PORT COLBORNE

CHAP

COMMUNITY HEALTH
ASSESSMENT PROJECT

Protocol B

Decision document for proceeding with case-control methodology

25 September, 2003

Protocol B: Decision Document

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SYNOPSIS OF DECISION METHODOLOGY

TITLE	Decision document for proceeding with case-control methodology
SPONSOR	INCO Limited
OBJECTIVES OF THE DECISION DOCUMENT	The objective of the decision document is to clearly establish the criteria and rationale for proceeding with one or more case-control studies based on the findings from Study A and Study C before data are analysed. In Study A, it was stated that additional research using case-control methods would be pursued if we observed differences in the prevalence of health conditions in Port Colborne relative to the general population, or if there were differences in selected health indices across previously identified regions of Port Colborne.
DECISION PROCESS	The decision criteria are based on the nature of the data collected in Study A and Study C, and the results that will be obtained from the accompanying statistical analyses. Findings from the two studies will be weighted equally within this process. A positive association observed in either of the two studies could be used to justify conducting a case-control study. Information collected on health conditions in the Self-Reported Health Questionnaire (SRHQ) will be considered for a case-control study. For some conditions where associations with the CoCs have been reported in the scientific literature, self-reported data on symptoms collected in the SRHQ have been incorporated into the decision process. These conditions are asthma, eczema and contact dermatitis. The criteria will be applied separately to three age groups: children, children and adolescents, and adults. Further research may be conducted using case-control methodology if Port Colborne residents are found to have a higher risk of the health conditions under study. The steps to further evaluate the association between adverse health and the CoCs using a case-control study are listed below: **Step 1: Study Comparison (A and C)** **1. Case Definition** • Data collected with the Self-Reported Health Questionnaire (SRHQ), namely questions pertaining to physician diagnosis and, where applicable, symptoms or self-reported presence of a condition, will be used to develop summary categorical variables that represent the case status for the health condition of interest. This will reduce the chance of a spurious association that may arise due to multiple testing of several related questionnaire items. • These identified cases will form the basis of the sample size calculations in Step 2. **2. Data Comparison** *Study A (122 total comparisons)* • Comparisons will be conducted across regions of Port Colborne (*internal*), between Port Colborne and other survey populations (*external*) • Comparisons will be done for 32 different health conditions among adults, and 11 among children and adolescents

- Comparisons will be performed for the following age groups: 1) childhood conditions: participants <13 years old; 2) childhood and adolescent conditions: <18 years old and 3) adult conditions: participants 18 years of age and older
- Relative risks will be calculated for each comparison (internal and external), and, where relevant, for each case definition (probable and possible.) Probable cases represent a more strict case definition, and are regarded as a subset of possible cases
- The decision criteria will use those relative risks that have been adjusted for the potential confounding influence of other known or suspected risk factors collected from the General Health Survey.

Study C (51 total comparisons)

- Comparisons will be made using discharge rates for 17 health conditions across three age groupings
- Comparisons will be performed for the following age groups: 1) childhood conditions: participants <15 years old; 2) childhood and adolescent health conditions: <20 years old and 3) adult conditions: participants 20 years of age and older. These age groups differ from those for Study A as we are constrained by the nature of the aggregate data that have been provided to us in five-year age intervals
- As these codes are based on discharge codes assigned by health professionals, this is equivalent to the "probable" case designation used within Study A
- The decision criteria will use those relative risks that have been calculated using the comparator communities as a referent group. By design, these communities have been selected to be similar with respect to numerous indicators of socio-economic status as collected in the Canadian census. As a result, we are controlling for the potential confounding influence of these variables by design. For respiratory conditions, the comparison involving the comparator communities will exclude those communities with potential environmental exposures relevant to respiratory diseases.

3. Risk Evaluation

Study A

- The risk estimate must demonstrate a positive association between adverse health events and residential areas where average levels of CoC exposure are elevated. The risk estimates will be adjusted for the potential confounding influence of known or suspected risk factors that are available from the survey. These factors will vary according to the health condition under study.
- If the relative risk estimate is statistically significant using a one-tailed alpha ($p \leq 0.05$), sample size calculations will be performed to determine the feasibility of a case-control study. For those conditions with two case definitions (probable and possible) a two-tailed alpha of 0.05 will be applied to take both case definitions into account
- If the relative risk estimate for disease-specific discharge rates is **not** statistically significant based on the alpha levels, we will recommend that a case-control study **not** be undertaken to further evaluate this association.

Study C

- The comparator communities will serve as the referent group
- The risk estimate must demonstrate a positive association between hospital discharge rates and residential areas with higher levels of potential exposure to the CoCs. The relative risk using the comparator communities is adjusted for age group, sex and the potential confounding influence of community-specific

indicators of sociodemographic status

- If the relative risk estimate is statistically significant using a one-tailed alpha ($p \leq 0.05$), sample size calculations will be made in order to determine case-control study feasibility
- If the relative risk estimate for disease-specific discharge rates is **not** statistically significant based on the specified alpha levels, we will recommend that a case-control study **not** be undertaken to further evaluate this comparison.

IMPORTANT NOTE

A statistically significant association for a particular health condition need only be observed in either Study A or Study C to be considered as a candidate for a case-control study. It is not required that a significant finding be observed in both.

Step 2: Sample Size and Power Calculation

- If the sample size based on the number of cases identified within the Study A dataset provides sufficient power for detecting an association in the case-control study that has **at least the same magnitude** as the positive association that was observed, then Step 3, Hazard Identification, will be initiated. As noted in Step 1, this positive association may have arisen either from Study A or Study C.

Step 3: Hazard Identification

- For each comparison that 1) yields a positive statistically significant adjusted relative risk, and 2) fulfils the sample size requirements for conducting a case-control study, a hazard identification process will be implemented to determine whether exposure to a substance **may** be causally related to the incidence of the health effect
- This process will be separated into four steps:
  A. Gathering and analysing the relevant toxicology data on the CoCs (arsenic, cobalt, copper and nickel) as it relates to the health condition
  B. Gathering and analysing the relevant epidemiological data on associations between the CoCs and the health condition in question
  C. Weighing the evidence that any of the exposures could cause a toxic effect
  D. Deciding whether the toxic effect could occur from exposure in a real-life and non-occupational setting
- For those health conditions where an excess in Port Colborne is observed, and a review of the literature suggests that the CoCs are not responsible for this excess, we will:
  - Provide possible explanations for the increased prevalence of the health condition in Port Colborne. This would incorporate a systematic review of other relevant risk factors and outline features of Study A or Study C (as relevant) which may have contributed to reporting the increased risks
  - Provide research recommendations to further investigate such associations
- A document that summarizes this process and recommendations resulting from the hazard identification will be prepared in consultation with the EAC and reviewed by an independent external scientific body. In addition, community feedback will be solicited at this point.

1. INTRODUCTION

The Community Health Assessment Project (CHAP) is an integrated series of health studies designed to address community concerns regarding the potential health risks associated with the presence of four Chemicals of Concern (CoCs) in Port Colborne soil. These CoCs are arsenic, cobalt, copper and nickel. The CHAP studies are the first community-wide human health investigations to be conducted in Port Colborne. To date, previous human health studies conducted in this municipality have not provided a comprehensive assessment of the many community-level health concerns that may be related to environmental contaminants (VCRC, 2002).

1.1 Objectives of the CHAP Research

As outlined in the Overview of Proposed CHAP Research in Port Colborne (VCRC, 2001), the CHAP identified four critical study areas. These study areas represent converging health assessment strategies (including general and comprehensive health questionnaires, population-based registry databases and medical testing) that are outlined in Protocols A, C and D, and will subsequently be developed in Protocol B, if warranted. The four studies of the CHAP are listed below.

Study A: *A self-reported health assessment of the Port Colborne community*

Study B: *Case-control study(ies) of selected health conditions using a population-based sample of Port Colborne residents* **[If warranted]**

Study C: *Hospital discharge patterns among Port Colborne residents: A comparative analysis to Ontario rates*

Study D: *Cancer incidence and causes of mortality in a historical cohort of Port Colborne residents*

The overall objectives of the body of research outlined in these protocols are:

- To determine whether the health of the Port Colborne community varies significantly from comparison populations, and
- To better understand the relationship between environmental exposure to the CoCs and the health of the community.

The specific research objectives of each study are outlined in detail in the corresponding protocols.

Higher than background levels of the CoCs have been observed through extensive soil sampling conducted in the Port Colborne area, and have been attributed to historical emissions from the refinery operations of INCO Ltd (MOE, 2000). Although there have been few epidemiologic studies carried out in populations with similar exposure levels, laboratory and occupational studies have demonstrated associations between exposures occurring at much higher levels and several deleterious health outcomes. Overall, this body of research suggests that these exposures may have implications for the health of Port Colborne residents.

1.2 Overview

Health is a multidimensional concept that is frequently measured in terms of

- Absence of physical pain, physical disability or the absence of a condition that is likely to cause death
- Emotional well-being, and
- Satisfactory social functioning.

There is no single standard measurement of health status for individuals or population groups. The health of an individual may be measured in a number of ways using either objective or subjective measures, with both capturing distinct and important elements of health status. For example, objective measures such as hospital discharges, physician records and histology reports can record data for health events serious enough to require medical intervention. Study C collects such objective measures with hospital discharge data coded by trained nurses or physicians that reflect the hospitalization patterns among all Port Colborne residents.

In contrast, subjective data such as those obtained from the Self-Reported Health Questionnaire (SRHQ) allow for the collection of a detailed grouping of health indicators. Specifically, there is the opportunity for each respondent to provide information on physician diagnoses, symptoms, residential and occupational history, lifestyle and demographic characteristics. Comparisons of health indices using such data can readily take into account the confounding influence of a wide range of factors.

For the above reasons, both objective and subjective measures play important roles in characterizing the overall health of the Port Colborne community. Therefore, we recommend that the findings obtained from Study A and Study C be used to characterize the health of the Port Colborne community and, consequently, recommend whether or not to undertake a case-control study(ies) with the specific goal to evaluate the relationship between environmental exposure to the CoCs and adverse health.

The decision to recommend proceeding with a case-control methodology must consider the impact that the relatively small size of the Port Colborne community has on the feasibility of conducting additional research. Specifically, the analysis of data from small geographic areas such as Port Colborne (i.e. calculating rates for a small number of events) may produce results that are unstable and, moreover, may not yield a sufficient number of cases to proceed with a case-control study. Consequently, we would only recommend undertaking a case-control study for those conditions that have a sufficiently high prevalence and are thus of concern for the community at large.

2. BACKGROUND

Members of the Port Colborne community have raised a number of health concerns related to environmental exposure to the four CoCs. Previously, studies conducted in the community have suffered from important limitations, and were therefore unable to resolve many questions concerning the health issues that may be related to the observed environmental contamination. This is the driving force behind the health assessment of Port Colborne. While providing valuable information, the general health survey (Study A) has a limited ability to draw causal inferences between exposures to the CoCs and the occurrence of adverse health conditions. As previously outlined in Protocol A, it was determined that the decision regarding the initiation of any future case-control studies be made only for those conditions for which an association to the CoCs is plausible. Such increased risks have been demonstrated for several health endpoints at different levels of exposure and in different settings.

The Public Liaison Committee (PLC) requested that the criteria for the recommendation to conduct a case-control study be developed before analyzing data from the health survey (Study A). We have outlined these criteria herein as the data analysis and reporting of the results from Study A and Study C draw near. As agreed by the CHAP investigators, the criteria set forth in this decision document will be shared with the community.

In consultation with an Expert Advisory Committee (EAC), the investigators of the CHAP series of studies decided that Protocol B be developed only after:

- Data collected from the SRHQ had been analyzed, and
- The results from Study A or Study C suggested a need to further characterize the risk of disease associated with exposure to the CoCs in Port Colborne.

This two-step process was deemed the most prudent avenue for the investigation of health in the Port Colborne community, as any study that relied on medical testing to ascertain exposure to the CoCs would require considerable resources both on the part of the investigators and the participants. Moreover, it was also recognized that detailed information collected from the general health survey would provide valuable data that could be incorporated into the design of a case-control study. For example, data collected in Study A can be used as a starting point to screen prospective cases and controls, and detailed questionnaire data collected from the SRHQ could reduce the information that needs to be collected in further studies.

It was decided through external scientific review and extensive discussions with the EAC and Technical Subcommittee (TSC) that the case-control study represents the most robust design to examine the possible causal role of the exposure to CoCs on selected health conditions. This design would allow for a comprehensive evaluation of individual levels of exposure to be incorporated into the study design. For example, individual levels of exposure to the CoCs could be evaluated using blood or urine samples in conjunction with a detailed residential and occupational history, and by measuring CoC levels in the soil. Therefore, the undertaking of case-control studies in Port Colborne would provide the

opportunity to make an important research contribution to the existing scientific literature and, more importantly, to address the health concerns of the community.

It is also important to note that an etiologic case-control study that requires biological samples could not be conducted unless there is a plausible mechanism linking exposure to the CoCs and adverse health. Such a study would not meet the basic criteria needed by ethical review boards, nor adhere to established principles of conducting research (World Medical Association, 2002). For such conditions, it has been decided in consultation with the EAC and the TSC that the decision criteria process identify possible explanations for excess rates of health conditions that may be found in Port Colborne, and where appropriate, recommend additional research that could prove valuable. This process is also outlined within the decision criteria described herein.

2.1 Health Conditions

A variety of health conditions will be evaluated as candidates for future case-control studies designed to evaluate the effect(s) of CoCs. This evaluation will incorporate self-reported data on physician diagnoses (Study A adults), self-reported presence of health condition (Study A children and adolescents) and hospital discharge data (Study C). Within Study C, stratified analyses of hospital discharge data allow for comparisons to be conducted for both adult and child populations.

The SRHQ was designed to include targeted questions on disease symptoms for selected conditions for which previous studies have demonstrated an association with the CoCs. For these conditions, the collection of self-reported symptom data is valuable given that many prevalent cases have not been formally diagnosed by a physician. The health conditions for which self-reported symptoms will be incorporated into the decision criteria include eczema (atopic dermatitis), contact dermatitis, and asthma.

The criteria used to define "probable" and "possible" case definitions for these specific health conditions are presented in Tables 1 through 4 of Appendix A. This will permit comparison of disease prevalence rates within Port Colborne to be made using probable and possible case definitions. The possible definition will allow risk estimates to be calculated using a less stringent case definition, while the probable cases will form a subset of the possible cases. Specifically, prevalence rates calculated using the possible case definition include individuals who report the symptoms of the health conditions, in addition to those who have been diagnosed by a health professional (probable case).

The listings of the "other" health conditions that will be examined are shown in Tables 5 and 6 of Appendix A. This list includes an additional 29 adult health conditions and 8 childhood/adolescent conditions. The decision to undertake a case-control study will be applied separately to three age groups: childhood, childhood and adolescent, and adults. Moreover, the decision criteria will be applied separately to the results from Study A and Study C. It is possible that a case-control study could be performed if a positive association was noted in only one study. However, should positive association be

observed in both studies, the need to further study the association would be more compelling.

3. DECISION PROCESS

The decision to conduct future case-control studies will be based on the findings from either Study A or Study C, and the extent to which those findings fulfill the criteria outlined in this section. To provide concise information for this decision process, it was decided in consultation with the EAC that, where applicable, summary variables would be created for a series of health conditions (see Appendix A).

For all health conditions under consideration (other than asthma, eczema and contact dermatitis), prevalence rates will be calculated using self-reported data on physician diagnoses.

For the health conditions of asthma, eczema and contact dermatitis, summary variables will synthesize questionnaire data collected on self-reported symptoms as well as self-reported medical history including physician diagnoses. These summary variables would indicate whether a person had the disease in question; in this manner, each summary variable would be binary in nature. These summary measures could readily be constructed from self-reported data from the SRHQ, as this survey includes questions on symptoms for conditions that have been found to be associated with the CoCs.

As a result, these summary variables would allow for probable and possible case definitions to be incorporated into the calculation of prevalence rates, and subsequently applied to the decision criteria for these conditions. These summary variables have been developed using several associated questionnaire items related to self-reported physician diagnoses and self-reported symptom data. Two respiratory and dermatologic clinical specialists have contributed to the definition of these summary measures.

The complete sequence of steps to decide whether a case-control study is warranted is presented in Figure 1. This process will be followed for each health condition under consideration by age grouping (i.e. childhood, childhood/adolescent and adult), and in some instances more than one case definition. As described earlier, the two case definitions for probable and possible cases will be applied to the comparisons for asthma, eczema and contact dermatitis. It is important to recognize that the comparisons are performed using data from both Study A and Study C, and that positive associations do not have to be observed in both studies in order to recommend that a case-control study be pursued. Assuming the other criteria are satisfied, it is only necessary to observe increased rates from one of the two studies. As such, both studies will be treated equally.

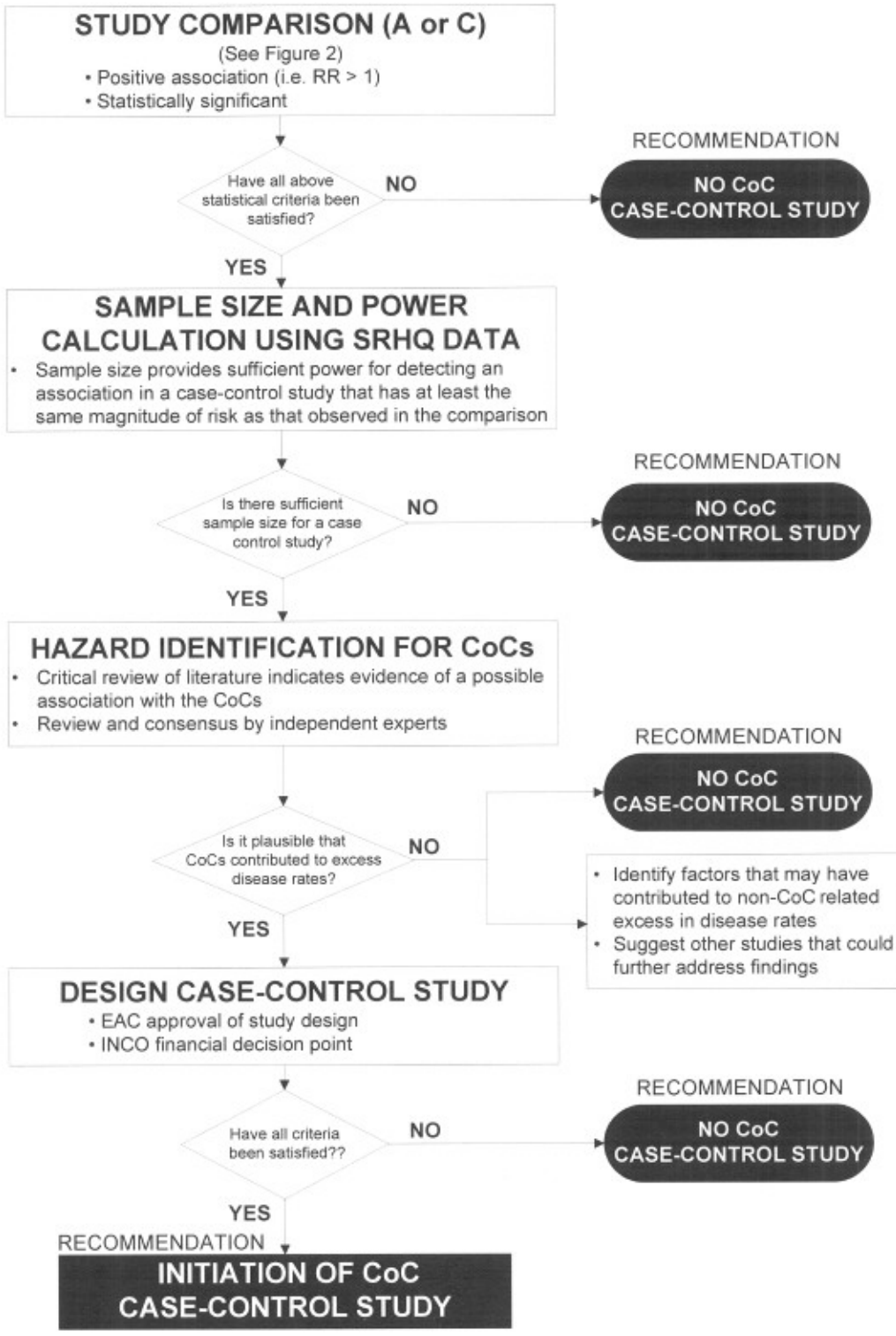
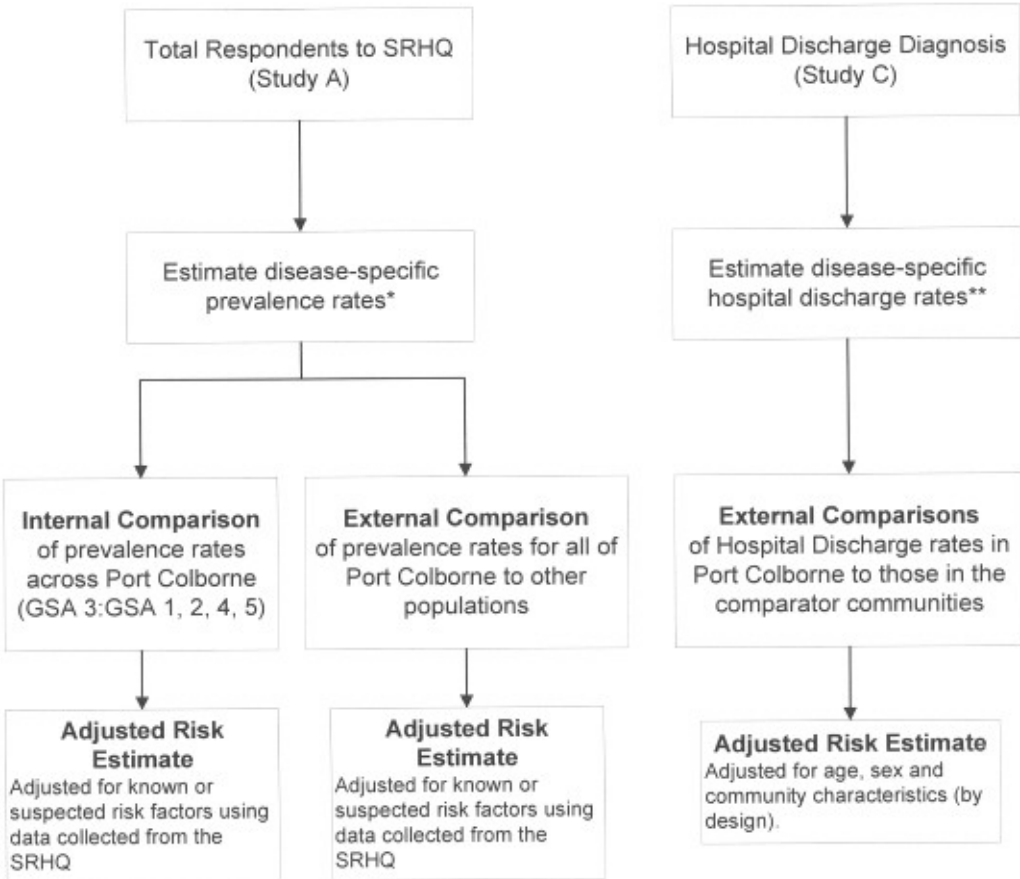


Figure 1: *Decision process for pursuing a case-control study.*

3.1 Step 1: Study Comparison (A and C)

The process for obtaining relative risk estimates, which in turn forms the first step of the decision to proceed with a case-control study for a given candidate health condition, is outlined in Figure 2. This process will be followed separately for each age group under consideration (i.e. children, children and adolescents, and adults).



* Prevalence rates estimated using self-reported data collected from the SRHQ. For three conditions (asthma, eczema and contact dermatitis), prevalence rates will be calculated using both self-reported data and physician diagnosis. For the remaining health conditions, prevalence rates will be calculated using physician diagnosis only.

** Discharge rates estimated using ICD-9 codes. These codes are assigned by health professionals as most reasonable diagnosis at time of discharge

Figure 2: *Process for deriving risk estimates to be used in the decision process for establishing the need for case-control study(ies).*

As shown in Figure 2, the following model will be used for each health condition under consideration in order to determine whether to proceed to the next step in the decision process:

1. Case Definition

- The survey data collected in Protocol A will be used to identify participants according to their case status; this case identification will differ depending on the health condition under study as outlined below:

  Asthma, Eczema and Contact dermatitis (Tables 1 through 4 of Appendix A)

  - Individuals will be identified as either probable or possible cases
  - The case definition category of possible has less stringent criteria than probable, as no self-report of physician diagnosis is required; this will allow us to capture prevalent cases not yet diagnosed by a physician. Probable cases form a subset of the possible case definition
  - Clinical specialists have contributed to the development of the two case groupings based on the responses to symptom and physician diagnosis questionnaire items.

  Other Health Conditions (Table 5 of Appendix A)

  - Adults will be classified as a probable case if there exists a self-reported confirmation of a physician diagnosis
  - Children will be classified as a possible case if there exists a self-reported presence of the condition.
- More information is included in the case definitions of asthma, eczema and contact dermatitis because the survey design, and therefore the data collected, allows for these more detailed definitions.
- The information from Study C will also be used in the decision to proceed with a case-control study. Because these data are based on discharge records completed by trained hospital staff, these cases will be regarded as probable.

2. Data Comparison

- Probable and possible case definitions will be used to calculate prevalence rates needed to conduct ***external*** comparisons, where the rate among Port Colborne residents will be compared to either Canadian or Ontario survey data (Study A). For Study C, the external comparison population consists of a series of Ontario comparator communities; no internal comparisons are possible with Study C.
- Probable and possible case definitions (Study A) will each be used to calculate prevalence rates to conduct ***internal*** comparisons, where rates among residents of GSA 3 are compared to residents of GSAs 1, 2, 4 and 5 combined. These regions have previously been defined according to varying levels of CoC contamination as measured in soil samplings.
- With the ***internal comparisons***, we are able to control for additional specific confounding data that have been collected in the SRHQ, offering a distinct advantage over external comparisons where such data is unavailable. As detailed in our study protocols, our risk estimates will be adjusted for the effects of other important variables that may confound the comparison of exposed and unexposed groups. These factors include age, sex and other known or suspected disease-specific risk

factors (e.g., smoking and sociodemographic factors) that are available in the datasets for Protocol A and Protocol C.

3. Risk Evaluation

- With each of the internal or external comparisons, a relative risk will be calculated based on the rates calculated using the case definitions (probable or possible) for each health condition
- For those conditions where two case definitions are applied (asthma, eczema and contact dermatitis), we will halve the one-tailed level of significance for testing. Although it is common practice to apply a significance level of 5%, because we are performing comparisons using two case definitions, the halving of the significance level is a method commonly used to adjust for multiple comparisons (referred to as the Bonferroni method). It is important to note that a one-tailed test of significance of $\alpha/2$ is equivalent to a two-tailed test of alpha if the underlying distribution used to perform the test (typically normal distribution) is symmetric. Therefore, for Study A, our assessment of statistical significance will be based on a two-tailed alpha of 5% which represents the standard output for regression parameters within the SAS software program. For Study C, only the probable case definition is used and, therefore, will be sufficient to obtain a significance level of 5% (based on a one-tailed test).
- Only adjusted relative risks will be considered in the decision criteria (see Adjustment for confounding below).
- The relative risk must demonstrate a positive association between residential areas with reported higher levels to the CoCs and disease and be statistically significant (as outlined above), before proceeding with sample size calculations to determine whether a case-control study is feasible.
- Statistical significance will be determined using standard methods for comparing rates or proportions. For external comparisons, this determination will make use of the sample size of the survey from which the external data were obtained.

Adjustment for confounding

Study A

- For each comparison, recognized or suspected disease-specific risk factors obtained from the SRHQ will be considered as potential confounders. They will be entered into multivariate regression models to determine the extent to which they confound the variable of primary interest, namely, exposure to CoCs as represented by place of residence. We will adopt the commonly used 10% rule to assess whether or not a variable is a confounder (Greenland, 1989; Maldonado, 1993) Those variables found to confound the risk estimates, while not unduly affecting either the confidence intervals for the variable of primary interest or other identified confounders, will be retained in the adjusted model. Age and sex will be retained in all models.

Study C

- The decision criteria will make use of the risk estimates generated using the comparator communities as the referent group. By design, these risk estimates adjust for the community effects of sociodemographic status and other census-

related indicators of health status. These relative risks will also be adjusted for by age and sex.

- Comparison of discharge rates for respiratory conditions will exclude comparator communities that were identified as having potential environmental concerns related to these types of health conditions

3.2 Step 2: Sample Size and Power Calculation

If the sample size calculations indicate that there will be a sufficient number of cases and controls to provide 80% power to detect at least the same level of risk that was found statistically significant using data from either Study A or Study C, then the next step in the decision process will be initiated.

See Appendix B for an example of a discussion of issues related to sample size and power. It is important to note that separate power calculations for a case-control study will be developed within the specific protocol that accompanies the case-control study.

3.3 Step 3: Hazard Identification for CoCs

Hazard identification represents the final step in our sequence to determine whether a case-control study is warranted. Hazard identification is concerned with determining whether exposure to a substance is causally related to the incidence of an adverse health effect (National Research Council, 1983). It characterizes the nature and strength of the evidence of causation and requires biomedical knowledge of the conduct and design of epidemiological and toxicological studies to define the likelihood that particular agents found or planned for use in the environment are safe. It is important to note that hazard identification is only the initial step of a formal risk assessment, and thereby does not encompass an entire risk assessment. The formal risk assessment process includes; hazard identification, dose-response assessment, exposure assessment and risk characterization (NRC, 1994).

The hazard identification process includes the following four steps (see Figure 3):

A. Gathering and analyzing the relevant toxicology data on the CoCs (arsenic, cobalt, copper and nickel) as it relates to the health condition under study
B. Gathering and analyzing the relevant epidemiological data on associations between the CoCs and the health condition in question
C. Weighing the evidence that any of the exposures could cause a toxic effect
D. Deciding whether the toxic effect could occur from exposure in a real-life and non-occupational setting.

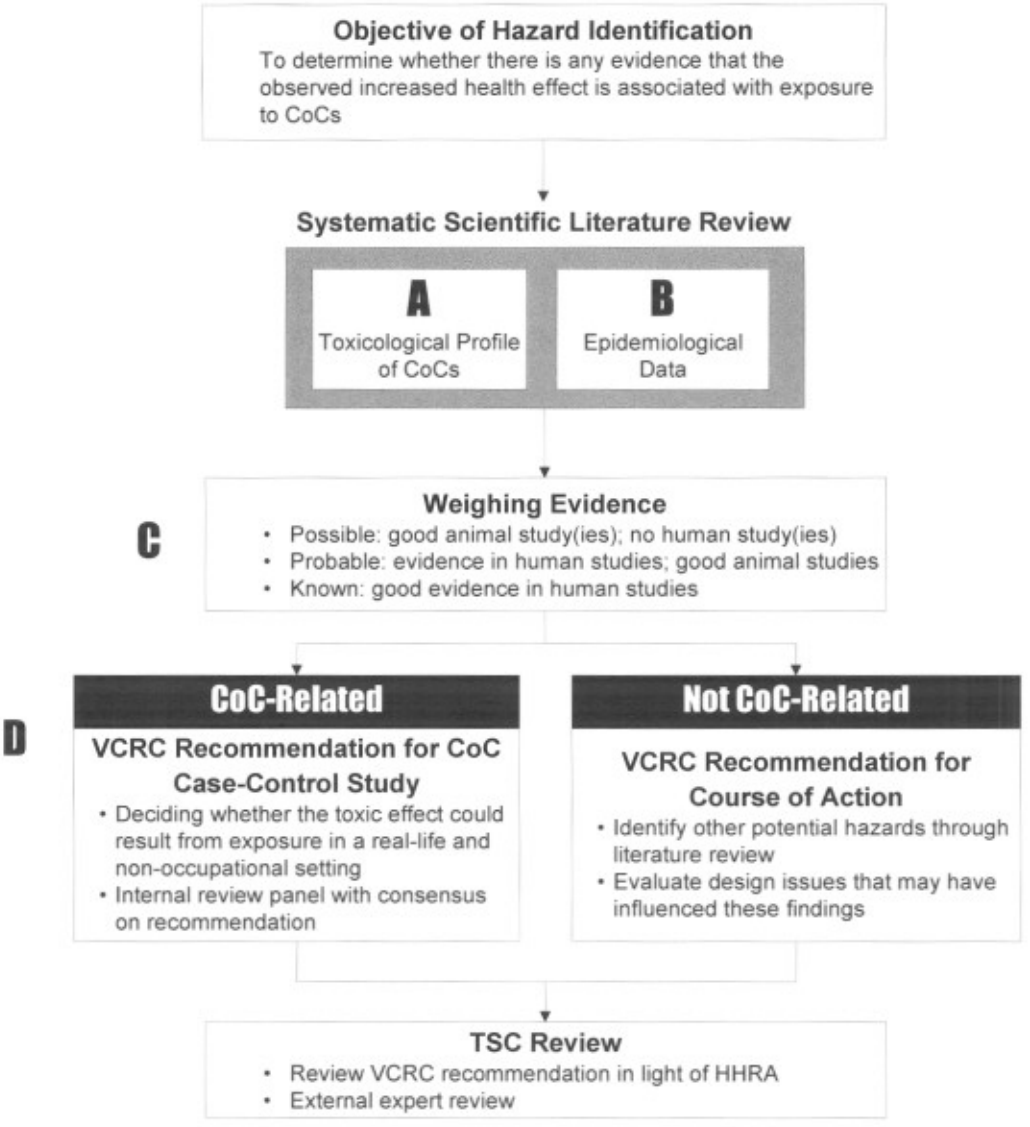


Figure 3: *Hazard Identification Process*

Steps A and B involve a detailed systematic review of the published scientific literature and are used to identify any evidence of association for the health effect and exposure to the CoCs. A number of search strategies will be used to identify the information and data required for the hazard identification. For example, the US EPA maintains an Integrated Risk Information System (IRIS) that is an electronic database containing information on human health effects that may result from exposure to various chemicals in the environment.

Step C involves evaluating all available information about the effects of the CoCs to estimate the likelihood that a CoC will cause a certain health effect in humans. The amount, type and quality of the evidence are all important factors in this determination.

Information that includes only animal studies will be classified as possible evidence of an effect, information from human and animal studies will be considered probable evidence of an effect and good quality evidence from human studies will be considered evidence of a known effect.

Our Hazard Identification Process has been augmented in a very important way. Specifically, it may be possible that increased rates of disease are found in Port Colborne and there is no supporting scientific evidence indicating the CoCs are plausible etiologic factors. Given that ethical guidelines (World Medical Association, 2002) that must be adhered to in the conduct of scientific studies involving biological sampling (e.g., blood or urine tests), neither a pilot nor case-control study in which objective is to evaluate CoC related effects could be conducted under such an exploratory scenario. For those positive associations which are deemed not to be CoC-related, we will identify possible explanations for these increased rates. This will involve a careful review of the disease-specific risk factors and an evaluation of whether or not design issues for Study A or Study C may have contributed to this finding. We will also make a recommendation as to what additional research could be undertaken to investigate these observed associations.

Step D is the recommendation by VCRC for proceeding with a CoC-related case-control study and is the stage where it is determined whether any toxic effect identified with Steps A through C could occur from exposure in a real-life and non-occupational setting.

Where a comparison involves a broader disease grouping as the health outcome under investigation (e.g., heart disease and diseases of the circulatory system), the hazard identification process will serve to identify specific disease sub-types that may warrant further study with case-control methodology.

A report summarizing the hazard identification process and decision to proceed with a case-control would then be disseminated for review by an independent group of experts. This same report would be made available so that the community of Port Colborne is given the opportunity to provide feedback into the hazard identification process.

3.4 Step 4: Design Case-Control Study

Before proceeding with a case-control study designed to evaluate the associations between the CoCs and a specific health outcome, a study protocol must be developed. This represents the fourth step of our process, and follows our recommendation based on the Hazard Identification phase. Once the protocol has been developed in consultation with the EAC, it will be submitted for review and approval by the TSC and subsequent receipt by the Public Liaison Committee (PLC). The budget for the study becomes a decision point for INCO Ltd.

4. SUMMARY

The criteria described in this document outline what findings are necessary to obtain our recommendation for conducting a case-control study. This has been done to ensure transparency to the overall conduct of the CHAP series of studies. There are several advantages to doing so, namely to ensure commitment to follow-up any noteworthy findings and to reduce the amount of subjectivity in the decision to move forward with future studies. Typically, the decision to conduct additional research is made after external scientific review of published findings has been performed. This permits an evaluation of all sources of potential bias, and therefore allows the key findings of the study to be better interpreted.

A document that summarizes the decision process for each health condition under study will be prepared in consultation with the EAC and reviewed by an independent external scientific body. This document will be disseminated to all stakeholders.

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Appendix A — Health Conditions Related to CoCs

Table 1: *Criteria used to define probable and possible asthmatic status among adult participants* in Study A and Study C, by comparison type*

Study and comparison type	Overall Comparison Number	Case Definition	Criteria
Study A Internal	1	Probable	Have you ever had asthma confirmed by a doctor? (ANSWER=YES) OR In the past 12 months, have you taken any medicine for asthma such as inhalers, nebulizers, pills, liquids, or injections? (ANSWER=YES) OR How many times in the past 12 months have you visited a hospital emergency room because of your asthma? (ANSWER>0)
	2	Possible	Includes all probable cases of adult asthma and is supplemented by individuals who fulfill the following criteria: I) Have you ever had wheezing or whistling in your chest at any time in the last 12 months? (ANSWER=YES) OR II) Have you had any asthma symptoms or asthma attacks in the past 12 months? (ANSWER=YES) And further to satisfy (II) an affirmative response must also be obtained for at least one of the following four questions: a) In the past 12 months, have you woken up in the night with a feeling of tightness in the chest? (ANSWER=YES) b) In the past 12 months, have you experienced shortness of breath made worse by exercise, which is unexpected in people your own age? (ANSWER=YES) c) In the past 12 months, have you been awakened in the night with an attack of shortness of breath? (ANSWER=YES) d) In the past 12 months, have you had difficulty breathing? (ANSWER=YES)
Study A External	3	Probable	Have you ever had asthma confirmed by a doctor? (ANSWER=YES)
	4	Probable	In the past 12 months, have you taken any medicine for asthma such as inhalers, nebulizers, pills, liquids, or injections? (ANSWER=YES)
	5	Probable	How many times in the past 12 months have you visited a hospital emergency room because of your asthma? (ANSWER>0)
Study C External	6	Probable	Hospital discharge ICD-9 Code 493; age-group 20+; using comparator communities

* In Protocol A, adults are defined as "18 years of age and older," while in Protocol C, the definition of adult is "20 years of age and older" due to the five-year age groupings of the comparator data.

Table 2: *Criteria used to define probable and possible asthmatic status among child and adolescent participants* in Study A and Study C, by comparison type*

Study and comparison type	Overall Comparison Numbers	Case Definition	Criteria
Study A Internal	7, 8	Probable	Has this child ever had asthma that was diagnosed by a health professional? (ANSWER=YES) OR Does this child use inhalers or puffers prescribed by a doctor for asthma? (ANSWER=YES) OR Does this child take any other prescribed medication for his/her asthma? (ANSWER=YES) OR How many times in the past 12 months has this child visited a hospital emergency room because of his/her asthma? (ANSWER>0)
	9, 10	Possible	Includes all probable cases of childhood/adolescent asthma and is supplemented by individuals who fulfill the following criteria: I. In the last 12 months, has this child had wheezing or whistling in the chest at any time? (ANSWER=YES) OR II. Has he/she had an attack of asthma in the last 12 months? (ANSWER=YES) And further to satisfy (II) an affirmative response must also be obtained for at least one of the following four questions: a) In the last months, how often, on average has this child been awakened due to wheezing? (ANSWER>0) b) In the last 12 months has wheezing ever been severe enough to limit this child's speech to only one or two words at a time between breaths? (ANSWER=YES) c) In the last 12 months, has this child had a dry cough at night, apart from a cough associated with a cold or chest infection? (ANSWER=YES) d) In the last 12 months, has this child's chest sounded wheezy during or after exercise? (ANSWER=YES)
Study A External	11, 12	Probable	Has this child ever had asthma that was diagnosed by a health professional? (ANSWER=YES)
	13, 14	Probable	Does this child use inhalers or puffers prescribed by a doctor for asthma? (ANSWER=YES)
	15, 16	Probable	Does this child take any other prescribed medication for his/her asthma? (ANSWER=YES)
	17, 18	Probable	How many times in the past 12 months has this child visited a hospital emergency room because of his/her asthma? (ANSWER>0)
Study C External	19, 20	Probable	Hospital discharge ICD-9 Code 493; age-group 0-19; using comparator communities

* In Protocol A, children and adolescents are defined as "less than 18 years of age," while in Protocol C, the definition of children and adolescents is "less than 20 years of age" due to the five-year age groupings of the comparator data. We will also conduct comparison for children only (< 13 for Study A and < 15 for Study C).

Note: An external comparison to other survey results using possible asthma status could only be performed if we were able to have access to individual-level data from other surveys. This would be required to classify individuals in that survey according to possible asthmatic status using the same methods applied to our own survey data.

Table 3: *Criteria used to define probable and possible eczema status among participants of Study A and Study C, by comparison type and age group (adult, childhood)*

Study and comparison type	Overall Comparison	Case Definition	Criteria
Study A Internal	21	Probable Adult	Have you ever had eczema (i.e. a long-lasting rash that itches in one or more of the following regions: face, hollow of the knee, elbow bends, ankles or wrists)? (ANSWER=YES) AND Was it confirmed by a doctor? (ANSWER=YES)
	22	Possible Adult	Includes all probable cases of adult eczema is supplemented by individuals who fulfill the following criteria: 1. Have you ever had asthma? (ANSWER=YES) OR 2. Do you have nasal allergies including hay fever? (ANSWER=YES) AND In the past 12 months have you experienced any of the following symptoms on the skin: 1. Persistent itching (ANSWER=YES) OR 2. Skin redness (ANSWER=YES) OR 3. Inflammation (ANSWER=YES)
Study A External	23	Probable Adult	Have you ever had eczema (i.e. a long-lasting rash that itches in one or more of the following regions: face, hollow of the knee, elbow bends, ankles, or wrists)? (ANSWER=YES) AND Was it confirmed by a doctor? (ANSWER=YES)
Study A Internal	24, 25*	Probable Childhood	Has this child ever had childhood eczema that was diagnosed by a health professional? (ANSWER=YES)
	26, 27*	Possible Childhood	Includes all probable cases of childhood eczema and is supplemented by individuals who fulfill the following criteria: 1. Has this child ever had an itchy rash, which was coming and going for at least six months? (ANSWER=YES) AND 2. Has this itchy rash at any time affected any of the following places: the folds of the elbow, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? (ANSWER=YES)
Study A External	28, 29*	Probable Childhood	Has this child ever had childhood eczema that was diagnosed by a health professional? (ANSWER=YES)
Study C External	None	Probable	No comparison will be done using Study C data as eczema seldom requires hospitalization, and as such there would be little utility to examining hospital discharge data for this condition.

* Risks calculated using two age groups: < 13 years and < 20 years.

Note: An external comparison to other survey results using possible eczema status could only be performed if we were able to have access to individual-level data from other surveys. This would be required to classify individuals in that survey according to possible eczema status using the same methods applied to our own survey data.

Table 4: *Criteria used to define probable and possible contact dermatitis status among participants in Study A and Study C, by comparison type and age group (adult, childhood)*

Study and comparison type	Overall Comparison Number	Case Definition	Criteria
Study A Internal	30	Probable Adult	Have you ever been told by a doctor that you have a metal contact allergy or dermatitis? (ANSWER=YES) AND After wearing earrings, a watch, metal buttons or other jewellery, do you get Eczema or a skin rash? (ANSWER=YES)
	31	Possible Adult	After wearing earrings, a watch, metal buttons or other jewellery, do you get Eczema or a skin rash? (ANSWER=YES)
Study A Internal	32, 33*	Possible Childhood	Has this child ever had another form of contact allergy that was diagnosed by a health professional? (ANSWER=YES)
Study A External	34, 35*	Possible Childhood	Has this child ever had another form of contact allergy that was diagnosed by a health professional? (ANSWER=YES)
Study C External	None	Probable	No comparison will be done using Study C data as Contact Dermatitis seldom requires hospitalization, and as such there would be little utility to examining hospital discharge data for this condition.

* Risks calculated using two age groups: < 13 years and < 20 years.

Note: An external comparison to other survey results using probable or possible contact dermatitis status could only be performed if we were able to have access to individual-level data from other surveys. This would be required to classify individuals in that survey according to probable contact dermatitis status using the same methods applied to our own survey data.

Table 5: *List of other chronic health conditions and criteria to define case status among Study A participants*

Adult Condition	Child Condition	Criteria
Chronic bronchitis	Food allergies	For each **adult** health condition: • The SRHQ question that asks for the indication of a doctor/physician diagnosis of the particular condition will designate a probable case definition for comparisons For each **child** health condition: • The SRHQ question that asks for the indication of ever having the particular condition will designate a "possible" case definition for comparisons
Emphysema	Learning problem	
Sinusitis	Epilepsy	
Rhinitis	Cystic fibrosis	
Psoriasis	Cerebral palsy	
Rosacea	Cancer	
Chronic fatigue syndrome	Down's syndrome	
Hypothyroidism	Developmentally delayed	
Hyperthyroidism		
High blood pressure		
Heart disease		
Heart attack		
Angina		
Congestive heart failure		
Stomach or intestinal ulcers		
Gastroenteritis		
Jaundice		
Cirrhosis		
Parkinson's disease		
Alzheimer's disease		
Infertility		
Food allergies		
Glaucoma		
Multiple chemical sensitivities		
Migraines		
Crohn's disease or Colitis		
Diabetes		
Arthritis		
Urinary incontinence		

Note:

- Both internal and external comparisons will be made where possible; for some conditions it may not be possible to generate stable risk estimates due to a small number of cases.
- A total of 58 comparisons will be conducted among adults using the above health conditions (29 health conditions x 2 comparisons (internal and external).
- A total of 32 comparisons will be performed among children/adolescent for the above listed health conditions (8 health conditions x 2 comparisons (internal and external) x 2 age groups (<13, and <20 years).

Table 6. *List of other chronic health condition groupings and criteria to define case status among Study C participants*

Health Condition	ICD-9 Code	Criteria
Diseases of the nervous system and sense organs	**320-389**	For each health condition: • The information from Study C is restricted to hospital discharge data, therefore these data will be considered a probable case definition for the purposes of the comparisons • For comparisons, adults are 20 years of age and older, children and adolescents are 19 years of age and younger, and children are < 13 years of age.
Diseases of the circulatory system	**390-459**	
Ischemic heart disease	410-414	
Acute myocardial infarction	410	
Heart failure	428	
Cerebrovascular disease	430-438	
Diseases of the digestive system	**520-579**	
Diseases of the genitourinary system	**580-629**	
Non-malignant respiratory disease	**460-519**	
Acute respiratory infections	460-466	
Other diseases of the respiratory tract	470-478	
Pneumonia and influenza	480-487	
Chronic obstructive pulmonary disease	490-494, 496	
Diseases of the skin and subcutaneous tissue	**680-709**	
Injuries	**E800-E999**	

Note:

- Only external comparisons will be made, therefore there are 45 possible comparisons.
- Adult and child age-groupings are the standard Statistics Canada definitions.

Appendix B – Sample Size and Power Calculations

Given that data collection is near completion, we are better able to estimate the total number of participants with selected health conditions. For example, the table below estimates the number of cases of adult and childhood asthma, eczema and contact dermatitis. With a 45% response rate, and presuming that 65% of these agree to participate in a case-control study where laboratory measures would be taken, we anticipate the following number of cases (see Table B1).

Table B1: *Approximate number of cases expected from study population for future case-control studies (if warranted)*

Health Condition	Prevalence rates from other population-based survey data	Expected number of cases
Childhood Eczema	10%	90
Childhood Contact Dermatitis	~15%	135
Childhood Asthma	10%	90
Adult Eczema	5%	193
Adult Contact Dermatitis	Women 5 – 15% Men 0.5 – 1%	208
Adult Asthma	5%	193
Total Asthma	8%	308
Total Eczema	5%	193
Total Contact Dermatitis	Women and Children 10% Men 0.1%	343

The number of cases and controls has implications for study power. The term "power" is used to describe the ability of a study to detect a true difference in risk. If a study has a power of 50% this means that it has a 50-50 chance of detecting a difference in risk. Typically, studies aim for a power of at least 80%, as it would be unsatisfactory if the chances of missing the true difference in risk were more than 20%.

If a case-control study were conducted to investigate associations between exposure to the CoCs and a specified health condition, we would ensure that the study population consisted of an adequate number of cases and controls to ensure the study had a power of at least 80%.

The sample size needed to ensure sufficient power will also be affected by several other considerations:

1. The magnitude of the risk that the study aims to detect among exposed individuals relative to those unexposed. For example, a case-control study that is designed to

detect an increased risk of 5% among exposed individuals would require a far greater number of subjects than a similar study designed to detect a risk difference of 50%.

2. The distribution of exposures in the study population. For example, if only 10% of individuals are exposed, the study would require many more subjects to assess the risk than if 50% of individuals were exposed.
3. The number of controls selected for each case. The power of a study can be augmented if several controls are selected for each case. However, the utility of multiple controls diminishes rapidly for a case-control ratio that exceeds 1:4.
4. Whether the study attempts to evaluate interaction effects. For example, a secondary objective of the study may be to determine whether smokers are more susceptible to health effects resulting from exposure to CoCs than non-smokers. To perform the analysis, the study must recruit a sufficient number of exposed (and non-exposed) smokers and non-smokers in order to accurately estimate the resulting health risks.

The sample size needed to conduct a case-control study does not vary according to the underlying prevalence rate for the disease under study. That is, assuming the exposure distributions were the same, a case-control study consisting of 30 individuals with pancreatic cancer and 30 controls would have the same study power as a case-control study consisting of 30 individuals with asthma and 30 controls.

When designing a case-control study, it is necessary to define power according to a specified difference in risk that the study is able to detect. For a case-control study, this risk is typically expressed in terms of the odds ratio (see Table B2). In some studies, the exposure is defined along a continuous scale (e.g., ppm), while in other studies, the subjects' exposure may be categorized according to the distribution of exposure (e.g., percentiles, quartiles, and tertiles). It is very important to acknowledge that the place to address these issues is within a study protocol so that the resulting study is designed with adequate power to address the research objectives. Studies require exposure to be well characterized with case diagnosis to have high rates of sensitivity and specificity. In summary, our expected numbers indicate that a case-control study for the health conditions of interest is feasible. However, a more detailed estimate of the power of such a study needs to be developed within the accompanying protocol.

Table B2: *Minimally Detectable Odds Ratios* for Various Sample Sizes*

Power = 80%, Alpha Error = 5% for selected case:control ratio

Number of cases	Number of controls	Case: control ratio	Odds ratio
50	50	1:1	3.62
75	75	1:1	2.76
100	100	1:1	2.36
125	125	1:1	2.14
150	150	1:1	1.99
175	175	1:1	1.88
200	200	1:1	1.80
50	100	1:2	3.00
75	150	1:2	2.37
100	200	1:2	2.09
125	250	1:2	1.92
150	300	1:2	1.81
175	350	1:2	1.72
200	400	1:2	1.66
50	150	1:3	2.78
75	225	1:3	2.25
100	300	1:3	2.00
125	375	1:3	1.85
150	450	1:3	1.74
175	525	1:3	1.67
200	600	1:3	1.61
50	200	1:4	2.66
75	300	1:4	2.20
100	400	1:4	1.94
125	500	1:4	1.80
150	600	1:4	1.71
175	700	1:4	1.64
200	800	1:4	1.58

* Assumes that 50% of controls are exposed (upper median of exposure index) and 50% of controls are unexposed (lower median of exposure index).

Glossary

Confounding (From the Latin confundere, to mix together):

1. A situation in which the effects of two processes are not separated. The distortion of the apparent effect of an exposure on risk brought about by the association with other factors that can influence the outcome.
2. A relationship between the effects of two or more causal factors as observed in a set of data such that it is not logically possible to separate the contribution that any single causal factor has made to an effect.
3. A situation in which a measure of the effect of an exposure on risk is distorted because of the association of exposure with other factor(s) that influence the outcome under study.

Relative risk is the ratio of risk of disease among the exposed to the risk among the unexposed; this usage is synonymous with *risk ratio*. Alternatively, the relative risk is the ratio of the cumulative incidence rate in the exposed to the cumulative incidence rate in the unexposed (i.e. the cumulative incidence ratio).

Prevalence rate is the total number of all individuals who have an attribute or disease at a particular time (or during a particular period) divided by the population at risk of having the attribute or disease at this point in time or midway through the period.

Hospital discharge rates are calculated using hospital discharge data where the rate is the total number of discharges that occurred during a specified time period and geographic area divided by the population at risk during the same time period and same geographic region. These rates are tabulated in Protocol C.

Bonferroni Correction is a method used to adjust the level of significance for multiple comparisons. This method adjusts the *p*-value for the comparisons that will be conducted by dividing the value of alpha by the requisite number of comparisons.

Reference source: Last, JL. 1995. *A Dictionary of Epidemiology*. Oxford University. Press 3rd Edition. Toronto.