratio of Hospital Discharge Rates for IHD in Port Colborne Relative to Niagara Peninsula Comparison Group (n=11)

Appendix 9A All Ages

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R2	RATIO	SE	P
NONE	4.00	1.30	0.01	0.49	1.51	0.21	0.003
INCOME	3.37	1.04	0.01	0.72	1.39	0.16	0.004
					1.28	0.16	0.06

Appendix 9B < 20 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R2	RATIO	SE	P.
NONE	0.073	0.041	0.10	0.08	1.92	0.73	0.08
INCOME	-0.00	0.00	0.19	0.38	1.63	0.63	0.21

Appendix 9C 20 - 44 Year of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R2	RATIO	SE	P
NONE	0.65	0.24	0.02	0.42	1.72	0.36	0.01
INCOME	0.51	0.16	0.01	0.79	1.47	0.20	0.01

Appendix 9D 45 - 64 Years of Age

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R2	RATIO	SE	P
NONE	2.59	2.52	0.33	0.10	1.21	0.22	0.31
INCOME	1.12	1.65	0.52	0.67	1.07	0.13	0.59

Appendix 9E 65+

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R2	RATIO	SE	P
NONE	11.76	4.78	0.93	0.38	1.60	0.26	0.004
INCOME	10.97	5.07	0.06	0.41	1.45	0.21	0.01

Appendix 10 Same Analysis as in Table 10 for IHD in the text except that the Adjustment in this Analysis Includes only the Mean Income Covariate

Poisson Regression Analysis of Hospital Discharge Rates for IHD

Hospital Discharge Rates for IHD

Table 10a

	Our Analysis Using 338 Communities (CG)							CHAP C Using 35 Communities		
Age Group	CG Rate	PC Rate	Unadj Ratio	Adj ** Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	6.11	11.80	1.93	1.33	0.86	2.07	0.20	**1.18**	1.09	1.27
< 20	0.06	0.15	2.36	1.58	0.62	4.07	0.34	----	----	----
20 =< 44	0.80	1.56	1.95	1.33	0.66	2.69	0.42	1.37	1.11	1.69
45 =< 64	11.03	15.06	1.37	1.02	0.60	1.74	0.93	1.04	0.97	1.11
65+	29.04	42.84	1.26	1.24	0.89	1.80	0.19	1.15	1.09	1.20

Table 10b

	Our Analysis Using 11 Niagara Peninsula Communities (NG)							CHAP C Using		
Age Group	NG Rate	PC Rate	Unadj Ratio	Adj Ratio	95% CI		P Value	Adj Ratio	95% CI	
All Ages	7.78	11.79	1.39	1.39	1.12	1.74	**0.004**	1.34	1.24	1.44
< 20	0.08	0.15	1.92	1.63	0.76	3.47	0.21	----	----	----
20 =< 44	0.90	1.56	1.72	1.47	1.12	1.92	**0.005**	1.54	1.25	1.91
45 =< 64	12.46	15.06	1.21	1.07	0.84	1.36	0.59	1.18	1.10	1.26
65+	31.08	42.84	1.38	1.34	1.01	1.78	**0.04**	1.31	1.25	1.38

** The adjustment involves only the mean income predictor variable.

Appendix 11 Detailed Analysis of the IHD Variable

		N = 338					Comparison Group	N = 11				
Age Group		RR	SE	LO	HI	P		RR	SE	LO	HI	P
All	Unadj	1.92	0.68	0.97	3.85	0.06	Unadj	1.51	0.21	1.16	1.98	0.003
	Income	1.33	0.30	0.86	2.07	0.20	Income	1.39	0.16	1.12	1.74	0.004
	Income^2	1.21	0.24	0.83	1.78	0.32	Income^2	1.28	0.16	0.99	1.64	0.06
	All ***	1.16	0.19	0.84	1.60	0.38						
		RR	SE	LO	HI	P		RR	SE	LO	HI	P
<20	Unadj	2.36	1.35	0.77	7.23	0.13	Unadj	1.92	0.73	0.91	4.03	0.08
	Income	1.58	0.76	0.62	4.07	0.34	Income	1.63	0.63	0.76	3.47	0.21
	Income^2	1.74	0.84	0.67	4.49	0.25	Income^2	1.14	0.50	0.48	2.69	0.76
	All	1.70	0.79	0.69	4.22	0.25						
		RR	SE	LO	HI	P		RR	SE	LO	HI	P
20 -44	Unadj	1.95	0.94	0.76	5.03	0.17	Unadj	1.72	0.36	1.14	2.60	0.009
	Income	1.33	0.48	0.66	2.69	0.42	Income	1.47	0.20	1.12	1.92	0.005
	Income^2	1.15	0.36	0.62	2.12	0.66	Income^2	1.44	0.25	1.03	2.01	0.03
	All	1.29	0.36	0.74	2.23	0.37						
Group		RR	SE	LO	HI	P		RR	SE	LO	HI	P
45 -64	Unadj	1.37	0.51	0.66	2.82	0.40	Unadj	1.21	0.22	0.84	1.74	0.31
	Income	1.02	0.28	0.60	1.74	0.93	Income	1.07	0.13	0.84	1.36	0.59
	Income^2	0.93	0.23	0.58	1.50	0.77	Income^2	1.08	0.16	0.80	1.44	0.62
	All	1.05	0.23	0.68	1.60	0.83						
Group		RR	SE	LO	HI	P		RR	SE	LO	HI	P
45 -64	Unadj	1.48	0.31	0.98	2.23	0.07	Unadj	1.38	0.18	1.06	1.79	0.02
	Income	1.26	0.23	0.89	1.80	0.19	Income	1.34	0.19	1.01	1.78	0.04
	Income^2	1.19	0.20	0.86	1.65	0.30	Income^2	1.34	0.25	0.93	1.92	0.11
	All	1.24	0.19	0.92	1.67	0.16						

*** All discharge rate ratios are adjusted for the linear effect of income alone (Income) or for the linear and quadratic effect of income (Income^2) . Also for the larger comparison group estimates adjusted for all seven predictors are also reported.

Appendix 12

List of 8 Models for the IHD Hospital Discharge RATE Ratio for All Ages in order of their Predictive Power from the Model using no Adjustment to the Model Adjusting for All Seven 7 Predictor Variables

	Number of Variables used in the Adjustment										
MODEL	0	1	2	3	4	5	6	7	Ratio	SE	P
PORT COLBORNE	Y	N	N	N	N	N	N	N	1.93	0.68	0.06
MEAN INCOME	Y	Y	N	N	N	N	N	N	1.33	0.30	0.20
MEAN AGE	Y	Y	Y	N	N	N	N	N	1.17	0.24	0.43
PERCENT MALES	Y	Y	Y	Y	N	N	N	N	1.08	0.20	0.67
HIGH SCHOOL	Y	Y	Y	Y	Y	N	N	N	1.04	0.18	0.81
SMOKER IN HOME	Y	Y	Y	Y	Y	Y	N	N	1.17	0.20	0.35
UNEMPLOYED	Y	Y	Y	Y	Y	Y	Y	N	1.18	0.19	0.32
PERCENT SMOKERS	Y	Y	Y	Y	Y	Y	Y	Y	1.16	0.19	0.38

Y=Yes N=No Variable is (is not) included in the model.

Appendix 13 Comparing the Cluster of the Four Niagara Peninsula Communities
Welland Port Colborne Niagara Falls Fort Erie
to the Remaining 335 Communities

Appendix 13A Asthma Rates < 20 Years

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	2.67	0.54	0.0001	0.07	1.75	0.20	0.0001
INCOME	2.16	0.51	0.0001	0.18	1.52	0.16	0.0001
ALL	2.04	0.48	0.0001	0.33	1.50	0.15	0.0001

Appendix 13B IHD Rates 65+ Years

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	4.64	2.67	0.08	0.01	1.16	0.10	0.08
INCOME	0.89	2.39	0.71	0.23	1.02	0.08	0.79
ALL	0.13	2.04	0.95	0.48	1.01	0.06	0.92

Appendix 14 Comparing 12 Niagara Peninsula Communities
to Remaining 327 Communities

Appendix 14A Asthma Rates =< 20 Years (N = 339)

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	0.84	0.36	0.02	0.02	1.24	0.11	0.02
INCOME	0.47	0.34	0.17	0.14	1.11	0.09	0.19
ALL	0.66	0.32	0.04	0.30	1.18	0.09	0.04

Appendix 14B IHD Rates 65+ Years

	WEIGHTED REGRESSION				POISSON REGRESSION		
ADJUSTMENT	BETA	SE	P	R^2	RATIO	SE	P
NONE	2.79	1.80	0.12	0.01	1.10	0.07	0.12
INCOME	0.28	1.60	0.86	0.23	1.01	0.05	0.90
ALL	0.72	1.38	0.60	0.48	1.03	0.04	0.52

Appendix 15

Summary of Socioeconomic Statistics for Niagara Peninsula Communities

NAME	POP2001	INCOME	%SMOKER	SHS	%GTHS	%MALES	UNEMP	AGE	RATE
Welland	48,402	50,708	30.7	25.3	36.7	48.7	13.5	40.1	7.09
Port C	18,450	48,493	29.3	18.3	35.1	48.8	12.9	42.0	6.84
FortErie	28,143	49,963	21.9	22.4	37.0	48.9	12.7	40.2	5.99
NiagaraF	78,815	53,276	25.8	23.8	38.3	48.7	10.4	39.9	5.68
Means		51,517	26.9	23.4	37.3	48.8	11.9	40.3	6.25

NAME	POP2001	INCOME	%SMOKER	SHS	%GTHS	%MALES	UNEMP	AGE	RATE
St.Cath	129,170	53,873	21.3	21.3	41.9	48.4	14.2	40.7	3.91
Thorold	18,048	56,279	29.7	41.1	39.1	50.2	12.3	38.0	3.15
Pelham	15,272	75,954	12.2	10.0	48.9	50.1	11.7	40.0	2.66
NiagoLake	13,839	75,539	16.5	20.0	46.0	50.5	4.0	44.6	2.52
Grimsby	21,297	74,697	13.9	14.9	45.1	49.9	9.3	38.6	1.97
Wainfleet	6,258	65,315	20.0	13.3	38.8	51.5	10.4	38.1	1.89
Lincoln	20,612	66,343	17.0	10.4	41.0	49.8	7.4	38.1	1.73
WestLinc	12,268	64,225	21.4	14.3	36.5	51.4	5.8	34.0	1.45
Means		60,545	20.0	19.9	42.2	49.3	11.7	39.9	3.14

POP2001 Population in 2001 census

INCOME Mean income

%SMOKER % Smokers

SHS % Regular smoker in home

%GTHS % More than high school

%MALES % Males

UNEMP % unemployed

AGE Mean age

RATE Hospital Asthma Discharges/1000

Appendix 16 Creating a Comparison Group Statistically Similar to Port Colborne

TABLE 16a TWO COMPARISON GROUPS DERIVED USING

	WEIGHTED REGRESSION	UNWEIGHTED REGRESSION
1	Addington Highlands	Addington Highlands
2		Arnprior
3	Brudenell, Lyndoch	Brudenell, Lyndoch
4		Carleton Place
5	Central Frontenac	Central Frontenac
6	Cobalt	Cobalt
7	Dysart and Others	Dysart and Others
8	East Hawkesbury	East Hawkesbury
9	Espanola	Espanola
10		Fort Frances
11	Galway-Cavendish	Galway-Cavendish
12	Gananoque	Gananoque
13	Georgian Bay	Georgian Bay
14	Hanover	Hanover
15	Havelock-Belmont-Met	Havelock-Belmont-Met
16	Hawkesbury	Hawkesbury
17	Huron Shores	Huron Shores
18	Lambton Shores	Lambton Shores
19	Laurentian Valley	Laurentian Valley
20	Leamington	Leamington
21	McDougall	
22	McNab/Braeside	
23	Montague	Montague
24	North Perth	North Perth
25	Northern Bruce Peninsula	Northern Bruce Peninsula
26	Parry Sound	Parry Sound
27	Pembroke	Pembroke
28	Ramara	Ramara
29	Red Lake	
30		Renfrew
31	Sherborne, Stanhope	
32	South Bruce Peninsula	South Bruce Peninsula
33		South Huron
34		St. Marys
35	Stone Mills	
36	Strong	Strong
37		Sundridge
38	The Archipelago	
39	Timiskaming	Timiskaming
40	Warwick	Warwick
41	Whitchurch-Stouffville	
42	Woolwich	Woolwich

TABLE 16b(1) COMPARISON OF WEIGHTED (%%) MEANS OF SEVEN COVARIATES USED TO CREATE TWO COMPARISON GROUPS SIMILAR TO PORT COLBORNE USING UNWEIGHTED AND WEIGHTED MULTIPLE LINEAR REGRESSION

COVARIATE		1.	2.	3.	4.	5.	6.	7.
GROUP	N	INCOME	%SMOKE	%UNEMP	%GTHS	MEANAGE	%MALES	%SHS
Port Colborne	1	48.493	29.3	12.9	35.1	42.0	48.8	18.3
Linreg 1 **	35	53.131	26.9	12.7	33.3	40.4	49.3	19.5
Linreg 2 $$	35	57.546	27.0	11.9	35.6	40.3	49.8	18.1
N338 ##	338	67.601	22.9	13.0	43.4	37.5	49.4	19.6
NIAGARA @	11	57.163	22.6	11.7	40.4	39.9	49.1	21.5

TABLE 16(2) COMPARISON OF UNWEIGHTED (%%) MEANS OF SEVEN COVARIATES USED TO CREATE TWO COMPARISON GROUPS SIMILAR TO PORT COLBORNE USING UNWEIGHTED AND WEIGHTED MULTIPLE LINEAR REGRESSION

COVARIATE		1.	2.	3.	4.	5.	6.	7.
GROUP	N	INCOME	%SMOKE	%UNEMP	%GTHS	MEANAGE	%MALES	%SHS
Port Colborne	1	48.493	29.3	12.9	35.1	42.0	48.8	18.3
Linreg 1 **	35	49.121	28.5	13.3	33.4	41.5	49.5	21.5
Linreg 2 $$	35	51.180	29.4	11.8	34.3	41.4	50.3	21.6
N338 ##	338	58.373	24.6	13.7	37.6	39.1	50.3	24.4
NIAGARA @	11	62.379	21.0	10.2	40.8	39.3	49.8	19.7

1. Mean Income
2. Percent current smokers
3. Percent unemployed
4. Percent greater than high school
5. Mean age
6. Percent males
7. Percent of resident smokers

%% Weights are the population sizes of the communities
** Derived using unweighted multiple regression analysis
$$ Derived using weighted multiple regression analysis with weights being the community population sizes.

These two comparison groups were much more similar to Port Colborne than the much larger group of 338 communities used in our first analysis with respect to five (1. to 5.) of the seven covariates..

Comparison group of 338 communities used in our first analysis.

@ The comparison group of 11 communities in the Niagara peninsula was much less similar to the City of Port Colborne than the comparison group of 338 communities.

Table 16c Ratio Estimates of Asthma Hospital Discharge Rates for Persons <20 Years of Age for Port Colborne, Welland, Niagara Falls & Fort Erie Using Three Comparison Groups

Comparison Group	No Adjustment			Income Adjusted			7-Variable Adjustment		
n = 338	RR	Std Err	P Value	RR	Std Err	PValue	RR	Std Err	Pvalue
1. Port Colborne	1.90	0.651	0.063	1.58	0.489	0.137	1.65	0.475	0.083
2. Welland	1.97	0.401	0.001	1.69	0.310	0.005	1.52	0.260	0.014
3. Niagara Falls	1.58	0.286	0.012	1.38	0.226	0.048	1.36	0.206	0.042
4. Fort Erie	1.66	0.496	0.089	1.53	0.446	0.144	1.68	0.477	0.067
Unweighted n = 35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.88	0.486	0.015	1.67	0.297	0.004	1.47	0.243	0.018
2. Welland	1.94	0.332	<0.0001	1.89	0.221	<0.0001	1.84	0.240	<0.0001
3. Niagara Falls	1.56	0.244	0.005	1.67	0.183	<0.0001	1.71	0.268	0.0006
4. Fort Erie	1.64	0.376	0.030	1.55	0.243	0.005	1.80	0.358	0.003
Weighted n = 35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	2.01	0.555	0.011	1.71	0.364	0.011	1.61	0.276	0.006
2. Welland	2.09	0.382	<0.0001	1.87	0.263	<0.0001	1.65	0.290	0.004
3. Niagara Falls	1.67	0.281	0.002	1.60	0.205	0.0003	1.45	0.326	0.097
4. Fort Erie	1.76	0.430	0.020	1.56	0.291	0.018	1.49	0.401	0.135

Table 16d Ratio Estimates of Hospital Discharge Rates for Ischemic Heart Disease in Persons of All Ages for Port Colborne, Welland, Niagara Falls and Fort Erie Using Three Comparison Groups

Comparison Group	No Adjustment			Income Adjusted			7-Variable Adjustment		
n = 338	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.93	0.679	0.062	1.33	0.299	0.202	1.16	0.193	0.380
Unweighted n = 35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.20	0.305	0.482	1.09	0.215	0.649	1.22	0.206	0.229
Weighted n = 35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.36	0.332	0.212	1.18	0.208	0.348	1.22	0.206	0.234

Table 16e Ratio Estimates of Hospital Discharge Rates for Acute Respiratory Infection in Persons of All Ages for Port Colborne Using Three Comparison Groups

Comparison Group	No Adjustment			Income Adjusted			7-Variable Adjustment		
n = 338	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.79	1.028	0.307	1.21	0.571	0.690	1.13	0.424	0.739
Unweighted n=35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.14	0.328	0.661	1.05	0.256	0.839	1.14	0.246	0.530
Weighted n= 35	RR	Std Err	P Value	RR	Std Err	Pvalue	RR	Std Err	Pvalue
1. Port Colborne	1.30	0.421	0.419	1.13	0.289	0.616	1.23	0.263	0.327

Tables 19c to 19e contain hospital discharge rate ratios, RR, estimated using Poisson regression. An adjustment is made for over dispersion. The p values reported in the table are associated with the standardized Gaussian ratios of the ratio of the $logRR$ to its standard error σ_{logRR}. Risk ratios RR, more easily understood than their logarithms, are reported along with their standard errors σ_{RR}. The following formula could be used to derive 95% confidence intervals of the risk ratios easily using the reported results for the relative risk RR and the standard error of the relative risk σ_{RR}.

$$95\%\ Confidence\ Interval\ of\ the\ log\ Risk\ Ratio\ logRR: \quad logRR \pm 1.96 \times SE(logRR)$$

$$95\%\ Confidence\ Interval\ of\ the\ Risk\ Ratio\ RR: \quad e^{logRR \pm 1.96 \times SE(logRR)}$$

$$= RR \times e^{\pm 1.96 \times SE(logRR)} \qquad = RR \times e^{\pm 1.96 \times \frac{\sigma_{RR}}{RR}}$$

Appendix 17 Sample Size Estimates for Possible Case-Control Studies

Six inputs are required for a sample size calculation for a case control study.

(a) The probability alpha of making a Type 1 error.
(b) The probability beta of making a Type 2 error.
(c) The size of the effect that one is searching for.
(d) The proportion of residents exposed to the potential hazard.
(e) The proportion of residents with the disease or condition
(f) The proportion of residents with the disease or condition among those who are exposed

A Type 1 error occurs when an observed association between an exposure and a condition is declared to be statistically significant when no real association exists. The probability of such an error is conventionally set at 0.05. A Type 2 error occurs when a real association between an exposure and a condition is missed. The probability of such an error is conventionally set at 0.20. Such a study is said to have 80 percent power of finding an elevated odds ratio of a specified size. The specified size of the effect used in the sample size estimation for each condition or symptom is the size of the significantly elevated odds ratio among the 18 conditions or symptoms reported in Exhibit 114 of the CHAP report A.

Formulae and appropriate tables for sample size estimates for a cohort study are found in the text by Fleiss (Appendix 18a). A SAS program was created whose accuracy was verified against the tables in Fleiss. These estimates incorporate Yate's correction factor for continuity. The effect size used in these tables is the difference between the probabilities of disease in two different exposure groups. These probabilities are

$$P_1 = P(Disease|Exposure) \text{ and } P_2 = P(Disease|No\ Exposure)$$

Estimates for these two probabilities that were used in the sample size calculation along with the associated odds ratio were obtained for five categories of conditions in the ten exhibits 79 and 82 for asthma, 86 and 90 for skin conditions, 93 and 96 for the endocrene, musculoskeletal and rheumatic conditions, 99 and 101 for cardiovascular disease and 103 ansd 106 for other conditions. With this information the adjusted relative risk $RR_{Adjusted}$ was estimated using the following two formulae.

$$P_{1Adjusted} = \frac{\frac{P_2 \times OR_{Adjusted}}{Q_2}}{1 + \frac{P_2 \times OR_{Adjusted}}{Q_2}} \quad from\ which\ RR_{Adjusted} = \frac{P_{1Adjusted}}{P_2}$$

For a case-control study it is the probabilities of exposure among cases and controls that are compared. These probabilities are

$$P_3 = P(Exposure|Disease) \text{ and } P_4 = P(Exposure|No\ Disease)$$

Tables for sample size estimates for a case-control study are given in the text by Schlesselmann (Appendix 18b) These sample size estimates were not used because they were not adjusted using Yate's correction factor for continuity and they were based on the assumption that the disease is rare, an assumption that is appropriate for cancer studies but not for many of the conditions and

symptoms reported in Exhibit 114. In order to use the program based on the formulae in Fleiss the following two formulae were used to produce P_3 *and* P_4 using the adjusted relative risk and the proportion of respondents who were defined as "exposed".

Formulae for the Sample Size Calculation for the Comparison of the Probabilities of Exposure for Cases and Controls (Ref A17c)

$$P3 = P(Exposure \mid Disease) = \frac{P(Exposure)\times RR}{1 + P(Exposure)\times(RR-1)}$$

$$P4 = P(Exposure \mid No\ Disease) = \left(\frac{1-P(Disease \mid Exposure)}{1-P(Disease)}\right)\times P(Exposure)$$

If $1-P(Disease \mid Exposure) \approx 1 - P(Disease)$ *as is the case for a rare disease then* $P4 = P(Exposure)$. *Schlesselman's sample size estimates were still not used because they were not adjusted with Yates' correction factor. Estimates of P3 and P4 were inputs in the Sample Size Formulae for a Cohort Study given in the Fleiss text.*

The estimate of the proportion of residents exposed used in the above equations is the proportion of residents in each of the three target groups in Exhibit 114. For example, from Exhibit 6 of the CHAP A Report there are 665 adults in GSA3 and 4,464 in GSAs 1 ,2 and 5. Therefore the proportion of adults in GSA3 is 665 / (665 + 4464) = 0.13. This is the exposure prevalence used in the sample size estimation associated with the comparison of residents in GSA3 compared to residents of GSAs 1 , 2 and 5 (COMP1).

The proportion of exposed residents for the second comparison had to be determined indirectly. For example, in Exhibit 108 is reported the proportion of residents reporting various symptoms among those who have been residents of GSA3 for at least 20 years compared to those who never have been a resident of GSA3. Consider the proportion of residents with migraine headaches. The proportion of respondents residing at least 20 years in GSA is 95 / N1 = 0.176 from which we can calculate that the number of residents in this category is N1 = 95 / 0.176 = 540. The proportion of respondents who have never resided in GSA 3 is 618 / N2 = 0.151 from which we can calculate that the number of residents in this category is N2 = 618 / 0.151 = 4093. Therefore the proportion of residents in the target group is 540 / (540 + 4093) = 0.12, (COMP2) which is, coincidentally, almost identical to the exposure prevalence for the previous comparison. This calculation was repeated for many conditions and symptoms in several tables and the estimates were always accurate to the second decimal place.

In the third analysis that used the Province of Ontario as the comparison group the exposure prevalence is found to be the number of adults living in Port Colborne divided by the population of Ontario. Using the database made available to us for the re- analysis of the hospital discharge rates we found that the exposure prevalence was 0.0017 which led to gigantic sample size estimates of over 2000. Therefore in Table A18a sample size estimates are reported only for the two comparisons internal to Port Colborne. Of the 18 conditions in Exhibit 114 in the Protocol A Report only eight had an odds ratio that was statistically significant for at least one of the analyses involving the two internal comparison groups. These eight are shown below in Table A18a.

Of these eight conditions three had an estimated pool of cases larger than the sample size estimates, that is, sufficient to carry out a case-control study with Type 1 and 2 error rates of 0.05 and 0.20.

(a) High Blood pressure (b) Arthritis and Rheumatism (c) Stomach or Intestinal Ulcers

Table A17 Sample Size Estimates Using Information from Exhibit 114 in Protocol A

Condition		OR	Estimated Pool of Available Cases	Beta = 0.20 N1	N2	
High Blood Pressure	C2	1.35	1422	**857**	**629**	<<<
Stomach or Intestinal Ulcers	C2	1.72	472	**446**	**326**	<<<
Using 50% correct P3 and P4	C2		236	511	374	***
Stomach or Intestinal Ulcers	C1	1.53	472	764	562	***
Using 50% Correct P3 and P4			236	836	616	
Arthritis and Rheumatism	C2	1.38	1351	**815**	**598**	<<<
Thyroid	C2	1.40	618	1569	1166	
Chronic Fatigue Syndrome	C2	3.46	60	79	57	
Multiple Chemical Sensitivity	C2	2.10	107	234	170	
Migraines	C2	1.34	721	1967	1942	
Peripheral Neuropathy	C2	1.49	368	821	604	
	C1	1.46		974	718	

N1 = # Cases needed for a case-control study with one control per case
C1 Comparison of respondents in GSA3 with residents in GSAs 1, 2 and 5.
C2 Comparison of respondents who have lived at least 20 years in GSA3 compared to those who have never lived in GSA 3.in

*** These sample size estimates and estimates of available cases are calculated under the assumption that the accuracy rate of ulcer reporting is 50 percent.

(A17a) Fleiss, Joseph L., Levin, Bruce and Paik, Myunghee Cho 2003 John Wiley & Sons

(A17b) Schlesselman, James J. Case-Control Studies Design, Conduct, Analysis 1982 Oxford University Press

(A17c) Schlesselman, James J. Sample Size requirements in Cohort and Case-Control Studies of Disease Journal of Epidemiology 1974 99:381–384.

(A17d) Bergmann, M.M., Byers, T., Freedman D.S. and Mokdad, A. (1998) Validity of Self-Reported Diagnoses Leading to a Hospitalization: A Comparison of Self Reports with Hospital Records in a Prospective Study of American Adults American Journal of Epidemiology Vol 147 No.10 969–977.

Appendix 18 Selected Definitions

Bio-accessibility - Potential for a substance to come in contact with a living organism and then interact with it. This may lead to absorption. *Note*: A substance trapped inside an insoluble particle is not bio-accessible although substances on the surface of the same particle are accessible and may also be bio-available. Bio-accessibility, like bio-availability, is a function of both chemical speciation and biological properties. Even surface-bound substances may not be accessible to organisms which require the substances to be in solution.

Bio-availability - Extent of absorption of a substance by a living organism compared to a standard system.

Biomonitoring - Continuous or repeated measurement of any naturally occurring or synthetic chemical, including potentially toxic substances or their metabolites or biochemical effects in tissues, secreta, excreta, expired air or any combination of these in order to evaluate occupational or environmental exposure and health risk by comparison with appropriate reference values based on knowledge of the probable relationship between ambient exposure and resultant adverse health effects.

Exposure - 1. Concentration, amount or intensity of a particular physical or chemical agent or environmental agent that reaches the target population, organism, organ, tissue or cell, usually expressed in numerical terms of concentration, duration, and frequency (for chemical agents and micro-organisms) or intensity (for physical agents). 2. Process by which a substance becomes available for absorption by the target population, organism, organ, tissue or cell, by any route.

Sorption - Noncommittal term used instead of adsorption or absorption when it is difficult to discriminate experimentally between these two processes.

Speciation (in chemistry) - Distribution of an element amongst defined chemical species in a system.

Species (in chemistry) - Specific form of an element defined as to isotopic composition, electronic or oxidation state, and (or) complex or molecular structure.

Appendix 19: Acronyms and Abbreviations

ARI: Acute Respiratory Infection

AST: Asthma

ATSDR: Agency for Toxic Substances and Disease Registry

CHAP: Community Health Assessment Project

EXHIBIT: Word used instead of Table in the CHAP reports.

GTHS: Greater than High School Education

IARC: International Agency for Research on Cancer

IHD: Ischemic Heart Disease

IUPAC: International Union of Pure and Applied Chemistry

MAGE: Mean Age

MALE: Percent Males

MINC: Mean community income

MOE: Ministry of the Environment (of Ontario)

NAS: National Academy of Sciences (U.S.)

RC: Malignant Neoplasms of the Respiratory and Intrathoracic Organs

SHS: Percent of Households with at Least One Regular Smoker

SMOK: Percent Smokers

UNEM: Percent unemployed

USEPA: United States Environmental Protection Agency

WHO: World Health Organization