Port Colborne

Community Health Assessment Project (CHAP)

Protocol "B":

Health Questionnaire and Medical Testing: A Comprehensive Assessment of the Current Health Status of a Stratified Random Sample of Residents in Port Colborne

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Protocol Synopsis

TITLE	Health Questionnaire and Medical Testing: A Comprehensive Assessment of the Current Health Status of a Stratified Random Sample of Residents in Port Colborne.
STUDY SITE	Port Colborne, Ontario
PRIMARY OBJECTIVE (S)	To characterize the current health status of Port Colborne residents, using a comprehensive health assessment questionnaire and medical testing, by sampling 1000 residents using a stratified random sample approach. In addition, the current health status of Port Colborne residents will be examined with respect to specific metal exposures, and compared between separate geographical areas of Port Colborne and to areas outside of Port Colborne.
DESIGN AND METHODOLOGY	A random sample of 1,000 Port Colborne residents will be selected to participate in the study, which consists of a health questionnaire and medical testing. Questionnaire completion and medical testing will be conducted over a five-day period requiring a total of three visits at a central study facility in Port Colborne. For individuals who are not able to attend the facility, alternative arrangements will be made. The health questionnaire has been designed to generate current health information encompassing: a) background information, b) reported medical health status, and c) reported psychosocial health. The medical test battery will provide current physical health information related to: a) haematology, b) urinalysis, c) blood biochemistry, and d) system function tests and a skin sensitivity assessment.
POPULATION	A stratified random sample of residents in Port Colborne 12 years of age or older will be invited to participate in this study.
SUBJECT PARTICIPATION	The health questionnaire consists of 104 questions that should take each individual approximately 30 minutes to complete. Medical testing will require blood and urine collection, skin sensitivity testing, pulmonary function testing, blood pressure and ECG. All testing will be acute except for skin sensitivity testing, where a patch will be applied to the skin and remain for a period of 48 hours. Informed consent must be obtained from the individual prior to answering the health questionnaire and undergoing medical testing. The informed consent advises individuals of the voluntary nature of participation, confidentiality of their results, study procedures, and the benefits and risks of study participation. For subjects between the ages of 12 – 17 parental/guardian consent is required in addition to the assent of the child/adolescent.
OUTCOME MEASURES	Outcome measures from this study will include:

	1. Current reported medical health status as determined by the health questionnaire; 2. Current reported psychosocial health status as determined by the Bradburn Affect Balance Scale and the Health Related Quality of Life-4 scale; 3. Additional reported demographic and exposure-related information based on residential address and occupational history; and 4. Current measured physical health status as determined by the medical test battery, including: haematology, urinalysis, blood biochemistry, cardiovascular and lung function, skin sensitivity, and Chemicals of Concern levels in the body.
DATA COLLECTION & ANALYSES	Descriptive statistics will be performed using data collected from the health questionnaire and measures obtained from the medical testing. Demographic data of participants will be compared to 1996 Canadian census data to determine the extent in which the survey results can be generalized to the Port Colborne community. Response rates will be estimated across geographical regions of Port Colborne to evaluate the potential for response bias. Prevalence rates for selected health conditions will be summarized for the Port Colborne area, and where sample size permits, the rates will be compared across stratified sampling areas. Similarly, the occurrence of selected health conditions in Port Colborne will be compared to participants of the Canadian Community Health Survey, a recently conducted national health survey. Tests of significance, including confidence intervals will be presented for these comparisons. Multivariate methods will be used to adjust for differences in age and sex of the comparison populations. Levels of the individual Chemicals of Concern, as determined by biological specimens analysis, will also be summarized. Variations in exposure levels within Port Colborne will be explored by calculating descriptive statistics, and through the use of multivariate analysis of variance methods. Logistic regression will be used to evaluate the relationship between the selected health conditions and exposure to Chemicals of Concern from both biological specimens and relevant questionnaire items of the health questionnaire. These models will provide odds ratios that will be adjusted for the effects of other potential confounding variables, such as age, sex, smoking habits, alcohol use and other indicators of socio-economic status. In addition, multivariate analysis of variance will be used to compare laboratory measures of Chemicals of Concern taken in Port Colborne residents to a normative sample, while adjusting for age and sex.

Abbreviations

ATSDR	Agency for Toxic Substances and Disease Registry
CBRA	Community-Based Risk Assessment
CCHS	Canadian Community Health Survey
CDC	Center for Disease Control
CHAP	Community Health Assessment Project
CO	Carbon Monoxide
COHb	Carboxyhaemoglobin
CoCs	Chemicals of Concern
CRF	Case Report Form
DLC	Differential Leukocyte Count
ECG	Electrocardiogram
fT4	Free Tetraiodothyronine (Thyroxine)
FEV1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
Hb	Haemoglobin
Hct	Haematocrit
HRQoL	Health-Related Quality of Life
IARC	International Agency for Research on Cancer
ICP-MS	Inductively Coupled Plasma-Mass Spectrometry
IgE	Immunoglobulin E
JWEL	Jacques Whitford Environmental Limited
MCHC	Mean Cell Haemoglobin Concentration
MCV	Mean Cell Volume of Red Cells
MOE	Ministry of the Environment
MPV	Mean Platelet Volume
PEFR	Peak Expiratory Flow Rate
PLC	Public Liaison Committee
PLT	Platelet
PSC	Publication Steering Committee
QoL	Quality of Life
RBC	Red Blood Cell
RDW	Red Cell Distribution Width
T.R.U.E.	Thin-Layer Rapid Use Epicutaneous
TSC	Technical SubCommittee
TSH	Thyroid Stimulating Hormone
WBC	White Blood Cell

1.0 Rationale

Emissions from INCO have resulted in contamination of soils with nickel, copper, cobalt and arsenic covering a wide area in Port Colborne. Several studies have been conducted on the impact of INCO's emissions on soil, vegetation and human health risks associated with contamination. A relatively high proportion of Port Colborne residents have expressed concerns regarding their health and the health of their family members.

Both animal and human studies have characterized the relationship between the identified Chemicals of Concern (CoCs) and various health conditions. Nickel has been linked to respiratory ailments, including asthma, chronic bronchitis and emphysema in occupational settings (Cornell and Landis, 1984) and is a recognized cause of allergic contact dermatitis (ATSDR, 1997). The International Agency for Research on Cancer (IARC) recognizes some nickel compounds as human carcinogens. Cobalt has also been linked to allergic contact dermatitis (Schafer, Bohler, Ruhdorfer et al, 2001). Finally, arsenic, like nickel, is a recognized IARC human carcinogen, and also has been shown to underlie dermatological, neurological and cardiovascular health issues (for review, see (Goldfrank, 1998).

1.1 Definitions

1.1.1 Health

The health questionnaire and medical testing will adopt the World Health Organization definition of health. This definition states: "Health is a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity."

1.1.2 Chemicals of concern

A chemical can only be identified as a CoC for the purposes of the Port Colborne CBRA study if: 1) the chemical was historically used or generated in the Inco refinery or its processes; and 2) the chemical is present at a community level at concentrations greater than generic-effects-based guidelines; and 3) the chemical present in the soil shows a scientific link to INCO's operations.

1.2 CoCs and Health

The way in which the four identified CoCs affect human health is dependent upon a number of factors, including speciation (the form in which the chemical is present) and the chemical's toxicology (the level at which the chemical becomes a health risk). In addition, the route by which the chemical enters the body can have a marked effect on the toxicological effects that occur.

1.2.1 CoCs: Toxicology

1.2.1.1 Nickel (Ni)

Nickel is a naturally occurring element that exists mainly in the form of sulphide ores found underground and in silicate minerals found on the surface. In the environment, nickel is found mainly combined with oxygen (oxides) and sulphur (sulfides). Nickel has been shown to be an essential element in certain microorganisms, animals, and plants; and is probably an essential element for humans (ATSDR, 1997).

Nickel is a natural component of the soil. Nickel is also dispersed as particulate dust in the atmosphere due to both human activities (eg. industry) and natural activities (eg. volcanoes). The general population is exposed to nickel via the inhalation of dust, ingestion of food and water, and by contact with objects containing nickel, such as jewelry and coins.

Although the general population is not affected adversely by nickel at typical levels, long-term or high-level exposure to nickel compounds, such as that experienced by workers in nickel refineries or nickel processing plants can negatively impact human health. Some nickel compounds are recognized by the IARC as human carcinogens, notably when present in the upper respiratory tract (nasal passage) and lungs. Chronic nickel inhalation has been linked to respiratory ailments, including asthma and emphysema (Barceloux et al., 1999a; Malo et al., 1982). Moreover, nickel is a well-recognized cause of allergic contact dermatitis in nickel-sensitized individuals (Barceloux et al., 1999a; Shah et al., 1998). Nickel exposure has demonstrated fetal risk (Sunderman

et al., 1980) and spermatotoxic effects (Pandey et al., 1999) in animal studies. In addition, Chashschin et al. (1994) reported an apparent association between maternal employment in a nickel refinery and an increase in risk of adverse pregnancy outcomes (eg. spontaneous abortions, stillbirths, ectopic pregnancy). Further studies, however, are required and are currently being planned by other researchers (Nieboer et al.) to evaluate the specific role of nickel exposure in pregnancy outcome.

1.2.1.2 Copper (Cu)

Copper is an element that is found naturally in the environment. Small amounts of copper are necessary for good health. On the other hand, acute ingestion of large doses may result in nausea and vomiting; and inhalation may result in acute respiratory irritation. Copper is not listed as either an animal or human carcinogen by the IARC. Though long-term effects of copper exposure are generally not well-characterized, symptoms may be potentiated in those with Wilson's Disease, an inherited condition of deficient copper metabolism (Barceloux, 1999).

1.2.1.3 Cobalt (Co)

Cobalt is a compound that occurs in nature. Small amounts of cobalt naturally occur in food. In addition, vitamin B12 is a cobalt-containing compound that is essential for good health. Everyone is exposed to cobalt at low levels in air, water, and food. However, people who live near hazardous waste sites containing cobalt may be exposed to higher

levels of this chemical and workers may be exposed to cobalt in industries that process it or make products containing cobalt. (ATSDR, 1997)

Chronic cobalt exposure may affect various organ systems. Occupational exposure to cobalt metal has been linked to "hard metal asthma" and "hard metal disease" characterized by respiratory problems of variable severity (Barceloux, 1999b; Cugell et al., 1990). Also, the so-called "beer-drinkers cardiomyopathy" has been observed in individuals exposed to cobalt-supplemented alcohol (Barceloux, 1999b). Prolonged cobalt exposure also may be linked to altered thyroid function (Prescott et al., 1992). Like nickel, cobalt is a recognized cause of allergic dermatitis, particularly in workers in hard metal industries, but also in the general population (Barceloux, 1999b; Schafer et al., 2001).

1.2.1.4 Arsenic (As)

The final CoCs of interest, arsenic, is a naturally occurring element widely distributed in the earth's crust. Exposure to higher than average levels of arsenic occurs mostly in the workplace, near hazardous waste sites, or in areas with high natural levels. Arsenic interferes with cellular metabolism on a number of levels, and can therefore affect many organ systems. Moreover, chronic arsenic exposure is linked to haematological conditions (eg. anemia); peripheral neuropathy (headache, numbness, weakness); gastroenterological illness; dermatological conditions (eg. hyperkeratosis; hypo- and hyper-pigmentation); and peripheral vascular disease (Ford et al., 1998; Abernathy, 1992; Aposhian, 1989; Schoolmeester and White, 1980).

1.3 Community concerns

In summer 2001, Ventana launched an extensive community outreach program in Port Colborne in an effort to ascertain the community's main concerns regarding its health and chemical contamination. Through various meetings, Port Colborne residents identified general themes regarding their health-related issues and concerns.

1.3.1 Metals

While many residents believe that health experts should ultimately be responsible for identifying the CoCs, they nevertheless indicated that lead, nickel and arsenic stood out as chemicals that should be targeted in future health assessment studies. A smaller percentage of residents mentioned cobalt and copper, while some were concerned about other chemicals such as mercury.

1.3.2 Health issues

Of primary importance to Port Colborne residents were concerns about potential effects of the above chemicals on the health of individuals, and on the well-being of the community. Individuals who participated in the outreach program indicated that they were concerned that certain medical conditions might be related to the high levels of chemicals identified in the Port Colborne region. When asked general health concerns, the community identified cancer, respiratory, general health, cardiovascular, skin, gastrointestinal, child development, mental health, thyroid, and reproductive health issues. When asked to select the health concern of most importance to them, the majority

of residents chose cancer; this health outcome will be addressed specifically in protocol D.

2.0 Objectives

The primary objective is to characterize the current health status of Port Colborne residents, using a comprehensive health assessment questionnaire and medical testing, by sampling 1000 residents using a stratified random sample approach. In addition, the current health status of Port Colborne residents will be examined with respect to specific metal exposures, and compared between separate geographical areas of Port Colborne and to areas outside of Port Colborne.

3.0 Study Design

3.1 Overview

To accomplish the objectives outlined above, data will be gathered from a stratified random sample of 1,000 Port Colborne residents aged 12 years of age and older. Each participant will be asked to complete a questionnaire and undergo medical testing.

3.2 Health questionnaire and medical testing

The health questionnaire (see Appendix 11.1) consists of 104 questions and three general components: Background Information; Current Medical Health Status, and Psychosocial Health. Medical testing comprises three main batteries of medical tests: 1) General

Medical Laboratory Screen Tests, 2) Metal Tests, and 3) Non-Specimen Related Tests and Data Points. These will be further discussed below.

3.2.1 Health questionnaire

3.2.1.1 Background information

Background information will be gathered by way of 39 questions covering the following: 1) Demographics (10 questions related to age, sex, race/colour, height, weight, marital status, level of education, household income); 2) Residential Information (two questions related to type of dwelling and length of residency); 3) Occupational Information (two questions asking about employment in specific industries); 4) Lifestyle/Dietary Information (21 questions related to source of drinking water, hobbies, smoking and drinking); 5) Educational Information (name of school and years of attendance); 6) Other Exposure (three questions related to jewelry).

3.2.1.1.1 Demographics

Demographic information, such as ethnoracial classification, average annual income, and education level, are routinely obtained in community surveys for the purpose of evaluating the data on the basis of sociodemographic factors, rather than simply the population as a whole. Such "stratified" analyses can reveal important underlying factors in the determination of health status in a diverse population, as well as identify potential at-risk subpopulations.

3.2.1.1.2 Qualitative exposure

A vital goal of the questionnaire is to obtain general exposure information and to determine if a relationship exists between such exposure and potential health issues. "Exposure" refers to "total exposure," and thus includes both exposure related to residential and occupational sources (e.g. where you have lived and worked and for how long, nature of the job), as well as other secondary sources, such as diet and lifestyle (e.g. water sources, hobbies). Accordingly, detailed questions are included that encompass these areas to gauge both current and past individual exposure.

3.2.1.2 Current medical health status

The questions under the Current Medical Health Status section of the questionnaire are designed to help determine the prevalence of specific health conditions. These questions will address a number of specific health areas that have been linked to CoCs exposure or that have been expressed as community concerns. These include health areas relating to respiratory, dermatologic, cardiovascular, thyroid, gastrointestinal, hepatic, neurological, and reproductive questions. These questions come primarily from the Canadian Community Health Survey (CCHS) an existing, validated questionnaire used by Statistics Canada to provide regular and timely cross-sectional estimates of health determinants, health status and health system utilization for 136 health regions across the country. Therefore, much of the data extracted from the Current Medical Health Status section of the questionnaire can be compared to existing data.

3.2.1.3 Psychosocial health

Psychosocial health is of concern to the residents of Port Colborne. The effects of environmental contamination on physical health are determined in relation to the degree and duration of exposure and are, in general, easily characterized. For example, there is substantial published scientific literature on the effects of certain metals on the central nervous system and various neurological sequelae (eg. arsenic-related encephalopathies and peripheral neuropathy) (Bahiga et al., 1978; Bolla-Wilson and Bleecker, 1987). However, the complexity of psychosocial health, and the issue of perceived exposure and the potential health consequences, makes it more difficult to determine the influence of chemical exposure on psychosocial aspects of health such as mental well-being and quality of life. As such, the questions in this section are designed mainly to address community concerns stemming from real or perceived issues relating to health in Port Colborne.

3.2.1.3.1 Mental health

Given the concern of residents over mental health issues, and the dynamic of the situation in Port Colborne, due attention is being given to the mental health of the community.

Eleven questions taken from the Bradburn Affect Balance Scale, a measurement of psychological well-being developed by Norman M. Bradburn, are included to establish the way the subject has felt over the past few weeks (Bradburn, 1969). Five questions reflecting positive feelings and five questions reflecting negative feelings as well as a

final question reflecting overall happiness comprise the Mental Health section of the questionnaire.

The CCHS also draws upon the Affect Balance Scale for questions relating to mood. Therefore, an extensive dataset exists for comparative analysis.

3.2.1.3.2 Quality of life

In assessing general health, researchers and medical health experts have begun to pose health-related questions more broadly in terms of quality of life (QoL). In basic terms, QoL relates to general well-being, including happiness and satisfaction with life.

To measure QoL, the Health Related Quality of Life-4 (HRQoL-4) Questionnaire has been included in the health questionnaire. This four-item scale, a set of questions called Healthy Days measures, has been in continuous use in the U.S. state-based Behavioural Risk Factor Surveillance System, a division of the Center for Disease Control (CDC), since 1993. Unhealthy days are defined as the overall number of days during the previous 30 days when the respondent felt that either his/her physical or mental health was "not good," and is calculated by summing the total number of "not good" days (mental and physical), with 30 days as the maximum assigned value. Healthy days are considered the positive complementary form of unhealthy days, all of which are calculated from responses to the Healthy Day measures.

The HRQoL-4 has been used extensively in the last several years in many U.S. nationwide studies and government programs, including those related to HIV/AIDS and cardiovascular health. Though developed and initially validated in the United States (Newschaffer, 1998), the HRQoL-4 instrument also has been validated in Canadian cities (Ôunpuu et al., 2000). Researchers administered the HRQoL-4 to 1,042 randomly selected adults in Hamilton, Ontario, and found that the patterns of association among HRQoL-4 questions, and the direction of the relationships among independent variables and HRQoL-4 were consistent with those hypothesized, thus validating the Healthy Days measures as a tool for monitoring health within a Canadian population. The HRQoL-4 has also been validated in specific Canadian demographic populations, such as the elderly, where physical and mental health and physical activity limitation were each shown to relate to self-perceived health (Ôunpuu et al., 2001).

The demonstrated ability of the HRQoL-4 in identifying health disparities, tracking population trends, and broadly measuring population health in Canada and abroad underlie its use in the health questionnaire. Given its extensive application in the US and in Canada, there will be a comprehensive dataset for comparative purposes.

3.2.2 Medical testing

Medical testing will be divided into three categories including: 1) General Medical Laboratory Screen Tests, 2) Metal Tests, and 3) Non-Specimen Related Tests and Data Points. The utility of such tests is discussed below.

3.2.2.1 General medical laboratory screen tests

Acute and chronic exposure of Port Colborne residents to nickel, copper, cobalt and arsenic may result in some specific and non-specific changes, which may be reflected in blood- and urine-related analyses (Jasmin and Solymoss, 1975). Even in the absence of obvious clinical manifestation of diseases, these changes help characterize pre-clinical disease states. Therefore, a standard battery of routine, but informative, non-invasive tests will be administered to generate current physical health information related to the haematology, urinalysis, and blood biochemistry of a stratified random sample of residents in Port Colborne from both high and low level exposure areas.

3.2.2.1.1 Haematology profile

The haematology profile (automated complete blood count) is one of the most commonly performed laboratory studies in clinical practice to evaluate the general health of a subject. Elevated or low measurements may indicate certain deficiencies, metals exposure, or other conditions. Specifically, we will examine the following: haemoglobin (Hb), white blood cell (WBC) count, red blood cell (RBC) count, haematocrit (Hct), mean cell volume of red cells (MCV), mean cell haemoglobin concentration (MCHC) of red cells, platelet (PLT) count, red cell distribution width (RDW), mean platelet volume (MPV), and differential leukocyte count (DLC).

3.2.2.1.2 Urinalysis

Urine removes toxins and excess liquid from the body and can therefore contain important clues regarding a person's general health and exposure to contaminants.

Urinalysis can be used to detect certain types of disease, particularly in the case of metabolic disorders and kidney disease. Urinalysis will include macroscopic examination (test strips) for: blood (Hb, erythrocytes), leukocytes, protein, pH, nitrite, and glucose for all the residents tested. Microscopic examination of urine sediment will be performed if there is a positive macroscopic result for blood, leukocytes protein (greater than trace), or if the glucose concentration is greater than 55 millimicromolars (nmol/l).

3.2.2.1.3 Blood biochemistry

Blood biochemistry tests can be indicative of the efficacy of various organ systems. These tests will examine bilirubin, creatinine, plasma cotinine, blood urea nitrogen (BUN), serum thyroid stimulating hormone (TSH), and free thyroxine 4 (fT4) concentrations as well as. Bilirubin is a yellow-orange pigment produced when the liver processes waste products. Excess levels in the blood produce the yellow appearance observed in jaundice and are thus indicative of liver function. Creatinine in a waste product of protein metabolism. Elevations in creatinine levels can be used to measure overall kidney function. Plasma cotinine is a breakdown product of nicotine and is widely used to verify recent exposure to cigarette smoke. TSH leads to the production and release of thyroid hormones, fT4 being one of the most important, and is responsible for regulating general growth and metabolism. Serum TSH and fT4 measurement is an important test for many aspects of pituitary and thyroid function. BUN is a measure primarily of the levels of urea (cleared by the kidney) in blood. Therefore, conditions associated with compromised kidney function frequently lead to increased levels of urea in the blood.

3.2.2.2 Metal tests

The four CoCs, nickel, copper, cobalt, and arsenic can be detected in urine following ingestion or inhalation exposure. It is possible that a relationship may exist between concentrations of these metals in urine samples and the environmental concentrations to which subjects have been exposed. In addition, it is possible that the data from these analyses may provide a better understanding of the relationship between the CoCs and the residents' health status.

In addition to measurements of CoCs levels in urine, mercury, lead and cadmium levels will be assessed in urine and blood, respectively. These non-CoCs tests are elaborated upon in the section 4.3.5, under Confounders.

3.2.2.3 Non-Specimen related tests and data points

This series of tests and measures is designed to provide critical health information not generated by the specimen-related tests. Non-specimen related tests and data points include a lung function test, skin sensitivity assessment, electrocardiogram (ECG), blood pressure measurement, carbon monoxide (CO) breath test, and general measures (eg. height and weight).

3.2.2.3.1 Lung function

The lung function test will assess lung volume and forced ventilatory flows. The following three tests will be used to measure each subject's ability to move air rapidly in

and out of the lungs: 1) FVC (forced vital capacity), the volume of gas delivered during an expiration made as forcefully and completely as possible starting from full inspiration; 2) FEV1 (forced expiratory volume in 1 second), the volume of gas exhaled in one second from the start of the FVC maneuver and; 3) PEFR (peak expiratory flow rate), the maximal flow during an FEV maneuver starting from a position of full inspiration. The specific ventilatory mechanics of the lungs are indicative of a number of pulmonary diseases (e.g. asthma, emphysema, obstructive air disease).

3.2.2.3.2 Skin sensitivity

Finally, skin sensitivity to nickel and cobalt also will be assessed. Long-term exposure to both nickel and cobalt contaminated dust has been shown to result in allergic sensitization leading to an increased incidence of allergic contact dermatitis. While primary allergic contact dermatitis has a good medical prognosis, continued exposure to the putative allergen may lead to chronic forms of dermatitis sites, such as the hands (Christensen, 1990; Schubert, 1990). Contact allergy is never inborn, although there may be some genetic factors that play a role in the development of the allergy (Menne and Neiboer, 1989). Following chronic exposure, sensitization to these metals can often occur, at which point the hypersensitivity is likely lifelong. Studies of the prevalence of delayed type hypersensitivity reactions/allergy to nickel in the general population have shown a prevalence range of 8% to 11% in females and 1% to 2% in males (Nielsen and Menne, 1993; Peltonen, 1979). More recently, considerably higher prevalence rates have been reported in the northern regions of Norway and Finland, namely, 27.5% to 39% of females (Smith-Sivertsen et al., 1999) and 5% of males (Smith-Sivertsen et al., 1999).

The prevalence of nickel allergy found in selected clinical populations referred for patch testing has shown a uniform prevalence of 14.3% (Marks et al., 1998, 1999, 2000, 2001) the prevalence for cobalt has been in the range of 6.8% to 9%. The marked difference between genders appears to be due to differences in the prevalence of ear piercing and the use of jewelry (Nielsen and Menne, 1993; Smith-Sivertsen et al., 1999; Smith Sivertsen et al., 2002). Based on the classification of both nickel and cobalt as CoCs and the clear relationship between chronic exposure to these metals and their dermatologic effects, the present study will include a skin patch test to assess sensitization to both nickel and cobalt.

3.2.2.3.3 Additional tests and general measures

Cardiovascular and circulatory issues will be assessed using the ECG and blood pressure tests. The ECG measures the electrical potential of the heart during contraction, while the blood pressure test will assess systolic and diastolic pressure. The CO breath test can be used to assess lung disease and to determine the exposure to smoke. In addition to these tests, general measures, such as height and weight, will be taken.

3.2.2.5 Validation

The individual medical tests described above have been included both for their utility in measuring general health and health conditions associated with exposure to the CoCs, as well as for purposes of validation. That is, specific medical tests also can be used as objective measures to validate reported medical health information from the health

questionnaire that is subjective in nature (Moffat et al., 2000; Smith- Sivertsen et al., 2000).

Medical tests that will serve as validators in this study include:

- Bilirubin test: validates the jaundice question in the questionnaire,
- Plasma cotinine test: validates recent smoking history question in the questionnaire,
- Serum TSH and fT4 test: validates thyroid condition questions in untreated individuals,
- ECG test: validates history of heart attack question in the health questionnaire,
- CO breath test: validates recent smoking history question in the health questionnaire,
- FEV1/FVC/PEFR tests: help to validate chronic bronchitis, emphysema, chronic obstructive pulmonary disease, asthma and other respiratory questions from the health questionnaire, and
- Skin patch tests: validates contact dermatitis question from the health questionnaire.

3.3 Confounders

"A confounder is a variable that (a) is causally related to the disease or condition under study independently of the exposure of interest or, as often occurs in practice, serves as a proxy measure for unknown or unmeasured causes, and (b) is associated with the exposure under study in the study population, but is not a consequence of this exposure. It

follows from (a) that within each level of the exposure under study, the confounder is related to the disease conditional on exposure level" (Kelsey et al., 1996). An example of confounding may better explain this phenomenon. Consider a study of cigarette smoking and lung cancer. Many factors that are related to cigarette smoking are independently related to lung cancer. For example, age is strongly associated with lung cancer, with the incidence rates of this cancer much higher among those 65 years of age and older. To assess the association between cigarette smoking and lung cancer, one must control for the effects of this potential confounder. If controlling for this factor does not affect the association between smoking and lung cancer, then there is little or no confounding effect present.

Two methods are used for controlling for confounding in cross-sectional studies: matching in the study design or adjustment in the analyses of the data. Matching is rarely used in cross-sectional studies for two reasons. First, these types of studies are often conducted in general population groups where information on potential confounding variables on individual participants is not known prior to sample selection. Second, information on the level of exposure is frequently unavailable at the outset of the study, so it is not feasible to divide subjects into groups based on levels of exposure for the purposes of matching. In this study, the only exposure information known in advance to sample selection is the current location of residence. This information will not be used for matching, but will be used in the sampling strategy where individuals will be grouped according to predefined boundaries of exposure.

The alternate approach for removing the effects of potentially confounding variables is to control for them in the analyses. This is typically the only feasible method available for controlling for confounding in a cross-sectional design. Two analytic methods are used to take into account the influence of confounding variables. Stratified analysis sometimes is employed to assess whether the effects are similar across each category of a variable of interest. Alternatively, multivariate modelling techniques can be used to examine correlations between variables and to evaluate changes in effects when other variables are taken into account. With a large series of variables, stepwise regression techniques are sometimes employed to objectively identify a series of adjustment variables. However, this will sometimes identify extraneous variables that have no biological rationale for being included in the model. An alternative approach uses a series of potential confounders identified apriori through a review of the scientific literature and examines the influence that each variable has on the measure of risk after it is entered into the model. Adjustment variables that change the risk estimates by at least 10% will be treated as confounders and included in the multivariate model. Possible collinearity of the adjustment factors will be examined by examining correlations between the confounders and by examining the changes in the standard errors of these variables in the multivariates model. Paramater estimated will be presented for unadjusted, minimally adjusted models (age and sex), and fully adjusted models (age, sex and other identified confounders).

A commonly used technique to adjust for differences in the age distribution of different populations for comparative purposes is called direct age standardization. We will make

use of all of the above techniques in this study to control for differences in the distributions of these confounding variables in the study populations. These methods are outlined in greater detail in several epidemiological textbooks (Kelsey et al., 1996; Lilienfeld and Stolley, 1994; Rothman and Greenland 2000).

3.3.1 Demographics

The previous example used for explaining the concept of confounding effects illustrates the need to control for demographics such as age and gender. These variables along with others, such as body mass index and socio-economic status will be controlled for in this study.

3.3.2 Lifestyle

Certain lifestyle choices may act as potential confounders in that they are related to the outcome of interest and the exposure being examined. Lifestyle information that will be collected in this study includes smoking status and alcohol use.

3.3.3 Current medical health status

Certain medical outcomes are related to one another, as is the case for the presence of heart disease and high blood pressure. If it is possible that high blood pressure could be related to an exposure of interest, it is best that high blood pressure be controlled for when examining heart disease with respect to that exposure.

3.3.4 Medications

In this study, subjects will report their medication use in the health questionnaire. Medications could be related to both an exposure and a clinical health assessment. In these cases, the effect of the exposure may be masked by the use of a medication and thus make the relationship between the exposure and clinical outcome difficult to discern. One example in this study could be the presence of abnormal results when testing thyroid hormone levels. An individual may have results that are within normal ranges but that individual is taking thyroid medication. Thus, this potential confounder will need to be controlled for in the analyses.

3.3.5 Additional Metals

Mercury, lead, and cadmium will be examined as a potential confounders in the search for association between the CoCs and any reported health effects.

Exposure to mercury in small amounts is common. Three distinct chemical forms exist: elemental, organic, and inorganic. The toxic manifestations depend on the form of mercury and the degree of exposure. Chronic exposure to mercury compounds can affect a variety of organ systems, most notably the nervous system, kidneys, skin, and gastrointestinal systems (Clarkson, 1977; Baselt, 2000; Sue, 2002). Mercury is also a recognized teratogen.

Lead-induced disease typically occurs after inhalation or ingestion of lead-containing compounds. Leaded gasoline (pre-1976), lead paint and dust (in older homes), and

industrial emissions are responsible for a large portion of environmental lead. Chronic exposure to lead has been linked to adverse health outcomes in a number of organ systems including the nervous system, liver, kidneys, reproductive, endocrine, skeletal, gastrointestinal and cardiac systems (Needleman et al., 1990; Philip and Gerson, 1994; Baselt, 2000). Given community concerns, the potential confounding effects of the health effects described, it is proposed that both mercury and lead be included in the Metal Tests in the present study.

3.3.6 Cigarette Smoking

Exposure to cigarette smoke has long been recognized as a leading cause of adverse health effects on respiratory symptoms and diseases (Bartal, 2001). Not only can smoking cause lung disease, it can make the lungs more susceptible to the negative pulmonary effects of other agents. In addition to its pulmonary effects, exposure to cigarette smoke may have other health consequences, including various types of cancer, cardiovascular disease, suppression of the immune system, and reproductive disorders (Bartal, 2001; Tengs and Osgood, 2001; Sopori, 2002). Given the broad effects of tobacco on human health, exposure to cigarette smoke should be considered a potential health confounder.

There are several biomarkers available to assess cigarette smoke exposure. For example, carboxyhaemoglobin (COHb) is often increased in smokers and can be assessed by single breath carbon monoxide (CO) levels (Middleton and Morice, 2000). Additionally, nicotine, the active substance in cigarette smoke, is intensively metabolized in the liver

and oxidized into cotinine (Berny et al., 2002). The measurement of cotinine allows the differentiation between non-exposed and tobacco-exposed individuals. As such, both breath CO and plasma cotinine tests will be included as part of the medical test battery to gauge cigarette smoke exposure, and to validate self-reported smoking patterns.

3.4 Study Limitations

Many factors can influence health and confound the measures of health including: age, gender, family history, as well as social, physical and economic environment. These have been taken into account in the CHAP project wherever possible. There has been the addition of the three confounding metals, lead, mercury and cadmium. We will be able to determine the levels of CoCs in the body but where there is the presence of multiple chemicals, it may be difficult to deduce any association with one particular contaminant. In evaluating the exposure and levels of CoCs in the body, it should be noted that the exposure does not indicate the level of lifetime exposure or the highest exposure that an individual has had. The level of CoCs detected in the body measure the level of metal at that moment of time. The measures will not be able to differentiate between recent exposure or levels of metal from a previous or historical exposure, in addition the measures will not be a reflection of the highest exposure or the duration of the exposure. The tests for CoCs will only measure the presence of CoCs and not the end organ effect of the CoCs.

In measuring any parameter of health, it needs to be noted that measurements need to be evaluated in reference to other measures in the body. An elevation of one parameter may seem to be an issue as it is out of range and yet when viewed holistically, the data can be normal for the age and gender. The data will all be viewed accordingly and any values that are of concern will be put into context both in the analysis and in communication with the subject and local physician. This is especially important when one considers that in general there is a background level of most metals and trace elements in everybody. The levels of CoCs found in the community of Port Colborne will be compared to standard reference ranges. In the analysis, the confounder data collected will be utilized to add context to the data. There may be instances where the very nature of the confounder will result in the fact that an outcome could be due to more than one cause. Confounders include, diet and food in general. Arsenic levels can be elevated by the ingestion of shellfish. This can be differentiated by utilizing a fractionated arsenic measure methodology that will identify organic and non-organic arsenic. The asthma symptoms and signs could be due to atopy (genetic susceptibility to allergies) in the subject, and therefore the person has hypperreactive airways to a number of airborne irritants. Hypersensitivity to nickel could be confounded by the level of jewelry that pierces the skin. Cobalt could be elevated due to the presence of a prosthesis device. This will all be clearly addressed during the review of each participants data and in the analysis. Other confounders that will be taken into account are lifestyle factors, such as smoking or use of alcohol. These are associated with many health risks including cancer and heart disease, use of prescription medications, OTC, Health supplements, such as those that contain vitamin B12 and other natural products. The use of medicinal products,

although treating one set of specific symptoms, may effect other haematological parameters. For example the use of Lithium can increase TSH levels, certain anti-inflammatory drugs can effect T-4 levels, codeine can effect liver enzyme levels.

Additional study limitations that bear mentioning include: the sample size of Port Colborne residents will preclude assessment of certain outcomes that occur at low frequencies (i.e., cancer); the fact that the cross-sectional design of the present study provides only a snapshot that makes it difficult to discern a temporal pattern (cause-effect relationship); and limitation of exposure data.

4.0 Methodology

4.1 Sampling Procedures

A sampling strategy that addresses the primary objectives of the health questionnaire, and satisfies the sample size estimated as a necessary requirement for meaningful comparisons to be made (section 7.0) is critical to the success of the study. A random sample of 1,000 individuals will be selected from an eligible population of Port Colborne residents. In order to obtain a representative sample of this community, it is necessary that the individuals who are included are selected from a comprehensive and fairly complete enumeration using an unbiased approach. Random selection is a preferred sampling method that can be used to avoid selection bias. However with any approach there will always be some bias. In this case, there will be an element of self-selection when subjects are given the choice to participate. In most cases, willingness to participate in a study is linked to the personality of the subject and an openness to participate in research. For this reason, when analyzing the results, it will be critical to assess whether non-response is systematically linked to the purpose or to the content of the study, or to some specific characteristic (e.g., socioeconomic status), thereby limiting the generalizeability of the study. This can be done by comparing demographics characteristics of the sample to the population of Port Colborne, using data from the Canadian census.

Further to randomization, a stratified sampling approach will be taken. In stratified sampling, the population is divided into strata, or groups that have certain characteristics

in common, and a sample is drawn from within each stratum. In this study, the strata will be defined as geographic areas categorized by approximation to level of exposure to the chemicals of concern. Stratified random sampling has several advantages over random sampling alone. First, by stratifying it can be ensured that each subgroup of the population is represented and that the carefully designed allocation of subjects can permit comparisons across strata. Second, when the population can be subdivided into groups that are more homogeneous than the population as a whole, more precise estimates of population parameters are obtained than when a random sample is taken of the whole population. This is because the variance computed for the entire sample is based on each within-stratum variance. Finally, strata can be constructed so that those that may have the largest number of individuals of interest (i.e, those with high exposures) can be sampled most heavily (Kelsey et al., 1996).

In order to perform comparisons among those individuals with potentially higher levels of exposure, an "oversampling" of residents in the Rodney Street area of Port Colborne must be done. Specifically, a proportionally higher number of people in this area will be included in the study relative to other areas of the city. The inclusion of a larger sub-sample in this area will allow for analysis of the results within this stratum and for comparisons to be made between this stratum and the rest of Port Colborne. Thus, even though the health questionnaire and the medical testing will not necessarily be administered to all residents of the Rodney Street area, the sample that emerges from that area will be large enough to be representative of the whole Rodney Street area in the

same way that the total sample (after weighting to adjust for oversampling) will be representative of the whole population of Port Colborne.

In addition to the weighting that adjusts for the oversampling in the Rodney Street area, it may be necessary to make adjustments to the sample if there are more people in one demographic category or other grouping than there should be, based on the real or true distribution of these groups in the population. Using available census data, combined with the observable demographic characteristics of the created sample, mathematically-derived weighting formulas will be considered to put the final, weighted sample in line with what it should be based on the characteristics of the population. Although many mathematical adjustments are rarely required to bring a sample into line with the real distribution characteristics of a population, most studies involving large samples do require a re-weighting to some degree.

4.1.1 Population

Port Colborne has a population of 18,450. From this population, a sample of 1,000 people who are at least 12 years of age will be randomly selected to participate in the health questionnaire and the medical testing. This sample will be chosen from a listing of all households based on phone numbers.

4.1.1.1 Participant Selection Criteria

All Port Colborne residents meeting the following criteria will be eligible to be included in this study, regardless of their primary language or literacy levels.

4.1.1.1.1 Inclusion Criteria

Participants may be included in the study if ALL of the following criteria apply:

1) They have understood and signed an informed consent form.
2) They are 12 years of age or older.
3) They live within Port Colborne boundaries.

4.1.1.1.2 Exclusion Criteria

Participants will be excluded from the study if they cannot comply with the study procedures.

Participants may not be included in the skin sensitivity assessment if they:

1. Have had topical corticosteroids applied to patch test sites within 24 hours of the test date,
2. Have taken oral corticosteroids at a dose equivalent to greater than 15 mg of prednisone within one week of test date,
3. Have had injectable corticosteroid within one month of testing,
4. Have taken oral cyclosporine within one week of testing,
5. Have one or more patch test sites not free of dermatitis, or any other inflammatory skin condition (e.g. psoriasis, sunburn),
6. Are pregnant,
7. Are not available for the application or reading of the patch tests, or

8. Cannot keep the dermatological patch test dry for 96 hours (this includes keeping the test sites free of excessive perspiration that may effect the outcome of the test or cause the patch to detach from the skin).

4.1.1.2 Withdrawal from Study

Individuals may withdraw from participation in the study at any time for any reason. If, for any reason, an individual chooses not to complete the study, partial responses may be used and analyzed. Additional subjects will be sampled to compensate for study "drop-outs".

4.1.2 Geographic Areas Defined by Level of Exposure

The City of Port Colborne will be divided into five strata or categories (see Appendix 11.6). These categories will be based on approximate estimates of levels of exposure within the city. These strata ensure that each subgroup of the population is represented and that areas of interest can be "over-sampled." They also allow for internal comparisons within the city to be made (Kelsey et al., 1996). The first area is south of Clarence St. (included) and bounded by the Welland Canal and Augustine Rd. The second area is north of Clarence St. (excluded), and bounded by Minor Rd. and the Welland Canal (includes Rosedale Subdivision). The third area is north of Lake Rd. (included), south of Durham (included), bound by Welland St. and Davis St.. The fourth area is south of 2nd Concession, north of Durham (excluded), bounded by Welland and Snider Rd.. All other areas within the boundaries of Port Colborne not mentioned above, will contribute to a fifth category which will consist largely of rural residences.

4.1.3 Randomization of Subjects

In general, a sample consists of the sampling units chosen from the population eligible to be included. The sampling unit is the unit around which the sampling procedure is planned, and in this study, the unit will be defined as the individual. The sampling frame is the list of all the sampling units in the population. A list of all residential telephone numbers that are publicly listed will be used in this study. This phone list is sorted by area code, and includes phone, name and address information for roughly 6,700 households. Based on the most recent aggregate data from Canada Post, this represents 85.3% (6,700/7,856) of households in Port Colborne. The sampling method is the way in which the sampling units are chosen from the sampling frame. As described above, the sampling method for this study will be a stratified random sampling approach. For stratification, the sampling frame will be divided into five geographic areas categorized by level of exposure to the CoCs. By assigning a random number to each telephone listing within each stratum and then sorting these listings by this random number, the sorted listings can be used to randomly select households for inclusion in the study. Within each household, participants will be randomly selected taking into account the number of residents. Specifically, for a household with *r* residents, the *k*th oldest resident will be chosen where *k* is a random number between 1 and *r*. The telephone interviewers will be supplied with tables of random numbers for households ranging from sizes of 2 to 10 to select a value for *k*.

4.2. Study Procedures

4.2.1 Overview

The study procedures section will describe the methodology surrounding both the health questionnaire and Medical Tests. This section will further describe the co-ordination of these two components in the Schedule of Events section.

4.2.2 Health questionnaire

The health questionnaire has five major sections: demographic information; residential, occupational, lifestyle/dietary, educational, and other exposure information; a health related quality-of-life measure; current medical health status information; and mental health information. There are some questions that will be either adult (18+) or adolescent specific. The adult-specific questions include occupational-related questions; certain demographic questions (i.e. income, educational level); and lifestyle questions (i.e. smoking status and alcohol use). The adolescent-specific questions include information on multiple residences, if applicable, and school identification, location and duration of attendance. Otherwise, the questions asked of the adolescents are the same as those of adults, with the identical objective of obtaining key exposure and general health information.

4.2.2.1 Questionnaire development and internal testing

Questions from the demographic section of the questionnaire were derived from the CCHS. Most of the questions collecting exposure information were developed under the advisement of experts in the areas of toxicology and environmental health and safety.

Questions pertaining to the smoking of cigarettes and consumption of alcohol were borrowed from the CCHS. The questions that assess quality of life came directly from the HRQOL-4 questionnaire that was developed by the CDC. There are five symptom questions within the section of the questionnaire that collects information on current medical health status. These questions were used in the work done by Smith-Sivertsen and colleagues (2000). The rest of the health related questions come from the CCHS, with a few exceptions for health outcomes of particular interest for this study. Finally, all questions on drug use and mental health again come from the CCHS.

The only identifying information collected in this questionnaire is the individual's name and date of birth. This information will be entered into the data entry application and will only be used for identifying individuals if they request their data. Otherwise, all identifying information will be permanently removed before any analyses take place.

During the development of the health questionnaire, wording was not modified for the CCHS-derived health questions, the HRQOL-4 questions, or the questions borrowed from the research done by Smith-Sivertsen et al. (2000). These are pre-existing, validated questions that require consistent phrasing so as to allow for comparisons with other datasets.

Once the health questionnaire has been finalized, questionnaires will be prepared for pre-testing. This pre-testing will also allow for data entry, handling, and analyses procedures

to be checked, and thus they will need to be in place prior to the pre-testing. The questionnaire will be pre-tested while interviewer training proceeds.

During the pre-test, the interview team will duplicate as closely as possible the procedures that will take place during the administration/fielding of the final questionnaire. While the pre-test is being conducted, progress will be closely monitored, noting and addressing any problems that arise in terms of the content or administration of the questionnaire, or the data management and analyses process.

4.2.2.2 Questionnaire administration

The questionnaire will be administered at the central study facility within the City of Port Colborne. The method of face-to-face interviewing will be used. It is preferable to phone interviews or self-administered surveys for the following reasons:

- longer surveys can be employed (this questionnaire will likely have a duration of 15-minutes to one half-hour);
- each resident can be met individually and face-to-face;
- the physical and friendly presence of the interviewer increases the possibility that respondents will complete all questions/keep going with survey;
- personal contact and rapport with the interviewer increases the commitment that the respondent feels toward the survey, and they are more likely to be willing to invest the time needed to complete the health questionnaire;
- the method is feasible because the survey is being conducted within the confines of a relatively small city;

- typically better than other methods among low-education, low-income, minority populations;
- increased quality control;
- interviewers can facilitate completion of the survey, as they will be on hand to explain the meaning of questions, etc. – they will be trained to do this in a way that minimizes bias of responses

The interview team will take all reasonable steps to ensure that residents who request an interview in languages other than English are given this opportunity. Interviewers will be made available who can translate the questions for these respondents. This removes the need for the entire questionnaire to be translated. Alternate arrangements will also be made for those who cannot visit the central study facility in Port Colborne.

4.2.2.2.1 Interviewers

Ventana will secure a site of operation in Port Colborne and recruit and train supervisors and nurse interviewers to administer the questionnaire. None of the staff will be from Port Colborne, nor will they have any affiliation with anyone who lives in Port Colborne. The reasons for this are: i) all residents are potential survey respondents, ii) the sensitive nature of the inquiry, and iii) the need for respondents to feel secure regarding maintenance of the confidentiality of the information that they provide. All interviewers will be qualified nurses who are trained to administer this questionnaire. They will also be certified through an inter-rater reliability testing procedure known as the Objective Structured Clinical Exam (OSCE), which will be described below.

4.2.2.2.2 Quality assurance/Control

In addition to the pre-testing of the questionnaire and along with interviewer training and certification, quality checks will be in place throughout the administration of the interviews. Interviewers will not be able to erase or correct any response by scribbling or covering over, but will be asked to clearly cross out the response and indicate the revision. Questionnaires will also be checked immediately after completion by a site coordinator to identify any problems. Any items that are unclear will be addressed with the interviewer, including the assessment of missing data. The interviewers will get feedback on a regular basis with respect to their performance. In addition, interviews will be periodically monitored for quality control, if the interviewee grants permission.

4.2.2.2.2.1 Inter-Rater reliability

The Objective Structured Clinical Exam (OSCE) approach will be used to assess and certify the competence of 24 survey interviewers at the completion of their training.

The Objective Structured Clinical Examination is a performance-based assessment approach, introduced by Harden et al. in 1975, used extensively in medical and allied health education and the certification and licensing of professionals in these professions. Briefly, this approach uses short standardized and focused encounters between candidates and patients/clients, where candidates' performances are rated by 'expert' examiners guided by checklists and where total test scores are an aggregation of the results of the individual cases. The achievement of both valid and reliable results are facilitated by

using a number of patients/clients and examiners in such an assessment, standardizing the clinical presentations for all candidates, and using checklists to limit examiner subjectivity. The approach has been enhanced by developments in the training and use of "standardized" (simulated) patients/clients. Early studies demonstrated that test results reflecting comprehensive views of performance generally satisfied traditional psychometric criteria. Results of studies where specific components of performance were addressed, e.g. communication skills, interviewing skills, proficiency in English, also produced positive results (Hodges et al., 1996; Rothman & Cusimano, 2000; Rothman & Cusimano, 2001).

4.2.3 Medical tests

As mentioned, the medical tests that will be included in this study include 1) the General Medical Laboratory Screen Tests, 2) the Metal Tests and 3) Non-Specimen Related Tests and Data Points. All procedures will be carried out by a number of trained study nurses at the central study facility.

4.2.3.1 General medical laboratory screen tests

Under the supervision of a trained study nurse, subjects will provide blood and spot urine samples at the central study facility for the General Medical Laboratory Screen Tests. Samples will be stored at the central facility and prepared daily for transport to the central analysis laboratory. At the central analysis laboratory, samples will be sorted and prepared for analysis. Measures from the following general categories will be assessed: haematology, biochemistry and urinalysis. Please see Appendix 11.4 for additional

information regarding methodology, specimen volumes, specimen transport conditions, and reference values for each of the individual tests. Samples will be stored at the central analysis laboratory until such time as the data has been validated. All collection, storage, transport and analysis of samples will be carried out in strict accordance with applicable SOPs.

4.2.3.2 Metal tests

The Metal Tests will require subjects to provide blood at the central study facility under the supervision of a trained study nurse and 24-hour urine sample. The 24-hour urine sample collection procedure is described within Appendix 11.3. Samples will be stored at the central facility and prepared for daily transport to a metals analysis laboratory. This metals analysis laboratory will be responsible for sample sorting and analysis of levels of the CoCs nickel, copper, cobalt and arsenic as well as the additional metal confounders, mercury, lead and cadmium. Please see Appendix 11.4 for additional information regarding methodology, specimen type, specimen volume, specimen transport conditions, and reference values for each of the individual tests. All collection, storage, transport and analysis of samples will be carried out in strict accordance with applicable SOPs.

4.2.3.3 Non-Specimen related tests and data points

These tests and measures include lung function, skin sensitivity assessment, and additional general tests. All tests and measures will be carried out at the central study facility and supervised by trained study nurses. Lung function will be assessed by

spirometric tests including FVC, FEV1, and PEFR. Skin sensitivity testing will be assessed using the thin-layer rapid-use epicutaneous (TRUE) test. This test is described in further detail in the section below. Finally, additional general measures will be carried out including ECG, blood pressure, and weight and height measurements.

4.2.3.3.1 Skin sensitivity assessment

Prior to dermatology testing, subjects will have filled out the health questionnaire which contains dermatology questions that will be used to obtain information concerning dermatological points of interest including questions about jewelry that pierces the skin and the possible presence of atopic dermatitis. A standardized ready to use patch test system, the TRUE test, will be employed (Brasch et al 2001: Suneja and Belsito 2001). This system has been found to be at least as comparable in terms of accuracy and reproducibility, to the conventional Finn Chamber technique of patch testing in its detection of nickel and cobalt allergic individuals (Suneja 2001, Golhausen 1989).

A group of trained study nurses will perform all patch test administration, including application and removal. Patch test scoring will be carried out by a smaller group of specially trained study nurses to maintain high inter-rater reliability. Patch tests will be applied on the upper back. Their edges will be marked with a hypoallergenic marker. Patch tests will remain on the skin for a period of 48 ± 2 hours. During this time, subjects will be given written instructions on test compliance (see Appendix 11.3 for more information). Following this, patch tests will be removed by a trained nurse. Skin sensitivity will be scored 48 hours following removal of the patch test (at 96 hours).

Patch test responses will be scored as either negative, or positive. A positive patch test result is interpreted as a 1+, 2+ or 3+ reaction. This interpretation is based on the following scale (ICDRG 1984): a) 1+ = diffuse confluent erythema with palpable infiltration; b) 2+ = erythema and infiltration with papules and descrete vesicles; and c) 3+ = spreading strong erythema and infiltration with coalescing vesicles/bullous reaction and / or crust with ulceration. Irritant reactions (weak, macular erythema without infiltration or a follicular (pore) pattern restricted to the area covered by the patch) are not regarded as positive and are denoted as "IR".

4.2.4 Schedule of events

4.2.4.1 Overview

This section will describe the chronological flow of events experienced by a subject in this study. After being randomly selected as previously described, the potential subject will be contacted and asked to participate in the present study. A series of 3 visits at the central study facility will be scheduled for questionnaire and medical test administration, should the subject agree to participate in the study. In this event, a study participant will be given verbal study compliance instructions, they will be asked to pick up a 24-hour urine container at the central study facility and a study compliance instruction list will also be mailed to them (please see Appendix 11.3 for an outline of this information).

Subjects will then be required to attend their scheduled visits. These visits will take place over the course of 5 days. During the first visit (Day 1), study participants will complete and sign their informed consents/assent forms, complete the health questionnaire with the

assistance of a study nurse, donate blood and urine for the Medical Laboratory Screen and Metal Tests, and undergo cardiovascular, respiratory, dermatology, and general tests for the Non-Specimen Related Tests and Data Points. During this first visit the dermatology test will involve the application of a skin patch test. As such, a second (Day 3) and third visit (Day 5) will be required for removal of the patch test and scoring of the skin response, respectively. Specific procedures related to these tests will be discussed below.

4.2.4.2 Study visit 1 (Day 1)

4.2.4.2.1 Subject sign-In

The subject will arrive at the central test facility and be greeted by a study receptionist who will reference the subject's name against the appointment book, and collect the 24-hour urine sample. To confirm sobriety, the study participant will be given a breath alcohol test before proceeding. Any subject whose breath alcohol test exceeds the legal value of 0.08 will be disqualified. Subjects will then be assigned a Case Report Form (CFR) binder and be given a clipboard containing a Demographics Form to complete and Informed Consent Form to review. Adolescent subjects aged 12-17 years will be given an Adolescent Assent Form and their parents or guardian will be asked to review a Parental/Guardian Consent Form. Following this, the study participant will be greeted by a study nurse interviewer who will escort him/her into one of the four private interviewing stations. A parent or guardian may accompany adolescent subjects.

4.2.4.2.2 Interview administration

The interviewer will review the demographic information with the subject for completion and accuracy and validate it using a piece of photo I.D. supplied by the study participant. If the subject is an adolescent and does not have a piece of photo I.D., a birth certificate or a hospital card is acceptable. The nurse interviewer will confirm that the subject has complied with the parameters of the study over the past few days and then review the consent document(s) with the subject to ensure comprehension and answer any questions the subject may have. The interviewer will then have the subject sign and date both copies of the Informed Consent. The subject will be given one copy for his/her records.

If the subject is an adolescent the parent/guardian will sign their consent form and the subject will sign their assent form. At this point, the subject will be ready for the health questionnaire interview. Parents or guardians will be asked to wait in the waiting room during the questionnaire administration so that adolescent subjects are given the utmost opportunity to answer freely.

4.2.4.2.3 Medical tests

Upon completion of the questionnaire, the interviewer will escort the subject into the first waiting room and place the Subject's CRF binder in the charting holder. If the study participant is an adolescent the parent/guardian may accompany them throughout the remainder of the visit for support.

The subject will be escorted into the first examination room in which all Non-Specimen Related Tests and Data Points will be assessed. The subject's height and weight will be

measured and their blood pressure will be assessed. Following this, a skilled professional will then administer a lung function test. This test will assess the following parameters: forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), and peak expiratory flow rate (PEFR). In addition, a breath carbon monoxide (CO) test will also be performed to assess recent smoking history. All measures will be recorded in the subjects CRF binder. Upon completion of this initial round of medical tests, the study participant will be escorted into the second waiting room and the Subject's CRF binder will be placed in the charting holder in that area.

The subject will then be escorted into a second examination room in which blood and urine specimens will be collected. These specimens will be necessary to carry out the tests specified for the General Medical Laboratory Screen and Metal Testing. In addition, patients will be given an ECG test during this time to examine cardiac function. All applicable information will be recorded in the Subjects CRF binder. Upon completion of the specimen collection and ECG testing, the subject will be escorted into the first waiting room and the subject's CRF binder will be placed in the charting holder in that area.

The subject will be escorted into a third examination room where a specially trained nurse will conduct dermatology testing. The nurse will first carefully review all information regarding the skin patch test with the subject and then apply the patch. Following this, the nurse will review the test compliance instructions with the study participant to ensure compliance. Finally, the nurse will review with the subject their

return visit schedule. All applicable information will be recorded in the Subjects CRF binder.

Upon completion of the application of the dermatology patch, the Subject will be escorted to the sign out waiting area. Subjects will be signed out following a review of the CRF binder by the study nurse and confirmation that the subject completed all components of Visit 1, understood the dermatology patch compliance instructions, and understood when he/she must return for Visit 2 and Visit 3. If the subject is an adolescent, and if the parent/guardian has not been present throughout the specimen and data points collection, the parent/guardian must be present at the time of sign out to ensure an understanding of the above.

4.2.4.3 Study visit 2 (Day 3)

The study participant will return for their second scheduled appointment on day 3 and be greeted by the receptionist who will reference the subjects name against the appointment book. The receptionist will locate the subject's CRF binder and ensure the subjects identity. The subject is escorted to the first waiting room where the subject's CRF binder is placed in the charting holder.

The subject will then be escorted into an examination room. There, a trained study nurse will remove the patch. If the subject is an adolescent the parent or guardian may accompany them during this procedure.

Upon having the patch removed, the subject will be escorted back into the reception waiting room where the sign out nurse will review the subject's CRF binder and ensure that the subject has completed all components of visit 2 and understood when he/she must return for visit 3. If the subject is an adolescent, the parent or guardian must be present at the time of sign out to ensure an understanding of the above.

4.2.4.4 Study visit 3 (Day 5)

The study participant will return for their third scheduled appointment on day 5. The receptionist will again greet the subject and reference the subject's name against the appointment book, locate the subject's CRF binder, and ensure the subject's identity. The subject is escorted to the first waiting room where their CRF binder is placed in the charting holder.

The subject will be escorted into an examination room where a trained nurse will score the skin reaction to the patch. If the subject is an adolescent the parent or guardian may accompany them for the dermatology patch scoring.

Upon having the patch scored, the subject will be escorted back into the reception waiting room where the sign out nurse will review the subject's CRF binder and ensure that all they successfully completed visit 3, understood that following the completion of the study a final report indicating their test results will be held for them at the facility for pick up. If the subject is an adolescent, the parent or guardian must be present at the time of sign out to ensure an understanding of the above. The subject will then be given a payment of

$35 for completion of the study. This amount was determined based on transportation costs during the study, four return trips to and from the study facility.

4.3 Study milestones

The study described in the present protocol will progress though a number of milestones. These milestones include: 1) study development, consisting of Technical SubCommittee (TSC), scientific, ethics, and PLC review; 2) study conduct data management and data analysis; and 3) preparation and release of study reports. Approximate timelines for these milestones are elaborated upon below.

4.3.1 Study development

Development of the current study protocol will proceed through multiple phases, each involving review and submission of revised draft protocols.

4.3.1.1 TSC review

Following the development of this draft (Version 2.0) study protocol by Ventana, it will be presented to the TSC for review in late June 2002. The TSC will review the protocol and suggest any revisions though an interactive process of consultation. Ventana will then prepare and release a newly revised draft (Version 3.0) that will be released to the TSC and the community of Port Colborne in mid- to late July.

4.3.1.2 Scientific review

This revised draft (Version 3.0) will be submitted by the TSC for scientific peer review in mid- to late July. Comments from scientific reviewers will be due in early August to the TSC. The TSC will compile these comments and provide them to Ventana, keeping individual reviewer's comments anonymous. Ventana will then incorporate appropriate comments into its subsequent draft (Version 4.0) protocol.

4.3.1.3 Ethics review

This newly revised protocol (Version 4.0) will be submitted to the ethical review board, for review in mid-August. Comments from the ethical review board are due mid-September. These comments will be incorporated into the final protocol (Version 5.0) to be ready for implementation in mid-September.

4.3.1.4 PLC review

The protocol submitted for ethical review (Version 4.0) will be reviewed by the PLC in mid-August.

4.3.2 Study Conduct, Data Management and Analysis

Study conduct is scheduled to commence mid-September. This phase of the project will involve administration of the health questionnaire and medical testing to a stratified random sample of residents Port Colborne at a central study facility. Data collection is scheduled over a period of two months ending mid-November. Data management will occur concurrently with data collection starting in mid-September and extend one week

beyond study conduct through to late November. Data analysis will occur over the following two weeks commencing in late November and ending in early December.

4.3.3 Study reports

Ventana will prepare preliminary study reports, draft study reports and a final study report. A preliminary report will be made available to the TSC in early December. Following review by the TSC, a draft study report will be prepared for peer scientific review in mid-December. This review will require approximately one month. A revised draft study report then will be prepared based on the comments generated from the scientific review. This revised report will be presented to the TSC, the Port Colborne community and the PLC. Following input from all three of these parties, a final report will be prepared and released during the first quarter of 2003.

4.4 Consent

Informed consent for this study will be obtained prior to the administration of the questionnaire (see Appendix 11.2) The person obtaining consent must inform the respondent of all aspects pertaining to the respondent's participation in the study.

Participants 18 years of age and older will be required to read and sign an Adult Consent Form/Information Sheet (see Appendix 11.2.1) encompassing the administration of both the health questionnaire and medical testing, to participate in the study. Adolescent subjects (12 to 17 years of age) will be asked to read and sign an Adolescent Assent

Form/Information Sheet (see Appendix 11.2.2). Additionally, parents of adolescent subjects will be asked to read and sign a separate Parental or Guardian Consent Form/Information Sheet (see Appendix 11.2.3) to allow the adolescent's participation in the study.

The written Adult Consent Form/Information Sheet, Adolescent Assent Form/Information Sheet, and Parental or Guardian Consent Form/Information Sheet will include the following information:

- A description of the study;
- The purpose(s) of the study;
- Procedures to be followed, including, if applicable, all invasive procedures;
- The participant's obligations/responsibilities;
- All foreseeable risks/benefits and inconveniences to the participant;
- The voluntary nature of the study;
- That consent for study participation may be withdrawn at any time without penalty or loss of benefits to which the respondent is otherwise entitled;
- That records identifying the participant will be kept strictly confidential (see Section 5.5 Confidentiality);
- Contact information to obtain further information about the study (Adult Consent and Parental or Guardian Consent only);
- Foreseeable circumstances, if any, and reasons under which participation may be terminated;
- Expected duration of participation of the individual;

- Approximate number of individuals participating in the entire study;
- Details of compensation for the time and inconvenience of study participation;
- Details of provision of test results to study participants; and
- Details of provision of test results to participant's physician.

The process for obtaining informed consent will be in accordance with all applicable regulatory requirements. The person obtaining consent and the respondent, or the respondent's legally authorized representative, must both sign and date the informed consent and/or assent form before the respondent can participate in the study. The respondent, or the respondent's legally acceptable representative, will receive a copy of the signed and dated form, and the original will be retained in the study records.

4.5 Confidentiality

An Act to support and promote electronic commerce by protecting personal information that is collected, used or disclosed in certain circumstances, by providing for the use of electronic means to communicate or record information or transactions and by amending the Canada Evidence Act, the Statutory Instruments Act and the Statute Revision Act.

During the course of the study, Ventana personnel will collect the study information from the participants. This data will be collected and stored electronically. In compliance with The Statutes of Canada 2000, Bill C-6, (13/04/2000). All records in which the name of a participant appears will be kept confidential and will be provided with a unique identifier. The name will never appear on any forms, report or publication. The statute covers

personal health information with respect to an individual, whether living or deceased meaning:

- information concerning the physical or mental health of the individual;
- information concerning any health service provided to the individual;
- information concerning the donation by the individual of any body part or any bodily substance of the individual or information derived from the testing or examination of a body part or bodily substance of the individual;
- information that is collected in the course of providing health services to the individual; or
- information that is collected incidentally to the provision of health services to the individual.

In addition, Ventana assures that a respondent's personal data will not be used, disclosed, nor collected in any manner incompatible with the intended purpose of the research. Care will be taken to keep the information secure, whether on hard copy, computer or stored electronically. An individual respondent's identity will not be revealed during the course of the study. Unique identifying numbers will be used as an alternative to a personal identity. Once all of the data has been validated, all linkages between the unique identifier and personal identity will be erased. After this point, there will be no method whereby a person's name can be linked with individual, specific health outcomes. Unless otherwise specified, only aggregate data, not individual data, will be published or released to the general public, as with any scientific study.

Participants will be informed of the degree of confidentiality that will be maintained throughout the study during the process of obtaining informed consent.

Research specifications, such as background, objectives, and technical approaches or ideas, provided by Ventana, remain the property of Ventana and the contents will not be revealed to a third party without Ventana's permission or unless instructed by a court of law.

5. 0 Data Management

5.1 Data collection and quality control

All data, including the signed informed consent (Adult Consent, Adolescent Assent, Parental or Guardian Consent) will be collected on a two-part NCR document. The informed consent will be provided as a single document for adult consent, parental or guardian consent or adolescent assent. Once written consent has been given, a copy will be retained by the subject, and one by Ventana. The informed consent will be provided with a unique code and inserted into a case report form (CRF) for the study participant. The CRF will be two-part NCR. The top page (white sheet) will be classed as the original document and the second page (yellow sheet) will be classed as the file copy.

At the completion of each questionnaire, the interviewer coordinator will review for completeness. Alongside questions that have not been answered by the study subject, the interviewer will sign their initials. At the bottom of each page, the interviewer will sign

their initials. Each white page will be removed from the CRF upon completion and submitted for data entry.

All data provided on test samples from the laboratory will be provided in electronic format predetermined for compatability with the central data base. A common unique code will be utilized for each participant.

Data collection by the central laboratory will be done via electronic date capture.

Data from the health test machines will be provided from a print-out that will be used for double entry methodology.

Data from the ECG will be entered into the central data base as descriptive text.

5.2 Data storage

All hard copy (CRF) and electronic data will be stored by Ventana for five years. A copy of all data will be made available to the regional municipality of Niagara Public Health Department. This data will exclude any personal identifiers. All data stored by Ventana will be in compliance with the Personal Information Protection and Electronic Documents Act (January 1, 2002) and Good Clinical Practice.

5.3 Data transfer

All data collected in the CRF will be entered into the central data base by double entry methodology.

5.4 Chain of custody

Chain of custody will be implemented to ensure limited use, limited disclosure and accuracy of all test results. It will also ensure the integrity of all test samples. Original data will be collated in hard copy at the end of each interview session and transferred to a sealed container. All original data will be removed from the central facility in Port Colborne at the end of each day and carried to the Ventana central facility.

All test samples will be shipped in sealed containers via a designated courier to the central laboratory.

All CoCs test containers will be metal-free collection and storage containers. These will be dispatched in a tamper-proof form to the Port Colborne site.

All test samples will be shipped from the Port Colborne facility at the end of each clinical day; samples will not be stored at this facility overnight.

The areas in Port Colborne where test samples are stored prior to dispatch will be with limited access.

6.0 Data Analysis

6.1 Sample Size Calculation

Sample size is an important element that needs to be addressed when designing a health survey. When estimating community rates of a certain characteristic or health condition, random sampling or chance may partly explain the findings. For example, if the overall smoking rate in Port Colborne were 30%, taking repeated samples of 10 individuals would not be expected to result in the finding of three smokers in every sample of 10 individuals. For this reason, a sufficient number of individuals must be sampled so that reasonably accurate estimates of the health characteristics of the community can be obtained.

The term "Power" is used to describe the ability of a study to detect a true difference when making comparisons between two or more groups. If a study has a power of 50%, this means it has a 50-50 chance of detecting this difference. Typically studies aim for a power of at least 80% as it would be unsatisfactory if there was more than 20% chance of missing this difference. The number of participants that are needed to ensure sufficient power are influenced by several factors including: the size of the difference that is to be detected; the prevalence of the disease or characteristic of the population that is being compared, the variance of the characteristic that is being examined; and the size of the Type I error (probability of rejecting the null hypothesis when it is true). Each of these factors must be specified in order to estimate the power of a study.

The Power of a study may also be calculated in order to ensure that the average value of a variable, or prevalence of a health condition within a community, is calculated with sufficient precision. This is referred to as a one-sample statistical test. Alternatively, the objective of the study may be to compare differences in disease rates between two communities. In this case, the study power is calculated to ensure that there are sufficient numbers of participants in both communities so that a meaningful statistical test can be constructed to allow comparisons between two communities. This is referred to as a two-sample test.

6.1.1 Power calculations for the health questionnaire

Power was calculated based on the primary objective of the study which is to characterize the current health of residents in Port Colborne using a comprehensive health assessment questionnaire and medical testing. As mentioned previously, a stratified sampling strategy will be applied to recruit individuals from five geographical areas. The sample size of the Health questionnaire and medical tests was calculated by determining the number of individuals needed to measure the prevalence of selected health conditions with sufficient precision both within the Rodney Street Area, and the remainder of Port Colborne. Specifically, the sample size of 1,000 was selected to ensure that a 5% prevalence of asthma could be measured within an accuracy of 2% 16 times out of 20, and that the prevalence of nickel sensitivity estimated at 9.5% among women could be measured within 7% and 13% 16 times out of 20 (see Table 1 below).

Table 1: Sample Size Needed to Compare Disease Prevalence Rates (Proportions)

Health Condition	Anticipated Prevalence	Prevalence Range Permitted**	Subjects needed in Area 3	Subjects needed in remainder of Port Colborne	Minimally detectable Odds Ratio*
Asthma	5%	4-6%	418	777	2.0
Asthma	5%	3-7%	160	193	3.2
Asthma	5%	4.5%-5.5%	699	2662	1.7
Cancer	0.5%	0.4-0.6%	811	5630	3.4
Nickel Sensitivity (females)	9.5%	8%-11%	370	607	1.8
Nickel Sensitivity (females)	9.5%	7%-13%	181	223	2.4

* Comparison of prevalence of disease between Area 3 and the rest of Port Colborne
**with Power of 80% and an alpha error of 5%

Assuming that there is a response rate of 65%, and that 50% of residents in the region are female, there will be 234 female participants in the Rodney Street area and a remaining 251 female subjects in the rest of Port Colborne. This will enable nickel sensitivity to be measured with sufficient precision as outlined in the table above. Moreover, when supplemented with data obtained from males, there will be sufficient precision to measure the prevalence of asthma within an accuracy of 2% in both sexes (see Table 1). It is important to note that due to the rarity of cancer, the health questionnaire is unable to measure the prevalence of cancer in Port Colborne with sufficient precision. The evaluation of this health outcome will be addressed in a subsequent research protocol.

The estimated number of dwellings and individuals that make up the target population are listed in Table 1. This list is considered approximate as it is based on Canadian census data obtained in 1996.

Table 2: Estimated Number of Households and Individuals 12 years of Age and Older* within Each Sampling Region for the health questionnaire.

Region (EA's)	Number of private dwellings	Estimated population 12 years of age and older
1- West of the Welland Canal, south of Clarence and Augustine Road (151-156)	1,945	4,055
2- West of the Welland Canal, north of Clarence (116-120)	2,260	4,798
3- East of the Canal, south of Durham (includes Durham) and is bounded by Davis and Lake (110)	365	719
4 - East of the Canal, north of Durham (excludes Durham) and is bounded by Snider Road (106,108)	775	2,346
5- Other areas of Port Colborne (101-105,107,109,112-113)	2,030	4,437
Total	7,375	16,355

* assumes that 85% of the Port Colborne community is 12 years of age and older (based on 1996 Census data from Statistics Canada).

It is very important to note that while there are sufficient numbers to measure the prevalence of the selected health conditions with the desired precision, there is limited power to make comparisons between rates in the Rodney Street area to the remainder of Port Colborne. Specifically, with 500 subjects recruited in both the Rodney Street area and other parts of Port Colborne, the study has the power to detect an odds ratio of 2.1 for the comparison of asthma rates between the two regions with a power of 80% and a type I error rate of 5%. The odds ratio of 2.1 corresponds to a greater than two-fold increased prevalence rate in area 3 relative to the rest of Port Colborne. Similarly, for a comparison of nickel sensitivity rates in females between the two regions, there is power to detect an odds ratio of 2.2.

6.2 Outcome measures

6.2.1 Health questionnaire

The CHAP health questionnaire provides self-reported data within five categories: demographics, exposure, health related quality-of-life, current medical health status, and mental health.

6.2.1.1 Demographics

The demographic information collected will include: date of birth (from which age can be calculated), sex, race, height and weight (from which body mass index can be calculated), household size, marital status, education, and income. This information will be used to adjust the data if the sample distribution is different than that of the real or true distribution in the population. Thus, it is important in assessing whether a representative sample has been drawn. This data can also be used to adjust for differences when comparing to provincial or normative data.

6.2.1.2 Exposure

The exposure information collected falls into five categories: residential, occupational, lifestyle/dietary, educational, and other exposure. The residential information will include address, period of stay, type of dwelling, and age of residence. From this, information on the number of years of residency in Port Colborne can be calculated. There is a child specific section that collects information on children who have had more than one permanent address. Residential information will also be used to assign exposure to CoCs

into two categories. Specifically, exposed which equates to the Rodney Street area versus non-exposed which equates to all other geographical locations within Port Colborne. Occupational exposure is assessed for specific high exposure industries. Details are collected for job description, activity, and duration of employment. Lifestyle/dietary exposure includes information collected on the source of drinking water, gardening, high exposure non-occupational hobbies, smoking, second-hand smoke, and alcohol consumption. Education exposure is specific to children; the questionnaire is designed to collect information about schools attended and the duration of attendance. Other exposure information collected includes data on jewellery that pierces the skin.

6.2.1.3 Health related QoL measure

Quality-of-life will be assessed using the Health Related Quality-of-Life Measure developed by the Centre for Disease Control and Prevention (CDC). There are four questions in this tool that measure self-perceived health, recent physical and mental health, and recent activity limitation (Ôunpuu et al., 2000). Although the SF-36 will be used in the gHQ, it's application in the health questionnaire and medical testing study is considered onerous given the amount of additional information being collected.

6.2.1.4 Current medical health status

The current medical health status section covers symptomatology, the presence and duration of disease, and information on drug use. Types of diseases assessed fall under categories such as respiratory, upper airway, skin, cardiovascular, thyroid, gastro-

intestinal/liver, neurological, and reproductive health. A question will also be asked about multiple chemical sensitivities.

6.2.1.5 Mental health

Mental Health will be assessed using the Bradburn Affect Balance Scale, a measurement tool that has been used by Statistics Canada in the Canadian Community Health Survey. There are eleven questions in this assessment tool for which their categorical responses will be summarized independently.

6.2.2 Medical tests

In addition to the health questionnaire-related measures described above, current health status will also be assessed using a number of medical test-related outcome measures. These measures will be described for the general medical laboratory screen tests, metal tests, and non-specimen related tests and data points.

6.2.2.1 General medical laboratory screen tests

The general medical laboratory screen tests will include a number of measures that are based on the collection of blood and urine. Blood-based measures will include both haematology measures and biochemistry measures. Haematology outcome measures will provide concentrations, counts and volumes for blood-based parameters. Biochemistry outcome measures will include concentrations of total billirubin, creatinine, blood urea nitrogen, cotinine, TSH and fT4. Urinalysis outcome measures will include presence of blood, leukocytes, protein, and glucose as well as nitrate concentrations and pH levels.

These measures will be expressed both in terms of mean values and within reference range frequency counts. Where the distribution of measured values are found to be non-normal, median values will be presented rather than means.

6.2.2.2 Metal tests

The metal tests will assess levels of CoCs in blood or urine. Specifically, the mean specimen levels of nickel, copper, cobalt, and fractionated and non-fractionated arsenic will be evaluated. Three metal confounders will also be measured: mercury, lead and cadmium. Again, these measures will be expressed both as mean (or median) values and within reference range frequency counts.

6.2.2.3 Non-specimen related tests and data points

This battery of medical tests and assessments will include cardiovascular, respiratory, dermatology and general measures. Cardiovascular measures will be obtained via ECG and blood pressure tests. ECG tests are designed to exclude abnormal results across a number of different parameters and will include: sinus rhythm, QRS axis, P waves, PR interval, QRS complex, QT interval, ST segment, T wave and U wave. Blood pressure will also be assessed and abnormal results will be summarized in terms of frequency counts. Respiratory measures will include a breath CO test and a lung function test. Breath CO concentrations will be expressed in terms of whether they are above or below a smoking abstinence threshold value (this will be further validated using a cotinine plasma test). Outcome measures from the lung function test will include FEV1, FVC, and PEFR. Finally, general measures will include height and weight to determine body

mass index that will aid in interpreting test results. Both means and frequency values will be used to represent these data.

6.3 Comparator strategy

Many standardized questions were used in the development of the health questionnaire. Sources of these questions included the CCHS, the HRQOL-4, and work done by Smith-Sivertsen et al. (2000). The benefit of using standardized tests is that there exists data that has been previously collected for which comparisons can be made.

6.3.1 CCHS Data

The Canadian Community Health Survey is an instrument used by Statistics Canada to collect health data at both the health region and province/territory levels. The survey targets persons 12 years or older, living in private dwellings in 10 provinces and 3 territories. Exclusions include persons in institutions, persons living on Indian Reserves or Crown lands, full-time members of the Canadian Armed Forces and residents of remote regions. The CCHS takes a representative sample of approximately 98% of the Canadian population aged 12 and older (over 130,000 nationwide, approximately 30,000 in the province of Ontario). The data is currently available for the content of the September 2000 version, and comparisons will be made to that data for Ontario.

6.3.2 HRQOL-4 Literature

The HRQOL-4 was developed by the Centers for Disease Control and Prevention (CDC). In addition to the reference data available on U.S. citizens, a recent study performed in

Ontario provides data on 1, 042 individuals that was collected in a community-based study (Ôunpuu et al., 2000).

6.3.3 Smith-Sivertsen et al. (2000) Work

Smith-Sivertsen et al. (2000) published work in which they assessed the symptoms reported by 3,729 individuals, 18-69 years of age, who were exposed to occupational pollutants.

6.3.4 Reference Values and Population Normal Data

There are very few questions in the health questionnaire that do not come from standardized questionnaires. In these instances, prevalence data from published literature will be used to assess the data collected in this study.

With respect to laboratory and clinical data, standard reference ranges supplied by the laboratory (see Appendices 11.4 and 11.5) and standard clinical practice guidelines will be used to describe these outcomes.

6.4 Statistical Analysis

The frequency distributions of variables collected within the health questionnaire and medical tests will be tabulated. The number of missing responses for each variable will be presented, and where possible, these missing values will be treated as a separate category. Particular attention will be given to examining response rates for income levels, since this variable will be used as a proxy to socioeconomic status. If necessary, other factors, such as education, may need to be used instead.

Prevalence rates for health conditions will be calculated by age-group for males and females. Statistically significant differences across strata will be evaluated by using the Chi-Square and likelihood ratio tests for categorical data, and the Student's t-test for continuous data. Multivariate analysis of variance will be used to adjust comparisons for the influence of potential confounding variables. Comparisons will need to take into account possible differences in the age and sex structure of the populations being compared. Of particular interest will be the comparison of Area 3 (otherwise known as the Rodney Street area) to the rest of Port Colborne. Comparisons will also be made to reference data for Ontario or other normative data.

To evaluate the potential influence for response bias, where possible, socio-economic characteristics will be compared between non-respondents and participants. These variables will include: age, sex, family size, income level, and neighborhood of residence. Statistical tests of significance will be performed to determine whether non-responders differed from those who participated in the survey. Response bias will also be examined by comparing survey results obtained from the 1996 Canadian census data.

The prevalence of selected health characteristics will be compared to responses obtained from participants of the 2000 CCHS. In order to control for differences in the underlying populations, direct standardization will adjust for the age and gender make-up of the populations being compared. The ratio of these standardized rates will be calculated, and

95% confidence intervals of this ratio will be used to assess statistically significant differences.

Univariate statistics will be calculated for each chemical, as determined by laboratory analysis, to summarize the levels of the CoCs. These statistics will include: the mean, median, range, standard deviation and upper and lower percentiles. Tests for normality will be conducted to determine whether transformations of the CoCs values may be necessary for some multivariate modeling procedures. Variations in exposure levels within Port Colborne will be explored by calculating these summary statistics separately across different areas within the city. Differences across regions will be evaluated using multivariate regression analyses. Lognormal transformations are frequently applied to exposure distributions that are skewed. For CoCs with a large number of non-detectable levels, logistic regression analysis will be used to model those with exposure above the median CoCs level, relative to those with exposure below the median value.

Logistic regression methods will be used to evaluate the relationship between exposure to CoCs and selected health conditions. Because exposure to CoCs has been measured using two instruments (i.e., biological specimens and health questionnaire items), logistic regression analysis will be performed using these two series of independent variables. Pearson correlations coefficients and categorical analyses will be used to examine the concordance between the exposure measures from the laboratory and the summary measure estimated from the questionnaire.

The logistic regression model will provide a parameter estimate that can be readily transformed into an odds ratio. This odds ratio provides a measure of risk that can be used to determine whether those with high levels of exposure to CoCs are more likely to have a specified health condition. Survey participants will be categorized into tertiles based on their clinical exposure measurements and into binary groups based on the answers they give to the exposure question in the health questionnaire. Risk estimates will be calculated by comparing the prevalence of disease among those in the highest tertile of exposure to those in the lowest and for those indicating exposure in their answers to the questionnaire versus no exposure. The 95% confidence intervals for these odds ratios will also be calculated. This confidence interval can be used to determine whether or not the association may be due to chance. These estimates of risk will be adjusted for the potential confounding influence of other relevant variables, such as age, sex, smoking habits, alcohol use, and indicators of socio-economic status. All statistical analyses will be conducted by using SAS. The fit of the model will be assessed by using the Hosmer-Lemeshow goodness of fit statistic.

Multivariate analysis of variance will be used to compare laboratory measures of CoCs taken in Port Colborne residents to a normative sample. These multivariate models will be adjusted by age and sex of the subjects. Differences between the two populations will be evaluated by using the F-test statistics generated from the ANOVA model. Where necessary, measured levels of CoCs will be transformed in order to ensure that assumptions of normality are satisfied. If this assumption cannot be met through a

transformation, than non-parametric methods (e.g., Wilcoxon Rank Sum test) will be considered.

6.5 Results

The results proposed in the statistical analysis section will be summarized with the use of mock tables.

6.5.1 Mock Tables

Table 1.
Response Rates, by Sampling Areas,

CHAP Comprehensive Health Questionnaire, Fall 2002

Total Number of Randomly Selected Households
Total Number of Questionnaire Refusals
Refusals from Area 1
Refusals from Area 2
Refusals from Area 3
Refusals from Area 4
Refusals from Area 5
Overall Questionnaire Response Rate
Total Number of Biological Testing Refusals
Refusals from Area 1
Refusals from Area 2
Refusals from Area 3
Refusals from Area 4
Refusals from Area 5
Overall Biological Testing Response Rate

Table 2.
Demographic Characteristics of Participants, by Sampling Areas, Compared to Census Data
CHAP Comprehensive Health Questionnaire, Fall 2002

Characteristic	Area 3	1996 Census Data for Area 3	Areas 1, 2, 4, 5	1996 Census Data for Areas 1, 2, 4, 5
	N (%)	N (%)	N (%)	N (%)
Sex				
Female				
Male				
Age				
0 – 14				
15 - 19				
20 - 24				
25 - 54				
55 - 64				
65 - 74				
≥ 75				
Mean				
Mean Household Size				
Household Income				
< $20 000				
$20 000 to less than 40 000				
$40 000 to less than 60 000				
$60 000 to less than 80 000				
≥ $ 80 000				
Education				
Less than high school				
High School				
Post Secondary				
Ethnic Background				
Caucasian				
Oriental				
Native				
Other				
Marital Status				
Married/Common-law				
Single				
Divorced/Separated				
Widowed				

categorized by standard thresholds

Table 3.
Demographic Characteristics of Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

Characteristic	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	N (%)	N (%)	N (%)	
Sex				
Female				
Male				
Age				
0 – 14				
15 - 19				
20 - 24				
25 - 54				
55 - 64				
65 - 74				
≥ 75				
Mean				
BMI				
Underweight[‡]				
Average[‡]				
Overweight[‡]				
Obese[‡]				
Mean				
Mean Household Size				
Household Income				
< $20 000				
$20 000 to less than 40 000				
$40 000 to less than 60 000				
$60 000 to less than 80 000				
≥ $ 80 000				
Education				
Less than high school				
High School				
Post Secondary				
Ethnic Background				
Caucasian				
Oriental				
Native				
Other				
Marital Status				
Married/Common-law				
Single				
Divorced/Separated				
Widowed				
Years lived in Port Colborne				
< 5				
5 - <10				
10 - <20				
20+				

[†] p-value is based on Chi-square for comparison of proportions, likelihood ratio test for categorical variables and t-test for comparison of means.
[‡] categorized by standard thresholds

Table 4.
Lifestyle and Dietary Information of Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	N (%)	N (%)	N (%)	
Occupation related to Exposure [*]				
Yes				
No				
Primary Source of Drinking Water				
Municipal				
Well				
Bottled				
Gardening Activity				
Yes				
No				
Non-occupational Activities related to Exposure to CoCs [**]				
Yes				
No				
Cigarette smoking status				
Never				
Current				
Former				
Unknown				
Exposure to second-hand Smoke				
Never				
As a child only				
As an adult only				
As a child and adult				
Current alcohol consumption				
Less than once a month				
1 To 3 times a month				
4 to 12 times a month				
> 12 times a month				
Jewelry piercings				
Yes				
No				

[*] Includes the following occupations: mining; metal cutting, grinding and refining; smelting; foundry work; steel making; welding; plumbing; brazing; plumbing; shipbuilding; metal plating or electroplating; boiler maker/repairer

[**] Includes painting, renovations, landscaping and automotive work

[†] p-value is based on Chi-square for comparison of proportions.

Table 5.
Prevalence of Selected Health Conditions of Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	N (%)	N (%)	N (%)	
Chronic Bronchitis				
Emphysema / Chronic Obstructive Pulmonary Disease				
Other Allergies				
Asthma				
Hypertension				
Heart Disease				
Thyroid Condition				
Stomach / Intestinal Ulcers				
Gastroenteritis				
Peripheral Neuropathy				
Arthritis				
Parkinson's				

[†] p-value is based on Chi-square for comparison of rates from Area 3 to Areas 1, 2, 4, and 5 after adjustment for differences in the age and sex distribution of the two populations.

Table 6.
External Comparison of Selected Health Conditions of Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Port Colborne Prevalence	Ontario Prevalence	p-value[†]
Chronic Bronchitis			
Emphysema / Chronic Obstructive Pulmonary Disease			
Food Allergies			
Other Allergies			
Asthma			
Dermatitis			
High Blood Pressure			
Heart Disease			
Anaemia			
Thyroid Condition			
Stomach / Intestinal Ulcers			
Gastroenteritis			
Jaundice			
Parkinson's Disease			
Peripheral Neuropathy			
Parkinson's			

[†] p-value is based on Chi-square statistic of rates after direct standardization by age and sex. .

Table 7.
Comparison of the Mean Levels of Selected Biological Measures, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value†
	Mean (s.d)*	Mean (s.d)	Mean (s.d)*	
Haemoglobin				
White Blood Cell Count				
Red Blood Cell Count				
Haematocrit				
Mean Cell Volume of Red Cells				
Mean Heamoglobin Concentration of Red Cells				
Platelet Count				
Red Cell Distribution Width				
Mean Platelet Volume				
Differential Leukocyte Count				
Bilirubin				
Creatinine				
Plasma Cotinine				
Plasma Screen for Concentration of TSH				
Blood Urea Nitrogen				

† p-value is based on an ANOVA for comparing the means between Area 3, and Areas 1, 2, 4, and 5; after adjusting for difference in the age and sex distribution of the two populations.
* s.d. = standard deviation

Table 8.
Comparison of the Non-Specimen Tests Among Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	Mean (s.d)[*]	Mean (s.d)	Mean (s.d.)	
Calculated BMI				
Electrocardiogram	---	---	---	---
Blood Pressure				
Carbon Monoxide Breath Test				
Forced Expiratory Volume in 1 second				
Forced Vital Capacity				
Peak Expiratory Flow Rate				
Dermatology Patch: Nickel Sulfate				
Dermatology Patch: Cobalt Dichloride				

[†] p-value is based on an ANOVA for comparing the means between Area 3, and Areas 1, 2, 4, and 5; after adjusting for difference in the age and sex distribution of the two populations.
[*] s.d. = standard deviation

Table 9.
Comparison of the Selected Measures of Chemicals Among Participants, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
Chemical	Mean (s.d)[*]	Mean (s.d)	Mean (s.d)	
Nickel (Urine)				
Copper (Urine)				
Cobalt (Urine)				
Arsenic (Urine)				
Mercury (Urine)				
Lead (Blood)				

[†] p-value is based on an ANOVA for comparing the means between Area 3, and Areas 1, 2, 4, and 5; after adjusting for difference in the age and sex distribution of the two populations.
[*] s.d. = standard deviation

Table 10.
Comparison of the Proportion of Tests Outside Normal Range for Selected Biological Measures,
by Sampling Areas,
CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value†
	Proportion Outside Normal Range			
Haemoglobin (normal range)				
White Blood Cell Count (normal range)				
Red Blood Cell Count (normal range)				
Haematocrit (normal range)				
Mean Cell Volume of Red Cells (normal range)				
Mean Heamoglobin Concentration of Red Cells (normal range)				
Platelet Count (normal range)				
Red Cell Distribution Width (normal range)				
Mean Platelet Volume (normal range)				
Differential Leukocyte Count (normal range)				
Bilirubin (normal range)				
Creatinine (normal range)				
Plasma Cotinine (normal range)				
Plasma Screen for Concentration of TSH (normal range)				
Blood Urea Nitrogen (normal range)				

† p-value is based on logistic regression analysis controlling for differences in the age and sex distribution of the two sampling areas

Table 11.
Comparison of the Proportion of Non-specimen Tests Outside Normal Range, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	Proportion Outside Normal Range			
Calculated BMI (average range)				
Electrocardiogram[‡]				
Blood Pressure (normal range)				
Carbon Monoxide Breath Test (normal range)				
Forced Expiratory Volume in 1 second (normal range)				
Forced Vital Capacity (normal range)				
Peak Expiratory Flow Rate (normal range				
Dermatology Patch: Nickel Sulfate (normal range)				
Dermatology Patch: Cobalt Dichloride (normal range)				

[†] p-value is based on logistic regression analysis controlling for differences in the age and sex distribution of the two sampling areas

[‡] proportion with abnormal electrocardiogram

Table 12.
Comparison of the Proportion of Chemical Measures Outside Normal Range, by Sampling Areas, CHAP Comprehensive Health Questionnaire, Fall 2002

	Area 3	Areas 1, 2, 4, 5	Total for Port Colborne	p-value[†]
	Proportion Outside Normal Range			
Nickel (Urine) (normal range)				
Copper (Urine) (normal range)				
Cobalt (Urine) (normal range)				
Arsenic (Urine) (normal range)				
Mercury (Urine) (normal range)				
Lead (Blood) (normal range)				

[†] p-value is based on logistic regression analysis controlling for differences in the age and sex distribution of the two sampling areas.

7.0 Participant Compensation

It is anticipated that subjects will be compensated for their time for participating in all phases of CHAP – completion of the health questionnaire and medical testing. It is proposed that the compensation level be $35.00, payable upon completion of all study procedures.

8.0 Publication Policy

The study Investigator(s) has the right to publish, present or otherwise disclose his/her findings in the scientific literature with respect to data generated by the Investigator(s) from the study, subject to the following criteria:

- All final draft manuscripts, based on whole or in part on the study, must undergo a review and be approved by a Publication Steering Committee (PSC), implemented in conjunction with the community.
- Submission to the PSC for review must occur at least 60 days prior to submission by the Investigator(s) of such manuscript for publication.
- No less than 12 months must elapse following completion of the final study report before submission for publication.
- Should the PSC determine the manuscript discloses confidential or proprietary information, the Investigator(s) will either remove it or modify the manuscript to the satisfaction of the PSC, so that publication of the revised manuscript may proceed.
- Should the PSC determine the manuscript discloses any discovery, invention, or other intellectual property, which the PSC wishes to protect, whether by preparing any patent or other intellectual property applications or otherwise, the Investigator(s) will, upon request by the PSC, delay submission for a period not exceeding four months from the date the PSC receives such manuscript from the Investigator(s).
- Restrictions may be imposed on where to publish, subject to discussion with the PSC.

9.0 References

Abernathy, C. Non-carcinogenic effects of inorganic arsenate. *Environ Geochem Health* (1992) 14:35-41.

Aposhian, H. Biochemical toxicology of arsenic. *Rev Biochem Toxicol* (1989) 10:265-299.

ATSDR, Agency for Toxic Substances and Disease Registry: Toxicological Profiles. 1997

Bahiga, L.M., N.A. Kotb, and E.A. El-Dessoukey. Neurological syndromes produced by some toxic metals encountered industrially or environmentally. *Zernahrungswiss* (1978) 17(2):84-88.

Barceloux, D. Nickel. J Toxicol Clin Toxicol (1999a) 37(2):239-258.

Bartal M. Health effects of tobacco use and exposure. *Monaldi Arch Chest Dis* (2001) Dec;56(6):545-54.

Baselt RC. *Disposition of Toxic Drugs and Chemical in Man. 5th edition.* Chemical Toxicology Institute, 2000.

Berny C, Boyer JC, Capolaghi B, L'Homme GD, Desch G, Garelik D, Hayder R, Houdret N, Jacob N, Koskas T, Laine G, Moel GL, Moulsma M, Plantin-Carrenard E, Venembre P. Biomarkers of tobacco smoke exposure. *Ann Biol Clin*, Paris (2002) May 60(3): 263-272.

Bolla-Wilson, K. and M.L. Bleeker. Neuropsychological impairment following inorganic arsenic exposure. *J Occup Med* (1987) 29(6):500-503.

Bradburn, Norman M. *The Structure of Psychological Well-Being.* Chicago: Aldine Pub. Co., 1969.

Chashschin, V., G. Artunina, and T. Norseth. Congenital defects, abortion and other health effects in nickel refinery workers. *Sci Total Environ* (1994) 148(2-3):287-291.

Christensen, O.B. Nickel dermatitis. An update. *Dermatol Clin* (1990) 8(1):37-40.

Clarkson, T.W. The toxicology of mercury. *Crit Rev Clin Lab Sci.* (1977) 34:369-403.

Cornell, R. and J. Landis. Mortality patterns among nickel/chromium alloy foundry workers. *IARC Sci Publ* (1984) 53:87-93.

Cugell, D., W. Morgan, D. Perkins, et al. The respiratory effects of cobalt. *Arch Intern Med* (1990) 50(1):177-183.

Ford, M., *Arsenic,* in *Goldfrank's Toxicologic Emergencies,* L. Goldfrank, et al., Editors. Stamford: Appleton and Lange, 1998.

Harden, R.M., M. Stevenson, W.W. Downie, G.M. Wilson. Assessment of clinical competence using objective structured examinations. *BMJ* (1975) 1:447-451.

Hodges, B., J. Turnbull, R. Cohen, A. Bienstock, G. Norman. Evaluating communication skills in the OSCE format: reliability and generalizability. *Medical Education* (1996) 30:38-43.

Jasmin and Solymoss, 1975

JWEL Study: Draft report on potential CoCs identification using soil chemical concentration data in exceedance of MOE generic guidelines. Port Colborne, Ontario: JWEL, 2001.

Kelsey

Kempen, G.I. Psychometric properties of Bradburn's Affect Balance Scale among elderly persons. *Psychological Reports* (1992) 70:638.

Lee, A. and J. JF Fraumeni. Arsenic and respiratory cancer in man: An occupational study." *J Natl Cancer Inst* (1969) 42:1045-1052.

Lilienfeld, A.M. and P.D. Stolley

Malo, J.L., A. Cartier, M. Doepner, et al. Occupational asthma caused by nickel sulfate. *J All Clin Immunol* (1982) 69:55-59.

Marks, J.G., D.V. Belsito, V.A. DeLeo, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* (1998) 38(6 Pt 1):911-918.

Marks, J.G., D.V. Belsito, V.A. DeLeo, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* (1999) 40(5 Pt 1):726-735.

Marks, J.G., D.V. Belsito, V.A. DeLeo, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* (2000) 136:272-273.

Marks, J.G., D.V. Belsito, V.A. DeLeo, et al. North American Contact Dermatitis Group patch test results for the detection of delayed-type hypersensitivity to topical allergens. *J Am Acad Dermatol* (2001) 44:218-223.

McDowell, I., Praught, E. On the measurement of happiness: an examination of the Bradburn scale in the Canada Health Survey. *American Journal of Epidemiology* (1982) (116.6):949-958.

Menne, T. and E. Nieboer. Metal contact dermatitis: A common and potentially debilitating disease. *Endeavour* (1989) 13(3):117-122.

Middleton E.T., Morice A.H. Breath carbon monoxide as an indication of smoking habit. *Chest* (2000) Mar;117(3):758-63

Moffat, S, T.P. Mulloli, R. Bhopal, C. Foy, P. Phillimore. An exploration of awareness bias in two environmental epidemiology studies. *Epidemiology* (2000) 11:199-208.

Needleman, H.L., A. Schell, D. Bellinger, A. Leviton, E.N. Allred. The longterm effects of exposure to low doses of lead in childhood: An 11-year follow-up report. *New England Journal of Medicine* (1990) 322:83-88.

Newschaffer, C. Validation of Bahavioral Risk Factor Surveillance System (BRFSS) *HRQOL measures in a statewide sample*. Atlanta: CDC, 1998.

Nielsen, N.H. and T. Menne. Nickel sensitization and ear piercing in an unselected Danish population: Glostrup Allergy Study. *Contact Dermatitis* (1993) 29(1):16-21.

Ôunpuu, S., L. Chambers, D. Chan, et al. Validity of the U.S. Behavior Risk Factor Surveillance System's health related quality of life survey tool in a group of older Candians. *Chronic Dis Can* (2001) 22(3-4):93-101.

Ôunpuu, S., P. Krueger, M. Vermeulen, et al. Using the U.S. Behavior Risk Factor Surveillance System's health related quality of life survey tool in a Canadian city. *Can J Public Health* (2000) 91(1):67-72.

Pandey, R., R. Kumar, S. Singh, et al. Male reproductive effects of nickel sulphate in mice. *Biometals* (1999) 12:339-346.

Peltonen, L. Nickel sensitivity in the general population. *Contact Dermatitis* (1979) 5(1):27-32.

Philip, A.T. and B. Gerson. Lead Poisoning Part II- Effects and Assay. *Clin Lab Med* (1994) 14:651-70.

Prescott, E., B. Netterstrom, J. Faber, et al. Effect of occupational exposure to cobalt blue dyes on the thyroid volume and function in female plate painters. *Scan J Work Environ Health* (1992) 18(2):101-104.

Rothman, A.I., and M. Cusimano. Assessment of english proficiency in international medical graduates by physician examiners and standardized patients. medical education (2001) 35:1-3.

Rothman, A.I., and M. Cusimano. A comparison of physician examiners', standardized patients', and communication experts' ratings of international medical graduates' english proficiency. *Academic Medicine* (2000) 75:1206-1211.

Rothman and Greenland, 2000

Schafer, T., E. Bohler, S. Ruhdorfer, et al. Epidemiology of contact allergy in adults. *Allergy* (2001)56(12):1192-1196.

Schoolmeester, W.L. and D.R. White. Arsenic poisoning. *South Med J* (1980) 73(2):198-208.

Schubert, H.J. Nickel dermatitis in medical workers. *Dermatol Clin* (1990) 8(1):45-47.

Shah, M., F. Lewis, and D. Gawkrodger. Nickel as an occupational allergen: A survey of 368 nickel sensitive subjects. *Arch Dermatol* (1998) 134(10): 1231-1236.

Smith, A., C. Hopenhayn-Rich, M. Bates, et al. Cancer risks from arsenic in drinking water. *Environ Health Perspect* (1992) 97: 259-67.

Smith-Sivertsen, T., L.K. Dotterrud, and E. Lund. Nickel allergy and its relationship with local nickel pollution, ear piercing, and atopic dermatitis: A population-based study from Norway. *J Am Acad Dermatol* (1999) 40(5 Pt 1): 726-735.

Smith-Sivertsen, T., L.V. Tchachtchine, and E. Lund. Environmental nickel pollution: Does it protect against nickel allergy? *J Am Acad Dermatol* (2002) 46(3): 460-462.

Smith-Sivertsen, T., L.V. Tchachtchine, and E. Lund. Self-reported airway symptoms in a population exposed to heavy industrial pollution: What is the role of public awareness? *Epidemiology* (2000) Nov, 11(6): 739-740.

Sopori, M. Effects of cigarette smoke on the immune system. *Nature Rev Immunol* (2002) May;2(5):372-7

Stacey, C.A., M. Gatz. Cross-sectional age differences and longitudinal change on the Bradburn Affect Balance Scale. *Journal of Gerontology*, (1991) 46(2): 76-78

Sue, Y-J. "Mercury." in *Goldfrank's Toxicologic Emergencies, 7th ed.* L. Goldfrank, et al., Editors. New York: McGraw-Hill, 2002.

Sunderman, F., S. Shen, M. Reid, et al. Teratogenicity and embryotoxicity of nickel carbonyl in Syrian hamsters. *Teratog Carinog Mutagen* (1980) 1(2): 223-233.

Tengs T.O., N.D. Osgood. The link between smoking and impotence: two decades of evidence. *Prev Med* (2001) Jun;32(6):447-52.

10.0 Appendices

The appendices outlined below appear on the following pages:

10.1 Health questionnaire

10.2 Consent

10.2.1 Adult Consent Form/Information Sheet

10.2.2 Adolescent Assent Form/Information Sheet

10.2.3 Parental or Guardian Consent Form/Information Sheet

10.3 Instruction to Subjects

10.3.1 General Instructions Prior to Visit 1

10.3.2 Instructions Prior to Visit 1, Specific to T.R.U.E. (Thin-layer Rapid Use Epicutaneous Test)

10.3.3 Instructions Specific to T.R.U.E., Given Post-Application, before Subject Departs

Appendix 10.1: Health Questionnaire

CHAP Health Questionnaire

📂 indicates that the questions were derived from the HRQOL-4
📂 indicates that the questions were derived from the 2000 CCHS
📂 indicates that the questions were derived from the Smith-Sivertsen paper
ADULT indicates adult specific
CHILD indicates child specific

The following information will be kept strictly confidential. **Any information that can identify you or your family will be replaced with a unique number (as viewed at the top of this page). This identifying information will be kept separately and under restricted access.**

Last Name: 📂 _____

First Name: 📂 _____

Middle Name: _____

Current or Former Resident: **Current / Former**

Number of People in your Household: _____

ALL MEMBERS OF HOUSEHOLD (12+) ARE TO ANSWER THE FOLLOWING QUESTIONS. SOME QUESTIONS MAY NOT APPLY (CHILD OR ADULT SPECIFIC).

Demographic Information

1. What is your date of birth? DD/MM/YYYY

2. Please indicate your sex:
   Male
   Female

3. People living in Canada come from many different cultural and racial backgrounds. Are you:

INTERVIEWER: Read categories to respondent. Mark all that apply.

1 …White?
2 …Chinese?
3 …South Asian (e.g., East Indian, Pakistani, Sri Lankan, etc.)?
4 …Black?
5 …Filipino?
6 …Latin American?
7 …Southeast Asian (e.g., Cambodian, Indonesian, Laotian, Vietnamese, etc.)?
8 …Arab?
9 …West Asian (e.g., Afghan, Iranian, etc.)?
10 …Japanese?
11 …Korean?
12 …Aboriginal Peoples of North America (North American Indian, Métis, Inuit / Eskimo)?
13 Other – Specify

4. How tall are you without shoes on? (offer both ways of measuring, want metres)

5. How much do you weigh? (offer both ways of measuring, want kg)

6. Do you consider yourself:
   overweight?
   underweight?
   just about right?

7. What is your current marital status? ADULT
   Married
   Living Common-law
   Widowed
   Separated
   Divorced
   Single (never married)

8. Highest grade of elementary or high school completed:
   ___ Grade 8 or lower (Quebec: Secondary II or lower)
   ___ Grade 9 – 10 (Quebec: Secondary III or IV; Newfoundland: 1st year of secondary)
   ___ Grade 11 – 13 (Quebec: Secondary V; Newfoundland: 2nd to 4th year of secondary)

9. Highest degree, certificate or diploma: ADULT
   ___ No postsecondary degree, certificate or diploma
   ___ Trades certificate or diploma from a vocational school or apprenticeship training
   ___ Non-university certificate or diploma from a community college, CEGEP, school of nursing, etc.
   ___ University certificate below bachelor's level
   ___ Bachelor's degree
   ___ University certificate or diploma above bachelor's degree

10. Can you estimate in which of the following groups your household income falls? 

ADULT

Was the total household income …

___ Less than $20, 000?

___ Less than $10, 000?

___ Less than $5, 000?

___ $5, 000 or more?

___ $10, 000 or more?

___ Less than $15, 000?

___ $15, 000 or more?

___ $20, 000 or more?

___ Less than $40, 000?

___ Less than $30, 000?

___ $30, 000 or more?

___ $40, 000 or more?

___ Less than $50, 000?

___ $50, 000 to less than $60, 000?

___ $60, 000 to less than $80,000?

___ $80, 000 or more?

___ No Income

Residential Information

11. Please fill in the following table for your current and all past residences in Port Colborne.

Address[1]	Period of Stay[2]		Type of Dwelling[3]	Age of Residence[4]
	From	To		

[1]Please indicate street address, city, province, country, and postal code.
[2]Please indicate from MM/YYYY to MM/YYYY.
[3]Please indicate one of the following:

Single Detached House
Semi-Detached or Double (side-by-side)
Garden House, Town-House or Row House
Duplex (one above the other)
Low-rise apartment (less than 5 stories)
High-rise apartment (5 or more stories)
Institution
Collective dwelling (such as a Hotel/Motel, Rooming or Boarding House)
Mobile home
Farm or Acreage
Other (please specify _____)

[4]Please indicate number of years.

12. If you have resided or are residing in more than one home concurrently, please fill in the following table: CHILD

Address	Percentage of Time Spent
#1	
#2	

Occupational Information

13. a) Do you now or have you ever worked in one of the following industries/occupations: Y/N ADULT.

b) If yes, please specify which industry/occupation:

1 - Underground mining
2 - Smelting
3 - Metal Refining
4 - Foundry work
5 - Steelmaking
6 - Metal Cutting and grinding
7 - Boiler maker/repairer
8 - Welding
9 - Brazing
10 - Sintering
11 - Plumbing
12 - Metal plating/electroplating
13 - Shipbuilding/breaking
14 - Lumberyard/Sawmill

14. If yes to question 13. a), please provide details of any employment that falls into one of the categories listed above.

	Job Description (employer, city, job title)	Job Activity	Duration of Employment (years, months)
1			
2			

Lifestyle/Dietary Information

15. What is your primary source of drinking water?

___ Municipal water
___ Well water
___ Bottled water

16. a) Do you have a garden, or participate in a community garden? Y/N ADULT

b) If yes, do you grow: ___ flowers
___ fruits
___ vegetables

17. How frequently do you engage in each of the following non-occupational hobbies or activities? ADULT SPECIFIC

a) painting*	Never, Rarely, Sometimes, Often
b) landscaping	Never, Rarely, Sometimes, Often
c) renovations	Never, Rarely, Sometimes, Often
d) automotive work	Never, Rarely, Sometimes, Often

* We are interested in paints that are known to contain metals, such as, older water-based paints (pre-1992 paint may contain mercury), older lead based paint, or hobby/artist paints (may contain metals).

18. Does anyone in this household smoke regularly inside the house?

Yes
No

19. At the present time do you smoke cigarettes daily, occasionally or not at all?

Daily (Go to Q20)
Occasionally (Go to Q22)
Not at all (Go to Q24)
DK, R (Go to Q30)

20. At what age did you begin to smoke cigarettes daily?

__ Age (MIN: 5) (MAX: current age) (Go to Q22)

21. How many cigarettes do you smoke each day now?

__ Number of cigarettes (MIN: 1) (MAX: 99) (Go to Q30)

22. On the days that you do smoke, about how many cigarettes do you usually have?

__ Number of Cigarettes (MIN: 1) (MAX: 99) (Go to Q23)

23. In the past month, on how many days have you smoked 1 or more cigarettes?

__ Number of Days (MIN: 0) (MAX: 30) (Go to Q24)

24. Have you ever smoked cigarettes daily?

Yes (Go to Q25)
No (Go to Q28)
DK, R (Go to Q28)

25. At what age did you begin to smoke (cigarettes) daily?

__ Age (MIN: 5) (MAX: current age) (Go to Q26)

26. How many cigarettes did you usually smoke each day?

__ Number of Cigarettes (MIN: 1) (MAX: 99) (Go to Q27)

27. When did you stop smoking daily? Was it:
… Less than one year ago? (Go to Q28)
… 1 to 2 years ago? (Go to Q28)
… 3 to 5 years ago? (Go to Q28)
… More than 5 years ago? (Go to Q28)
DK, R (Go to Q28)

If Q19 = (current daily or occasional smoker) or if Q19 = DK or R, go to Q30.

28. In the past month, were you exposed to second-hand smoke on most days?
Yes (Go to Q29)
No (Go to Q29)
DK, R (Go to Q30)

29. Does smoke from cigarettes cause you any physical irritation (for example, to your eyes, your breathing, your throat)?
Yes (Go to Q30)
No (Go to Q30)

When we use the word drink it means:
- one bottle or can of beer or a glass of draft
- one glass of wine or a wine cooler
- one drink or cocktail with 1 and a 1/2 ounces of liquor.

30. During the past 12 months, have you had a drink of beer, wine, liquor or any other alcoholic beverage? ADULT
Yes (Go to Q31)
No (Go to Q34)
DK, R (Go to Q36)

31. During the past 12 months, how often did you drink alcoholic beverages? (Go to Q32)
Less than once a month
Once a month
2 to 3 times a month
Once a week
2 to 3 times a week
4 to 6 times a week
Every day

32. How often in the past 12 months have you had 5 or more drinks on one occasion? (Go to Q33)
    Never
    Less than once a month
    Once a month
    2 to 3 times a month
    Once a week
    More than once a week

33. Thinking back over the past week, did you have a drink of beer, wine, liquor or any other alcoholic beverage? (Go to Q 36)
    Yes
    No
    DK, R

34. Have you ever had a drink?
    Yes (Go to Q 35)
    No (Go to Q36)
    DK, R (Go to Q36)

35. Did you ever regularly drink more than 12 drinks a week?
    Yes (Go to Q 36)
    No (Go to Q36)
    DK, R (Go to Q36)

Educational Information

36. Please fill in the following table regarding all of the schools you have attended in Port Colborne up to and including high school: CHILD

School Name	Town, Province	Duration of Stay at School (YYYY to YYYY)

Other Exposure Information

37. Do you wear, or have you ever worn jewelry that pierces the skin?
    Yes
    No
    Don't Know/Refused

38. How many individual piercings do you have?

____

39. Did you ever have a skin irritation that was relieved by removing the jewelry?

Yes
No
Don't Know/Refused

Health-Related Quality-of-Life Measure

1. Would you say that in general your health is:
    a. Excellent
    b. Very Good
    c. Good
    d. Fair, or
    e. Poor?

2. Recent Physical Health

Now thinking about your physical health, which includes physical illness and injury, for how many days during the past 30 days was your physical health not good?

_____ days

3. Recent Mental Health

Now thinking about your mental health, which includes stress, depression, and problems with emotions, for how many days during the past 30 days was your mental health not good?

_____ days

4. Recent Activity Limitation

During the past 30 days for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?

_____ days

Current Medical Health Status

"We'd like to ask about certain chronic health conditions which you may have. We are interested in 'long-term conditions' that have lasted or are expected to last 6 months or more and that have been diagnosed by a health professional."

Respiratory:

1. Do you usually cough or clear your throat in the morning?
   Yes
   No
   Don't Know, Refused

2. Do you cough on most days for at least 3 months of the year?
   Yes
   No
   Don't Know, Refused

3. Do you bring up phlegm on most days for at least 3 months of the year?
   Yes
   No
   Don't Know, Refused

4. Are you breathless when you climb two flights of stairs at an ordinary pace?
   Yes
   No
   Don't Know, Refused

5. Are you breathless when at rest?
   Yes
   No
   Don't Know, Refused

6. Do you have Chronic Bronchitis?
   Yes
   No (Go to Q8)
   Don't Know, Refused (Go to Q8)

7. How old were you when this was first diagnosed?
   ____ Age in years
   (MIN: 0) (MAX: current age)

8. Do you have Emphysema or Chronic Obstructive Pulmonary Disease?
   Yes
   No (Go to Q10)
   Don't Know, Refused (Go to Q10)

9. How old were you when this was first diagnosed?
   ____ Age in years
   (MIN: 0) (MAX: current age)

10. Do you have food allergies?
    Yes
    No (Go to Q12)
    Don't Know, Refused (Go to Q12)

11. How old were you when this was first diagnosed?
    _____ Age in years
    (MIN: 0) (MAX: current age)

12. Do you have any other allergies?
    Yes
    No (Go to Q14)
    Don't Know, Refused (Go to Q14)

13. How old were you when this was first diagnosed?
    _____ Age in years
    (MIN: 0) (MAX: current age)

14. Do you have asthma?
    Yes
    No (Go to Q17)
    Don't Know, Refused (Go to Q17)

15. Have you had any asthma symptoms or asthma attacks in the past 12 months?
    Yes
    No

16. In the past 12 months, have you taken any medicine for asthma such as, inhaler, nebulizers, pills, liquids, or injections?
    Yes
    No

Upper Airway

17. Do you have an upper airway condition?
    Yes
    No (Go to Q20)
    Don't Know, Refused (Go to Q20)

18. What type of upper airway condition do you have:
INTERVIEWER: Mark all that apply.

___ Sinusitis
___ Rhinitis
___ Nasal Polyps
___ Nasal Septal Ulceration
___ Other, Please specify

19. How old were you when this was first diagnosed?

_____ Age in years
(MIN: 0) (MAX: current age)

Skin:

20. Do you have a skin condition?

Yes
No (Go to Q23)
Don't Know, Refused (Go to Q23)

21. What type of skin condition do you have:
INTERVIEWER: Mark all that apply.

1 Dermatitis/eczema
2 Pigmentation change (skin darkening or lightening; "change in skin color")
3 Hyperkeratosis (skin thickening)
4 Other, Please specify

22. How old were you when this was first diagnosed?

____ Age in years
(MIN: 0) (MAX: current age)

Cardiovascular:

23. Do you have high blood pressure?

Yes
No (Go to Q25)
Don't Know, Refused (Go to Q25)

24. How old were you when this was first diagnosed?

____ Age in years
(MIN: 0) (MAX: current age)

Remember, we're interested in conditions diagnosed by a health professional.

25. Do you have migraine headaches?
    Yes
    No (Go to Q27)
    Don't Know, Refused (Go to Q27)

26. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

27. Do you have heart disease?
    Yes
    No (Go to Q29)
    Don't Know, Refused (Go to Q29)

28. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

29. Have you ever had a heart attack (damage to the heart muscle)?
    Yes
    No (Go to Q30)

30. Do you currently have angina (chest pain, chest tightness)?
    Yes
    No (Go to Q31)

31. Do you currently have congestive heart failure (inadequate heart beat, fluid build-up in the lungs or legs)?
    Yes
    No (Go to Q32)

Thyroid:

32. Do you have a thyroid condition?
    Yes
    No (Go to Q34)
    DK, R (Go to Q34)

33. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

Gastro-intestinal/Liver:

34. Do you have stomach or intestinal ulcers?
    Yes
    No (Go to Q36)
    DK, R (Go to Q36)

35. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

36. Do you have Gastroenteritis?
    Yes
    No (Go to Q38)
    DK, R (Go to Q38)

37. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

38. Do you have Jaundice?
    Yes
    No (Go to Q40)
    DK, R (Go to Q40)

39. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

Neurological:

40. Do you have Peripheral Neuropathy (numbness or tingling in fingers or toes)?
    Yes
    No(Go to Q42)
    Don't Know/Refused (Go to Q42)

41. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

42. Do you have Parkinson's Disease?
    Yes (Go to Q44)
    No (Go to Q44)
    Don't Know/Refused

43. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

Reproductive Health:

44. Were you ever diagnosed with a fertility problem?
    Yes, specify
    No
    Don't Know/Refused

45. If female, have you ever had any of the following adverse pregnancy outcomes?
    1 Spontaneous Abortion/Miscarriage
    2 Still Birth
    3 Ectopic Pregnancy

Other:

46. Do you suffer from multiple chemical sensitivities?
    Yes
    No (Go to Q48)
    Don't Know/Refused (Go to Q48)

47. How old were you when this was first diagnosed?
    ____ Age in years
    (MIN: 0) (MAX: current age)

48. Do you have any other long-term conditions that have been diagnosed by a health care professional?
    Yes
    No (Go to Q50)
    Don't Know/Refused (Go to Q50)

49. Please specify other long-term conditions.

Drug Use:

We'd like to ask a few questions about your use of medications, both prescription and over-the-counter.

50. In the past month, did you take:
a) ... pain relievers such as aspirin or Tylenol (including arthritis medicine and anti-inflammatories)?

Yes
No
R (Go to Mental Health Section)

b) … tranquilizers such as Valium?

Yes
No

c) ... diet pills such Redux, Ponderal or Fastin?

Yes
No

d) ... anti-depressants such as Prozac, Paxil or Effexor?

Yes
No

e) ... codeine, Demerol or morphine?

Yes
No

f) ... allergy medicine such as Seldane or Chlor-Tripolon?

Yes
No

g) ... asthma medications such as inhalers or nebulizers?

Yes
No

h) ... cough or cold remedies?

Yes
No

i) ... penicillin or other antibiotics?

Yes
No

j) ... medicine for the heart?

Yes
No

k) ... medicine for blood pressure?
Yes
No

l) ... diuretics or water pills?
Yes
No

m) ... steroids?
Yes
No

n) ... insulin?
Yes
No

o) ... pills to control diabetes?
Yes
No

p) ... sleeping pills?
Yes
No

q) ... stomach remedies?
Yes
No

r) ... laxatives?
Yes
No

If female & age <= 49,

s) ... birth control pills?
Yes
No

If female & age >= 30,

t) ... hormones for menopause or aging symptoms?
Yes
No
DK, R

t.1) What type of hormones are you taking?
INTERVIEWER: Read categories to respondent.
1 Estrogen only
2 Progesterone only
3 Both
4 Neither

t.2) When did you start this hormone therapy?
|_|_|_|_| Year
(MIN: year of birth + 30) (MAX: current year)

u) ... thyroid medication such as Synthroid or Levothyroxine?
Yes
No

v) ... any other medication?
Yes - Specify
No

Mental Health Information

MOOD (Bradburn Affect Balance Scale) 

The next set of questions describes some of the ways people feel at different times. Please tell me if you have the feeling often, sometimes or never.

During the past few weeks, how often have you felt:

1. … on top of the world?
   - Often
   - Sometimes
   - Never
   - DK, R (Finished Questionnaire)

2. … very lonely or remote from other people?
   - Often
   - Sometimes
   - Never

3. … particularly excited or interested in something?
   - Often
   - Sometimes
   - Never

4. … depressed or very unhappy?
   - Often
   - Sometimes
   - Never

5. … pleased about having accomplished something?
   - Often
   - Sometimes
   - Never

6. … bored?
   - Often
   - Sometimes
   - Never

7. … proud because someone complimented you on something you had done?
   - Often
   - Sometimes
   - Never

During the past few weeks, how often have you felt:

8. … so restless you couldn't sit long in a chair?
   Often
   Sometimes
   Never

9. … that things were going your way?
   Often
   Sometimes
   Never

10. … upset because someone criticized you?
   Often
   Sometimes
   Never

11. Taking things all together, how would you say things are these days? Would you say you're:
   1 … very happy?
   2 … pretty happy?
   3 … not too happy?

Appendix 10.2 Consent

Appendix 10.2.1: Adult Consent Form/Information Sheet

ADULT CONSENT FORM / INFORMATION SHEET

Study Title: Community Health Assessment Project Health Questionnaire (health questionnaire) and Medical Testing: A Comprehensive Assessment of the Current Health Status of a Stratified Random Sample of Residents in Port Colborne

Investigators: Ventana Clinical Research Corporation/ Public Liaison Committee

Sponsor: Inco Limited

INTRODUCTION

1. Reading and understanding this adult consent form/information sheet is part of the process of informed consent. It tells you what this study is about and how you are involved. Please read this form carefully and feel free to ask questions. If you would like more detail about something mentioned here or information not included here, please ask about it.
2. If you do not wish to participate in this research study, your future medical care will not be affected, nor will you lose any benefits to which you are otherwise entitled.
3. Approximately 1,000 individuals will participate in this study. The opportunity to participate in this study is completely random, that is, you have been asked to participate purely by chance. However, participation is entirely voluntary, and you may refuse to participate if you so choose.
4. CHAP is being undertaken by Ventana Clinical Research Corporation, a clinical research organization based in Toronto, Ontario. The study is being conducted as part of a Community-Based Risk Assessment (CBRA), which involves the participation and input of the Ontario Ministry of the Environment, the City of Port Colborne, and the Niagara Regional Public Health Department. The CBRA was established to identify areas of concern regarding the environment and human health in Port

Colborne and recommend a remediation plan if necessary. The sponsor of the CBRA, Inco Limited, will pay Ventana for the time, effort and expense to conduct this study. However, Inco Limited is not involved in the development, organization, or conduct of this study. Ventana is guided by the community-based Public Liaison Committee (PLC), which reviews and approves all aspects of the study, including the administration of the CHAP Health Questionnaire (health questionnaire) and medical testing.

5. This study has two parts. The first part involves the administration of the health questionnaire, and the second part involves medical testing, which includes:
    - General medical laboratory screen tests (requiring blood and urine samples),
    - Metal tests (requiring blood and urine samples), and
    - Additional tests and measures (does not require blood or urine samples).
6. Prior to undergoing medical testing, you will be asked:
    - To provide the name and phone number for your family physician so that we may forward your medical test results to your physician's office should any of your results be critically abnormal.

PURPOSE

1. The health questionnaire comprises detailed health-related questions, which are asked to get a sense of specific, current health conditions in Port Colborne.
2. The medical testing portion of CHAP is intended to generate information related to possible exposure to chemicals of concern (CoCs) in the Port Colborne area—nickel, copper, cobalt and arsenic. Through these tests, we hope to better understand: (i) the general functioning of your body through a routine medical screen—this medical screen will involve general blood work, urinalysis, and system function tests (i.e., liver, kidney, lung, and thyroid), (ii) the levels of the CoCs as well as the levels of lead, mercury and cadmium in your body—this will indicate your current level of metal exposure, and iii) your general heart and lung function as well as any skin sensitivity to nickel or cobalt through additional tests. We will also take measurements, such as height and weight.

PROCEDURES

1. This study is being conducted on a group of randomly selected Port Colborne residents. Only those 12 years of age and older will be asked to complete the questionnaire and medical testing.
2. You will be asked to visit the CHAP central test facility (804 King St.) three times over the course of five days. This facility is where the questionnaire and all medical testing will be completed.
3. On your first visit (Visit 1, Day 1) to the central facility, you will be provided an in-depth schedule of your required visits and procedures. You will then be asked to complete the CHAP Health Questionnaire (health questionnaire) with a trained interview nurse who will guide you through just over 100 questions and explain any terms that you do not understand. The questionnaire takes about 30 minutes to complete. You will then be given a container and be asked to provide a urine sample. A nurse also will take several blood samples of roughly 1.5 tablespoons each for testing. You will then undergo additional tests and measures including a lung function test, electrocardiogram (ECG), blood pressure measurement, carbon monoxide (CO) breath test to determine exposure to tobacco smoke, and measurements, such as height and weight. Finally, a trained medical professional will apply a nickel/cobalt skin patch on your back, which will take only a few minutes. You must keep this patch on until your next visit (Visit 2, Day 3). All medical testing will take 30–45 minutes in addition to 30 minutes to complete the health questionnaire. Therefore Visit 1, Day 1 should take 1 hour–1 hour, 45 minutes.
4. You will return to the central test facility two days after your first visit (Visit 2, Day 3). The time of your second visit should be about the same as your first visit (i.e., morning, afternoon or evening). A nurse will remove your skin patch. You will be reminded to return two days later (Visit 3, Day 5) to complete the final part of your comprehensive health assessment. This visit should last about 15 minutes.
5. When you return the next day (Visit 3, Day 5), a trained nurse will "score" (evaluate) your skin patch test by examining any skin reaction on your back. Visit 3 on Day 5 should take about 15 minutes.

Timing of health questionnaire and Medical Testing:

Test	Visit 1 - Day 1	Visit 2 - Day 3	Visit 3 - Day 5
Health Questionnaire	-questionnaire interview		
General Medical Lab Screen	-blood/urine collection		
Metals Analysis	-blood/urine collection		
Additional Tests and Measures	-height, weight, ECG, blood pressure, CO breath test, lung function, skin patch test application	-skin patch test removal	-skin response scored

6. With respect to the health questionnaire and medical testing, please be advised that:
   a) You have the right to withhold information that would identify you.
   b) You have the right to choose not to answer any question in the health questionnaire.
7. Following the completion of the skin patch testing (Visit 3, Day 5), your participation in CHAP is complete, and you will be compensated for your time and inconvenience.

BENEFITS AND RISKS

1. The results of your medical tests will be available for you to pick up at this central study facility at the end of the study. There is no additional direct benefit to you from participating in this study. This study is designed to help us understand if a link exists between chemical exposure over a person's lifetime and his or her current health. Through this understanding, necessary steps can be taken to correct or better the situation in Port Colborne as it relates to CoCs. In addition, the results from CHAP may be used to identify other communities that may or may not be at an increased health risk.

2. Risks associated with drawing blood from a vein in your arm include pain, bruising, redness, light-headedness, dizziness and on rare occasion, infection. Rarely, individuals have been known to faint during the drawing of blood. Individuals with allergies to zinc oxide may develop a slight rash from the bandage that is applied afterward.

3. Risks associated with the skin patch test include skin discolouration or scarring that is occasionally permanent, redness, swelling or itchiness, and on a rare occasion, infection. The skin patch test includes the substances of interest—nickel sulfate and cobalt dichloride—and other substances that may be skin irritants and cause a reaction. These other substances include: wool alcohols, neomycin sulfate, potassium dichromate, caine mix, fragrance mix, colophony, paraben mix, balsam of Peru, ethylenediamine dihydrochloride, *p*-*tert*-butylphenol formaldehyde resin, epoxy resin, carba mix, black rubber mix, Cl+Me-isothiazolinone, quaternium-15, mercaptobenzothiazole, *p*-phenylenediamine, formaldehyde, mercapto mix, thimerosal, thiuram mix, and negative control.

CONFIDENTIALITY

1. Your results from the health questionnaire and medical testing will be kept strictly confidential at all times. Any information that can identify you or your family on the health questionnaire will be replaced with a unique number. All your identifying information (i.e. name, date of birth, sex, telephone number and address) will be kept under restricted access. The following special circumstances exist for breaking confidentiality:

    - Should any of your laboratory results be critically abnormal, we immediately will bring this information to the attention of your family physician.

2. Information gathered from this study, including results from the questionnaire, will be examined by an independent research ethics board. The results from this study also will be presented as a report made available to the sponsor of this study (Inco Limited), the Technical Sub Committee (TSC), the Public Liaison Committee (PLC), and the community of Port Colborne. Results from this study may also be published in a scientific journal or presented at scientific meetings. Your identity will NOT be disclosed in any report, publication, or presentation.

YOUR OBLIGATIONS AND RESTRICTIONS

1. If you choose to participate in the study, you are obligated to answer the questions honestly and completely.
2. If you can, you are requested to answer all questions.
3. If you choose to participate in the study, you are requested to complete all of the medical testing, make all of your required visits, and follow the procedures described to you.

COMPENSATION

1. In consideration of the time and inconvenience involved with completing this questionnaire and the medical tests, we will pay you $35.00 upon completion of Visit 3, Day 5.

VOLUNTARY PARTICIPATION AND STUDY TERMINATION

1. Your decision to participate in this research study is **entirely** voluntary. You may decide not to participate or to discontinue participation at any time without penalty.
2. Your participation may be terminated if you do not comply with the study procedures asked of you.

PARTICIPANT'S RIGHTS

1. CHAP has been reviewed and approved by the Public Liaison Committee (PLC), the Technical Sub Committee (TSC) and an ethics review board.
2. If you have questions or concerns about your rights in the study, you should contact your family doctor, lawyer, or write to the ethics review board (address to be provided within this document).
3. If you have questions about CHAP or the procedures involved in the study, you may call the following toll-free number at any time: 1-866-252-CHAP (2427).

SIGNATURES

To become a part of this study, you must sign and date this page and record the time of your signature.

By signing this page, you are confirming the following:

- The administrator of the questionnaire has discussed with you the requirements of your participation in this study;
- All of your questions have been answered to your satisfaction. If you did not understand any of the words, you have asked the questionnaire administrator to explain them to you and now you fully understand;
- You voluntarily agree to be part of this research study, to follow the study procedures, and to provide the necessary information in the questionnaire;
- You understand that you may freely choose to withdraw from this study at any time; and
- You have received a copy of this Adult Consent Form/Information Sheet to keep for yourself.

Following the completion of this comprehensive health assessment, a final report of your test results will be available for you to pick up at the central study facility. If any of the test results are critically abnormal, your family physician will be contacted immediately. Therefore, we request the name and telephone number of your physician below:

My physician's name is _____

My physician's telephone number is _____

Participant's Name (print or type)	Participant's Initials

Signature of Participant	Date	Time

PLEASE WRITE IN THE DATE AND TIME YOU SIGN YOUR NAME

Signature of Individual Obtaining Consent	Date	Time

Appendix 10.2.2: Adolescent Assent Form/Information Sheet

ADOLESCENT ASSENT FORM / INFORMATION SHEET

Study Title: Community Health Assessment Project Health Questionnaire (health questionnaire) and Medical Testing: A Comprehensive Assessment of the Current Health Status of a Sample of Port Colborne Residents

Investigators: Ventana Clinical Research Corporation/ Public Liaison Committee

Sponsor: Inco Limited

WHY ARE WE DOING THIS STUDY?

You are being asked be a participant in a health study of people living in Port Colborne. This form tells you about the health study and why you are involved. If there is anything that you find confusing or that you do not understand, you should ask your parents, guardian, or health study nurse.

Certain chemicals have been found in the soils of parts of Port Colborne. These chemicals are nickel, copper, cobalt, and arsenic. They have been found at levels higher than what is considered safe by the Ontario Ministry of the Environment. It is possible that if you touch, breath or accidentally eat very high levels of these chemicals, they could harm your health. The reason for this study is to see if these chemicals have harmed the health of people living in Port Colborne. To do this, we will be testing the current health of 1,000 people, selected by chance, from Port Colborne aged 12 and older.

WHAT WILL HAPPEN IN THIS STUDY?

The study will last for three visits over five days. The ***first visit*** will be the longest and will take you about an hour or two to complete. On this first study day, two different kinds of testing will occur:

1. The first kind of testing involves an ***interview with a nurse*** where you will be asked questions about yourself and your current health.

2. The second part will involves ***medical testing***. There will be a number of different medical tests and they will require you to do different things. For example, these medical tests will involve:

    a. measuring your height and weight;
    b. giving a small amount of blood and urine for several health tests;
    c. having your blood pressure test taken from around your arm;
    d. having wires attached to your chest to measure the electrical activity of your heart;
    e. blowing very hard into one breathing machine to measure your lung function and softly into another to measure your exposure to cigarette smoke; and
    f. having a skin test patch put on your back for two days to test if your skin is sensitive to nickel, cobalt and other chemicals.

You then will be asked to come back two days later for your ***second visit***, and have the skin test patch removed from your back by a nurse. This should take about 15 minutes.

Finally, two days after removing the skin test patch, you will be asked to come back for your ***third visit,*** and a nurse will look at your back to see if you have had any skin reaction to the skin test patch that was on your back. This should take about 15 minutes.

ARE THERE GOOD AND BAD THINGS ABOUT BEING IN THE STUDY?

If you are in this study you will help us to measure the current health of people living in Port Colborne. Learning about peoples' current health may help to determine what steps need to be taken to deal with problems related to the chemicals found in Port Colborne and to preserve the future health of residents in Port Colborne. As well, the information from all of the medical tests you complete will be provided to your parents or guardian if something is abnormal about them.

We do not know if this study will show if the chemicals found in Port Colborne have affected your health. If your health has been affected, being in this study may not help to make you better. While being in this study will not make your health worse, some parts of the study may cause you some discomfort and/or mild pain. These risks are described below.

1. Drawing a blood sample from a vein in your arm will involve getting a needle. Risks of drawing blood include pain, bruising, redness, light-headedness, dizziness and sometimes infection. Rarely, people have fainted during the drawing of blood. People with allergies to zinc oxide may develop a slight rash from the bandage that is applied afterward.
2. Risks of the skin patch test are a change in skin colour or scarring that is sometimes permanent, swelling or itchiness, and very rarely, infection. Besides small amounts of the chemicals nickel and cobalt, the skin patch test also contains other chemicals that could produce skin reactions as described above. These chemicals include wool alcohols, neomycin sulfate, potassium dichromate, caine mix, fragrance mix, colophony, paraben mix, balsam of Peru, ethylenediamine dihydrochloride, *p-tert*-butylphenol formaldehyde resin, epoxy resin, carba mix, black rubber mix, Cl+Me-isothiazolinone, quaternium-15, mercaptobenzothiazole, *p*-phenylenediamine, formaldehyde, mercapto mix, thimerosal, thiuram mix, and a negative control.
3. As with any study, other risks may happen that we do not know about.

During the medical testing, if you have any of the reactions that we have just described, please tell your parents, guardian or the study nurse right away.

DO I HAVE TO BE IN THIS STUDY?

It is your decision whether or not you participate in this study, as long as your parents or guardian agree and sign a consent form. It is OK if you decide not to be in the study. If you decide to be in the study, but change your mind later on and decide not be in the study, that is also OK.

ASSENT

I have read this form and understand what the study is about and why I have been asked to be involved. I have had a chance to ask questions about it and talk it over with my parent(s) or guardian. I have decided that I want to take part.

Participant's Name (print or type)	Participant's Initials	
Signature of Participant	Date	Time

PLEASE WRITE IN THE DATE AND TIME YOU SIGN YOUR NAME

Signature of Individual Obtaining Consent	Date	Time

Appendix 10.2.3: Parental or Guardian Consent Form/Information Sheet

PARENTAL OR GUARDIAN CONSENT FORM/INFORMATION SHEET

Study Title: Community Health Assessment Project Health Questionnaire (health questionnaire) and Medical Testing: A Comprehensive Assessment of the Current Health Status of a Sample of Port Colborne Residents

Investigators: Ventana Clinical Research Corporation/ Public Liaison Committee

Sponsor: Inco Limited

INTRODUCTION

1. Your child has been asked to read and sign an Adolescent Assent Form/Information Sheet, and you have been asked to read and sign this Parental/Guardian Consent Form/Information Sheet. Both you and your child will be given copies of your respective forms. For your child to participate in this study, both forms need to be completed and signed. Understanding and signing these forms is part of the process of informed consent. These forms tell you what this study is about and how your child is involved. Please read this form carefully, and feel free to ask questions. If you would like more detail about something mentioned here or information not included, please ask about it.
2. If you do not wish your child to participate in this study, his/her future medical care will not be affected, nor will he/she lose any benefits to which he/she is otherwise entitled.
3. Approximately 1,000 individuals, 12 years of age and older, will participate in this study. Parents or guardians of adolescents between the ages of 12-17 years are required to provide consent prior to their child's participation in this study. The opportunity to participate in this study is completely random, that is, your child has been selected to participate purely by chance. However, participation is entirely voluntary, and either you or your child may refuse your child's participation.

4. CHAP is being undertaken by Ventana Clinical Research Corporation, a clinical research organization based in Toronto, Ontario. The study is being conducted as part of a CBRACDC, which involves the participation and input of the Ontario Ministry of the Environment, the City of Port Colborne, and the Niagara Regional Public Health Department. The CBRA was established to identify areas of concern regarding the environment and human health in Port Colborne and recommend a remediation plan if necessary. The sponsor of the CBRA, Inco Limited, will pay Ventana for the time, effort and expense to conduct this study. However, Inco Limited is not involved in the development, organization, or conduct of this study. Ventana is guided by the community-based Public Liaison Committee (PLC), which reviews and approves all aspects of the study, including the administration of the CHAP Health Questionnaire (health questionnaire) and medical testing.

5. This study has two parts. The first part involves the administration of a CHAP Health Questionnaire (HQ) and the second part involves medical testing, which includes:
    - General medical laboratory screen tests (requires blood and urine samples),
    - Metal tests (requires blood and urine samples), and
    - Additional tests and measures (does not require blood or urine samples).

6. Prior to undergoing medical testing, you will be asked:
    - Whether you would like to receive your child's medical test results by mail once they become available, and
    - To provide a phone number that we may use to contact you should any of your child's laboratory results be critically abnormal. Upon bringing such information to your attention, we recommend that you discuss it with your family physician immediately. The decision to follow up with your doctor is entirely up to you and your child.
    - To provide the name and phone number for your child's physician so that we may forward your child's medical test results to his or her physician's office (if you so indicate on this form).

PURPOSE

1. The health questionnaire consists of a number of detailed health-related questions, which we ask to get a sense of specific current health conditions.

2. The medical testing portion of CHAP is intended to generate information related to possible exposure to the chemicals of concern (CoCs) in the Port Colborne area—nickel, copper, cobalt and arsenic. Through these tests, we hope to better understand: (i) the general functioning of your child's body through a routine medical screen—this medical screen will involve general blood work, urinalysis, and system function tests (i.e. liver, kidney, lung, and thyroid), (ii) the levels of CoCs and the levels of lead, mercury and cadmium in your child's body—this will indicate your child's current level of metal exposure, and iii) your child's general heart and lung function as well as any skin sensitivity to nickel or cobalt through additional tests. We will also take measurements, such as height and weight.

PROCEDURES

1. This study is being conducted on a group of randomly selected Port Colborne residents. Only those 12 years of age and older will be asked to complete the questionnaire and medical testing.

2. You will be asked to visit the CHAP central test facility (804 King St.) with your child a total of three times over the course of five days. This is where the questionnaire and all medical tests will be completed.

3. On your child's first visit (Visit 1, Day 1) to the central facility, you will be provided an in-depth schedule of all of your required visits and procedures. Your child will then be asked to complete the CHAP Health Questionnaire (health questionnaire) with a trained interview nurse who will guide him/her through just over 100 questions and explain any terms that he/she may not understand. The questionnaire takes about 30 minutes to complete. Your child will then be given a container and be asked to provide a urine sample. A nurse will also take several blood samples of roughly 1.5 tablespoons each for the various tests. Your child will then undergo additional tests and measures including a lung function test, electrocardiogram (ECG), blood pressure measurement, carbon monoxide (CO) breath test to determine exposure to tobacco smoke, and measurements, such as height and weight. Finally, a trained medical professional will apply a nickel/cobalt skin patch on your child's back, which takes only a few minutes. Your child must keep this patch on until his/her next visit (Visit 2, Day 3). All medical testing will take 30–45 minutes in addition to 30 minutes to

complete the health questionnaire. Therefore the first visit should take 1 hour–1 hour, 45 minutes.

4. You and your child will return to the central test facility two days after the first visit (Visit 2, Day 3). The time of your second visit should be about the same as your first visit (i.e., morning, afternoon or evening). A nurse will remove your child's skin patch. You and your child will be reminded to return two days later (Visit 3, Day 5) to complete the final part of your child's comprehensive health assessment. The second visit should take about 15 minutes.
5. When you and your child return two days later (Visit 3, Day 5), a trained nurse will "score" (evaluate) your child's skin patch test by examining any reaction on his/her back. The third and final visit should take about 15 minutes.

Timing of health questionnaire and Medical Testing:

Test	Visit 1 - Day 1	Visit 2 - Day 3	Visit 3 - Day 5
Health Questionnaire	-questionnaire interview		
General Medical Lab Screen Tests	-blood/urine collection		
Metal Tests	-blood/urine collection		
Additional Tests and Measures	-height, weight, ECG, blood pressure, CO breath test, lung function, skin patch test application	-skin patch test removal	-skin response scored

6. With respect to the health questionnaire and medical testing, please be advised that:
    a) Your child has the right to withhold his/her identifying information.

b) Your child has the right to choose not to answer any question asked of him/her in the health questionnaire.

7. Following the completion of the skin testing (Visit 3, Day 5), your child's participation in the comprehensive current health assessment is complete. At this time you will be compensated for time, inconvenience and expenses incurred relating to your involvement in this study.

BENEFITS AND RISKS

1. The information collected from the medical tests that your child completes will be provided to you if you indicate that you want them, or if your child's results are critically abnormal. There is no additional direct benefit to your child from participating in this study. This study is designed to help us understand if a link exists between chemical exposure over a person's lifetime and his or her current health. Participation in this study allows us to assess the current health of the residents of Port Colborne. Through this understanding, any necessary steps can be taken to correct or better the situation in Port Colborne as it relates to CoCs. In addition, the results from CHAP may be used to identify other communities that may or may not be at an increased health risk.

2. Risks associated with drawing blood from a vein in your child's arm include pain, bruising, redness, light-headedness, dizziness and on rare occasion, infection. Rarely, individuals have been known to faint during the drawing of blood. Individuals with allergies to zinc oxide may develop a slight rash from the band-aid that is applied afterward.

3. Risks associated with the skin patch test include skin discolouration or scarring that is occasionally permanent, swelling or itchiness, and on a rare occasion, infection. The skin patch test includes the substances of interest—nickel sulfate and cobalt dichloride—and other substances that may be skin irritants and cause a reaction. These other substances include: wool alcohols, neomycin sulfate, potassium dichromate, caine mix, fragrance mix, colophony, paraben mix, balsam of Peru, ethylenediamine dihydrochloride, *p-tert*-butylphenol formaldehyde resin, epoxy resin, carba mix, black rubber mix, Cl+Me-isothiazolinone, quaternium-15, mercaptobenzothiazole, *p*-phenylenediamine, formaldehyde, mercapto mix, thimerosal, thiuram mix, and negative control.

CONFIDENTIALITY

1. Your child's results from the health questionnaire and medical testing will be kept strictly confidential at all times. Any information that can identify your child on the health questionnaire will be replaced with a unique number. All of his/her identifying information (i.e. name, date of birth, sex, telephone number and address) will be kept under restricted access. The following special circumstances exist for breaking confidentiality:

   - If you choose to request your child's medical test results,
   - If you choose to request that your child's medical test results be provided to his or her physician, and
   - Should any of your child's laboratory results be critically abnormal, we will bring this information to your attention directly.

   In these cases, the confidential information will only be provided directly to you (or to your doctor should you indicate so on this form).

2. Information gathered from this study, including results from the questionnaire, will be examined by an independent research ethics board. The results from this study also will be presented as a report made available to the sponsor of this study (Inco Limited), the Technical Sub Committee (TSC), the Public Liaison Committee (PLC), and the community of Port Colborne. Results from this study may also be published in a scientific journal or presented at scientific meetings. Your child's identity will NOT be disclosed in any report, publication, or presentation.

YOUR OBLIGATIONS AND RESTRICTIONS

1. If you choose to consent to your child's participation, your child is obligated to answer the questions honestly and completely.
2. If your child is able, he/she is requested to answer all questions.
3. If you choose to allow your child to participate, your child is requested to complete all of the medical tests, to attend all of the required visits, and to follow the described procedures.

COMPENSATION

In consideration of the time and inconvenience involved with completing the CHAP Health Questionnaire and medical testing, we will pay you $35.00 upon completion of Visit 3, Day 5.

VOLUNTARY PARTICIPATION AND STUDY TERMINATION

1. Your decision to allow your child to participate in this study is **entirely** voluntary. You may decide to not allow your child to participate or to withdraw consent at any time without penalty.
2. Your child's participation may be terminated if he/she does not comply with the study procedures asked of him/her.

PARTICIPANT'S RIGHTS

CHAP has been reviewed and approved by the Public Liaison Committee (PLC), the Technical Sub Committee (TSC) and an ethics review board.

- If you have questions or concerns about your rights or the rights of your child in the study, you should contact your family doctor, lawyer, or write to the ethics review board (address to be provided within this document).
- If you have questions about CHAP or the procedures involved in the study, you may call the following toll-free number at any time: 1-866-252-CHAP (2427).

SIGNATURES

To give consent for your child's participation in this study, you must sign and date this page, and record the time of your signature.

By signing this page, you are confirming the following:

- The questionnaire administrator has discussed with you and your child the requirements of his/her participation in this study;
- All of your questions have been answered to your satisfaction. If you or your child did not understand any of the words, you have asked the questionnaire administrator to explain them to you and now you fully understand;
- You voluntarily agree to allow your child to be part of this study;

- You understand that you may freely choose to stop your child's participation in this study at any time; and
- You have received a copy of this Parental/Guardian Consent Form/Information Sheet to keep for yourself.

Following the completion of this comprehensive health assessment, a final report of your child's test results will be available for you to pick up at the central study facility. If any of the test results are critically abnormal, your family physician will be contacted immediately. Therefore, we request the name and telephone number of your physician below:

My physician's name is _____

My physician's telephone number is _____

_____

Child's Name

_____	_____	
Parent/Guardian Name (print or type)	Parent/Guardian Initials	
_____	_____	_____
Signature of Parent/Guardian	Date	Time

PLEASE WRITE IN THE DATE AND TIME YOU SIGN YOUR NAME

_____	_____	_____
Signature of Individual Obtaining Consent	Date	Time

Appendix 10.3: Instruction to Subjects

Preliminary Content for General Instructions To Subjects

1 General Instructions Prior to Visit 1

All subjects are responsible for picking up their 24-hour urine specimen collection vessel before Visit 1, Day 1. Upon return to the central facility on Visit 1, Day 1, the subject is required to bring back the urine specimen collection vessel, having filled it over the previous 24-hour period.

Subjects also will be instructed before Visit 1, Day 1 to bring the name and contact information of their family physician. On the Adult Consent Form/Information Sheet and the Parent or Guardian Consent Form/Information Sheet, subjects are given the option to provide this information should they want their medical test results, or those of their children, forwarded to their family physician. Therefore, subjects should have their physician's name and telephone number on hand for Visit 1, Day 1.

2 Instructions for Urine Collection over 24-Hour Period

To ensure the most accurate reading of the urine specimen, special care must be taken in its collection. Please note the following:

- Be advised that there are potentially hazardous preservatives within the collection container.
- Discard the first morning specimen and record this time of voiding.
- Collect all subsequent voided urine for the remainder of the day and night.
- Collect the first morning specimen on day two at the same time as noted on day one.

3 Instructions for T.R.U.E. (Thin-layer Rapid Use Epicutaneous Test)

3.1 Instructions Prior to Visit 1, Specific to T.R.U.E.

Before you have the patch test performed (Visit1), you should:

- NOT consume seafood (i.e., shellfish)
- NOT apply topical corticosteroids (e.g. hydrocortisone) to the patch test area (your back) for one to two weeks before your test date (Visit 1);
- NOT take oral corticosteroids at a dose equivalent to or greater than 15 mg of Prednisone within one week of your test date (Visit 1);
- NOT take an injectable corticosteroid within one month of your test date (Visit 1);
- NOT take oral cyclosporin within one week of your test date (Visit1);
- NOT apply lotions, creams or ointments to the test area before the test (Visit 1);
- Minimize sun exposure to the test area before the test (Visit 1).

Note: Excessive back hair may have to be shaved before patch testing to allow for adhesion of the test strips.

At the time of your first visit (Visit 1, Day 1), you must NOT:

- Have dermatitis on the patch test site, or any other inflammatory skin condition e.g. psoriasis, sunburn; or
- Be pregnant.

Note: If the tape strips become loose, you should have them re-attached at home with an extra piece of tape.

3.2 Instructions for T.R.U.E. Post-Application, Given to Subject before Departure

Note: The subject will be given written as well as verbal instructions concerning the care and protection of the test strips.

During the testing period (96 hours), you must:

- Keep the patch test area dry. Avoid activities that cause perspiration (e.g. exercise, manual labour) and do NOT take a shower until after the final visit (Visit 3, 96 hours after application of patch). You make take a shallow bath as long as you can keep your back dry;
- Wear loose clothing; and
- Call the facility immediately if the test site itches or burns severely.

You may develop itching under the patches. If itching occurs and becomes severe or painful, you should contact the facility, or carefully remove the painful patch yourself.

For the first day, the tape may feel tight. After the strips are removed, your back may feel sticky. During the two days that you wear the patches, you may experience some itching, but most people have little difficulty. One or more test spots may become itchy. These

areas may be red and swollen or sometimes oozy when the tests are removed at 48 hours. This reaction may increase over the next few days.

The results of your patch testing will be given to you along with an information sheet that explains the meaning of a positive test(s).

At least 72 hours is necessary for allergic reactions to develop fully and for some irritant reactions to subside.

The p-phenylenediamine site may turn black. This is because the allergen is a dye; it does not represent an allergic reaction. This discoloration may remain for up to four weeks.

Side Effects:

1. If in the past, you have experienced an allergic rash to one of the tested substances, your skin rash may recur ("wake up") if you develop a positive reaction to the substance during the patch testing procedure.
2. Uncommonly, reactions may persist a few weeks. They can be treated with cortisone creams.
3. As they heal, positive reactions at the test sites may sometimes leave brown or white spots on the skin. Most of these marks will fade slowly over time but on occasion may be permanent.
4. Rarely, a positive patch test site may become infected.
5. A person with psoriasis may develop psoriasis at the site of a positive patch test.

6. Very rarely, people may develop an allergy to a substance used in the tests. This usually appears as a positive reaction two to three weeks after the tests.
7. Extremely rarely, a systemic reaction may appear within one hour of a substance being applied on the skin.

Subject Return Visit Schedule:

	Visit 1 (Day 1)	Visit 2 (Day 3)	Visit 3 (Day 5)
Hour	0	48	96
Step	Application of Patch	Removal of Patch	Scoring of Site
Subject Appointments	**Date:_____** **Time:_____** **Initial:_____**	**Date:_____** **Time:_____** **Initial:_____**	**Date:_____** **Time:_____** **Initial:_____**

Appendix 10.4: General Medical Laboratory Screen Tests Information Table

Analysis	Test	Methodology	Specimen Minimum Volume	Specimen Transport Temperature	Reference Values		
					Gender	Age	Reference Ranges
Heamatology							
	Haematocrit	GENS	7 ml	Ambient storage/ ambient transport	F M B B B	18-120 18-120 0-0 1-7 8-17	0.35 - 0.47 0.37 - 0.51 0.28 – 0.42 0.32 – 0.42 0.33 – 0.44
	Haemoglobin (g/L)	GENS			F M	18-120 18-120	115 - 165 AL 50 130 - 174 AL 50
	Red Blood Cell Count (X10E12/L)	GENS			F M B B F M	18-120 18-120 0-0 1-7 8-17 8-17	4.00 - 5.50 4.50 - 6.00 3.30 – 5.30 3.70 – 5.30 3.80 – 5.10 3.80 – 5.60
	Mean Cell Volume				Calculation		
	MCHC				Calculation		
	White Blood Cell Count (X10E9/L)	GENS			B	18-120	3.6 - 11.0
	Differential Blood Count	GENS			Calculation		
	Absolute Platelet Count (X10E9/L)	GENS			B	18-120	150 - 400
BioChemistry	Total Bilirubin (umol/L)	BMC Hitachi 911	9.5 ml	Ambient storage / ambient transport	B B	13-120 1-12	0.0 - 22.1 0.0 – 25.6

Analysis	Test	Methodology	Specimen Minimum Volume	Specimen Transport Temperature	Reference Values		
					Gender	Age	Reference Ranges
	Creatinine (umol/L)	BMC Hitachi 911			M F M B B B B B B	10-49 10-120 50-120 9-9 8-8 7-7 6-6 5-5 0-4	0 - 114 AH 650 0 - 96 AH 650 0 - 123 AH 650 0 – 90 AH 650 0 – 80 AH 650 0 – 70 AH 650 0 – 60 AH 650 0 – 50 AH 650 0 – 40 AH 650
	Blood Urea Nitrogen (mmol/L)	BMC Hitachi 911			B B	14-120 1-13	1.7 - 8.3 AH 35.0 1.7 – 7.0 AH 35.0
	TSH (serum) (mIU/L)	Abbott AXSYM MEIA			B	0-120	0.30 – 5.50
	fT4 (serum) (ng/dl)	Abbott AXSYM MEIA			B B F M	1-9 10-17 18-120 24-120	6.0-12.5 5.0-11.0 5.0-12.5 5.0-12.5
Urinalysis (Routine & Microscopic)	Blood	Ames Multistix 10SG	10 ml	Ambient storage / ambient transport	Calculation		
	Leukocytes				Calculation		
	Protein				Calculation		
	pH				Calculation		
	Nitrates				Calculation		
	Glucose				Calculation		
	Possible Microscopic Analysis				Calculation		
Cotinine (plasma) (ng/ml)		Gas Chromotography	5 ml	Ambient storage / ambient transport	B	0-120	20-700 in smokers

Legend: F– Female M – Male B – Both AH – Alert Hi AL – Alert Lo

Appendix 10.5: Metal Tests Information Table

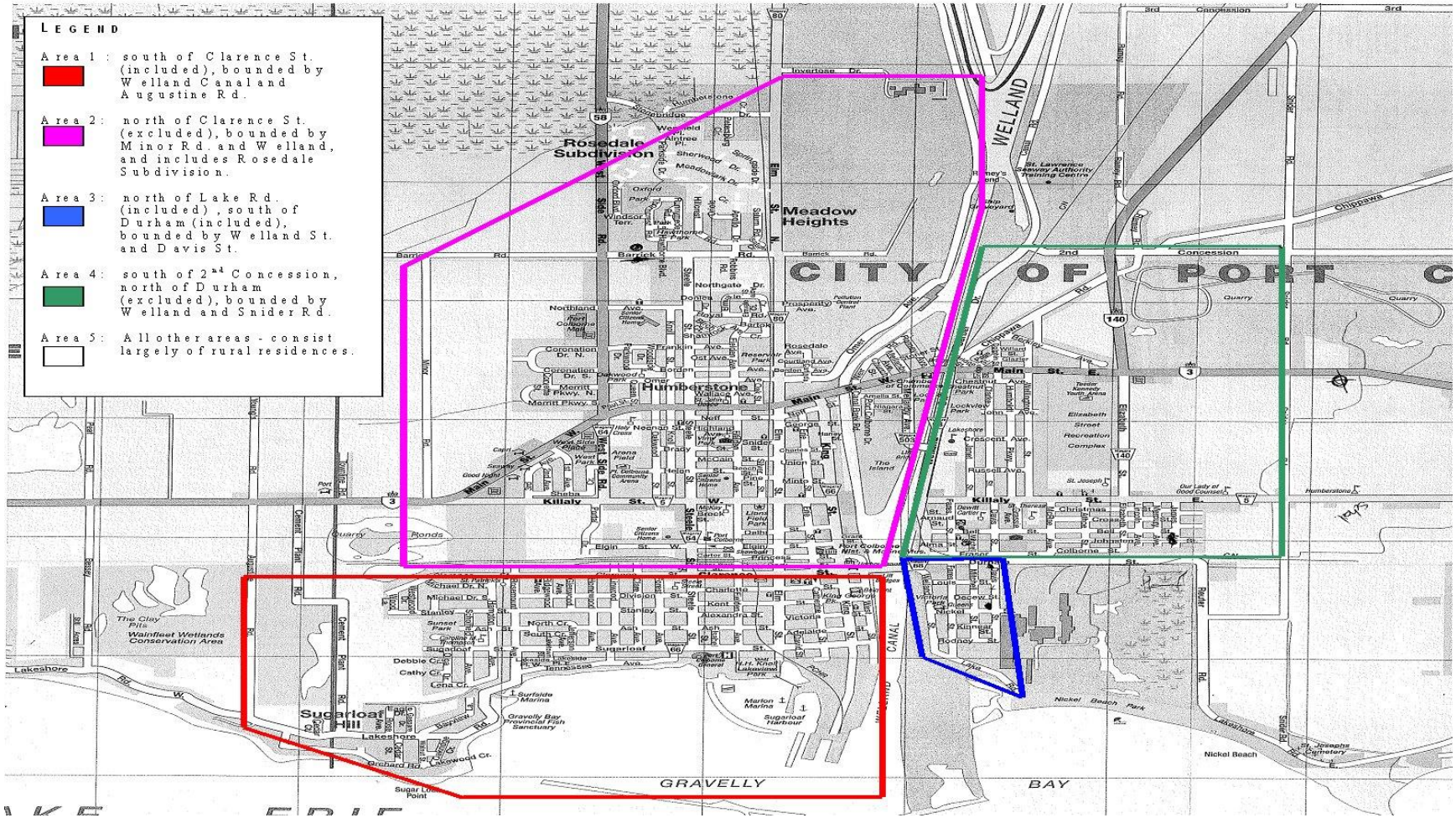
Test Name	Methodology	Specimen Type	Specimen Required	Specimen Minimum Volume	Specimen Transport Temperature	Reference Values
Lead with Demographics	Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)	Blood	▪ Draw blood in a royal blue-top (EDTA) Monoject trace element blood collection tube – product 8881-307022 (Supply T183) and send 2.0 ml (pediatric [<or = 15 years]: 0.5 ml – Becton Dickinson MICROTAINER {Supply T174} of EDTA whole blood.	0.5 mL	Refrig\Frozen OK\Ambient OK	Pediatric (<or = 15 years) ▪ Normal: <10 ug/dL ▪ Toxic concentration: > or =20 ug/dL Adults: ▪ Normal: <20 ug/dL ▪ Toxic concentration: >or = 70 ug/dL
Arsenic, Urine	Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)	Urine	▪ 10 mL from a 24-hour urine collection. No preservative. ▪ Collect in clean, plastic urine container(s) with no metal cap(s) or glued insert(s). ▪ Send specimen in a plastic, 13-mL urine tube or a clean, plastic aliquot container with no metal cap or glued insert. ▪ Refrigerate specimen within 4 hours of completion of 24-hour collection. Send specimen refrigerated. Note: Patient should not eat seafood for a 48-hour period prior to start of collection.	1.0 mL	Refrig\Frozen OK\Ambient NO	▪ Normal: <120 ug/specimen ▪ Toxic concentration: > or = 5,000 ug/specimen Note: The reference value is for a 24-hour collection.

Test Name	Methodology	Specimen Type	Specimen Required	Specimen Minimum Volume	Specimen Transport Temperature	Reference Values
Arsenic Fractionation, Urine	Liquid-Liquid Extraction/Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)	Urine	▪ 10 mL from a 24-hour urine collection. No preservative. ▪ Collect in clean, plastic urine container(s) with no metal cap(s)or glued insert(s). ▪ Send specimen in a plastic, 13-mL urine tube or a clean, plastic aliquot container with no metal cap or glued insert. ▪ Refrigerate specimen within 4 hours of completion of 24-hour collection. Send specimen refrigerated. If the specimen is collected ambient and with no preservative, the specimen must be refrigerated or frozen for transport and storage.	5.0 mL	Refrig\Frozen OK\Ambient\OK	Inorganic (non-dietary) arsenic:<25 ug/specimen Values >= 25 ug/specimen are considered to be toxic concentrations Note: The reference value is for a 24-hour collection. Organic arsenic: All results are normal (reported as ug/specimen)
Copper, Urine	Inductively Coupled Plamsa-Mass Spectrometry (ICP-MS)	Urine	▪ 10 mL from a 24-hour urine collection. No preservative. ▪ Collect in clean, plastic urine container(s) with no metal cap(s) or glued insert(s). ▪ Send specimen in a plastic, 13-mL urine tube or in a clean, plastic aliquot container with no metal cap or glued insert. ▪ Refrigerate specimen within 4 hours of completion of 24-hour collection. Send specimen refrigerated.	5.0 mL	Refrig\Frozen OK\Ambient NO	15-60 ug/specimen Note: The reference value is for a 24-hour collection.

Test Name	Methodology	Specimen Type	Specimen Required	Specimen Minimum Volume	Specimen Transport Temperature	Reference Values
Mercury, Urine	Inductively Coupled Plasma-Mass Spectrometry (ICP-MS)	Urine	▪ 10 mL (pediatric: 5.0 mL) from a 24-hour urine collection. No preservative. ▪ Collect in clean, plastic urine container(s) with no metal cap(s) or glued insert(s). ▪ Send specimen in a plastic, 13-mL urine tube or a clean, plastic aliquot container with no metal cap or glued insert. ▪ Refrigerate specimen within 4 hours of completion of 24-hour collection. Send specimen refrigerated.	5.0 mL	Refrig\Frozen OK\Ambient NO	▪ Normal: <10 ug/specimen ▪ Toxic concentration: >50 ug/specimen The concentration at which toxicity is expressed is widely variable between patients. 50 ug/specimen is the lowest concentration at which toxicity is usually apparent. Note: The reference value is for a 24-hour collection.
Nickel, Urine	Graphite Furnace Atomic Absorption Spectrometry	Urine	▪ 10 mL from a 24-hour urine collection. No preservative. ▪ Collect in clean, plastic urine container(s) with no metal cap(s) or glued insert(s). ▪ Send specimen in a plastic, 13-mL urine tube or in another clean, plastic aliquot container with no metal cap or glued insert. ▪ Refrigerate specimen within 4 hours of completion of 24-hour collection. Send specimen refrigerated.	5.0 mL	Refrig\Frozen OK\Ambient NO	0-7 ug/specimen Note: The reference value is for a 24-hour collection.
Cobalt	Inductively Coupled Plasma-Mass Spectrometery > (ICP-MS)	Urine	▪ 10ml urine aliquot from a 24 hour collection is preferred (no preservative, refrigerated)	1mL urine aliquot	Specimen transport temperature refrigeration, cool pack. Freezing NOT preferred due to the possibility of losing a small amount of Co from freeze/thaw.	<2 ug/24 specimen, 0.4 ug/l Note: The reference value is for a 24-hour collection.

Note: Reference Laboratory's Special Instructions for "Urine Preservative" for multiple collections and "Metals Analysis-Collection and Transport" will be complied with.

Appendix 10.6: Geographical Areas Defined by Level of Exposure



Appendix 10.7: Mayo Medical Laboratories Licensure and Regulations

Licensure and Regulations

Mayo Medical Laboratories is licensed/accredited by the following agencies:

American Association of Blood Banks

American Society for Histocompatibility and Immunogenetics

California Department of Health, HIV Antibody Detection – COS #800028

College of American Pathologists – Lab #18082-01

College of American Pathologists – Reproductive Accreditation Program #18082-32

California Department of Health Services Clinical Laboratory License (Lab ID# COS800028)

California Medi-Cal Program (Medi-Cal #XLAB00560)

Center for Disease Control and Prevention (Lipid Standardization Program)

College of American Pathologists Reproductive Accreditation Program (CAP# 18082-32)

Commonwealth of Pennsylvania Department of Health – CO9003

Florida Clinical Laboratory #800001975

Food and Drug Administration #697 (Transfusion Medicine)

Health Care Financing Administration (CLIA) – 24D0404292

Joint Commission on Accreditation of Healthcare Organizations (Hospital Laboratories) N006611490 (STM) and N006611483 (RMH)

Minnesota Department of Health

New Hampshire Division of Public Health

New York State Department of Health - PFI and Code #3263-824040AO

North Carolina Department of Human Resources (#LH00165)

Ohio Department of Health #C10016

OSHA approved for Blood Lead Analysis

Rhode Island Department of Health (#255)

State of Maryland – Lab Permit #476

West Virginia Department of Health and Human Services - HIV-RL45

Mayo - Department of Laboratory Medicine and Pathology is inspected by the following agencies:

College of American Pathologists

New York State Department of Health

Joint Commission on Accreditation of Healthcare Organizations

Food and Drug Administration (Tx Medicine)

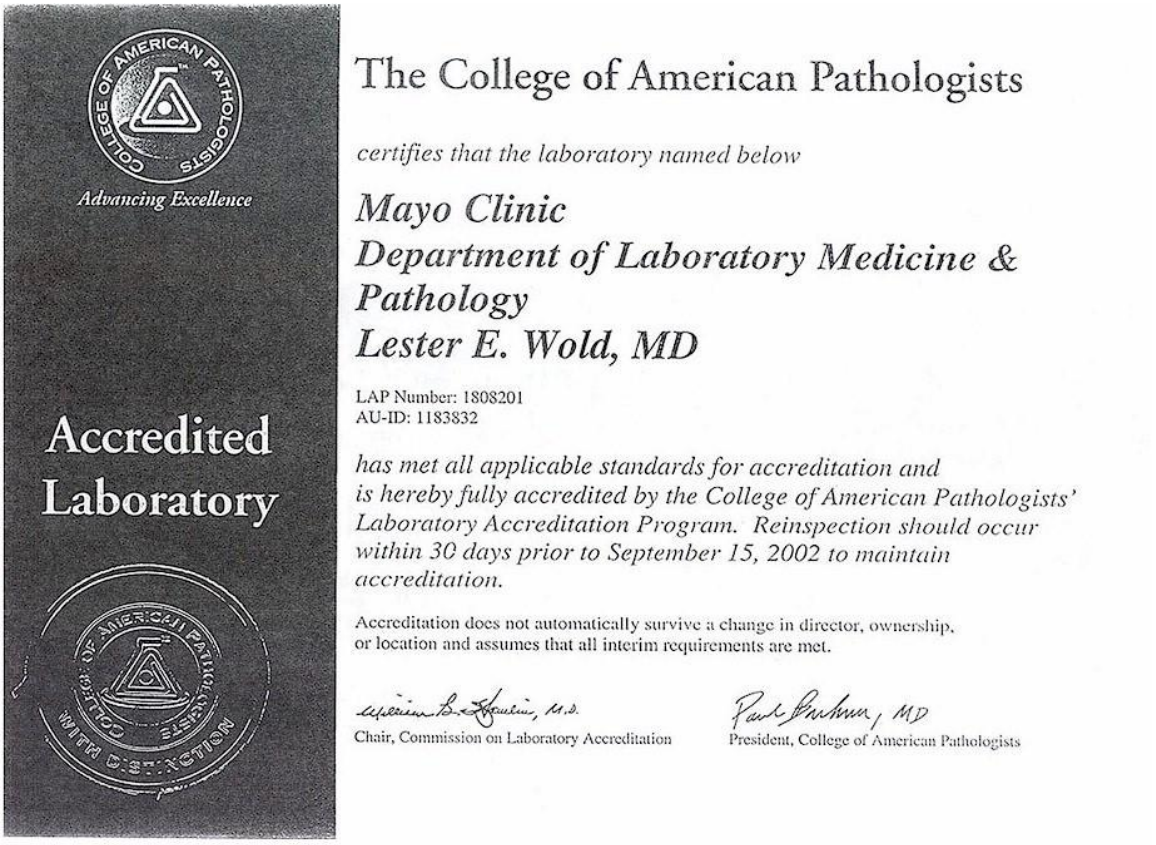
American Association of Blood Banks

American Society for Histocompatibility and Immunogenetics

On-site inspections are performed approximately every two years using specific checklists and standards for the clinical laboratory specialties being audited. Any deficiencies cited during the on-site inspections are corrected prior to receiving the accreditation and/or license.

Mayo performs a self-inspection during the year opposite CAP inspection. MML complies with all accrediting bodies consistent with CLIA 1967 and 1988. In compliance

with the Privacy Act (5 USC 552a(i)) all employees of MML follow requirements for patient records.



Advancing Excellence

Accredited Laboratory

The College of American Pathologists

certifies that the laboratory named below

Mayo Clinic
Department of Laboratory Medicine & Pathology
Lester E. Wold, MD

LAP Number: 1808201
AU-ID: 1183832

has met all applicable standards for accreditation and is hereby fully accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur within 30 days prior to September 15, 2002 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

President, College of American Pathologists

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing Administration

Laboratory: MAYO CLINIC DPT OF LAB MED & PATHOLOGY

Mailing Address: 530 HILTON BUILDING
ROCHESTER MN 55901

Laboratory Director: LESTER E WOLD JR MD

Physical Location: 200 FIRST STREET SOUTHWEST
530 HILTON BUILDING
ROCHESTER MN 55902

CLIA ID#: 24D0404292

Effective Date: February 28, 2001

Expiration Date: February 27, 2003

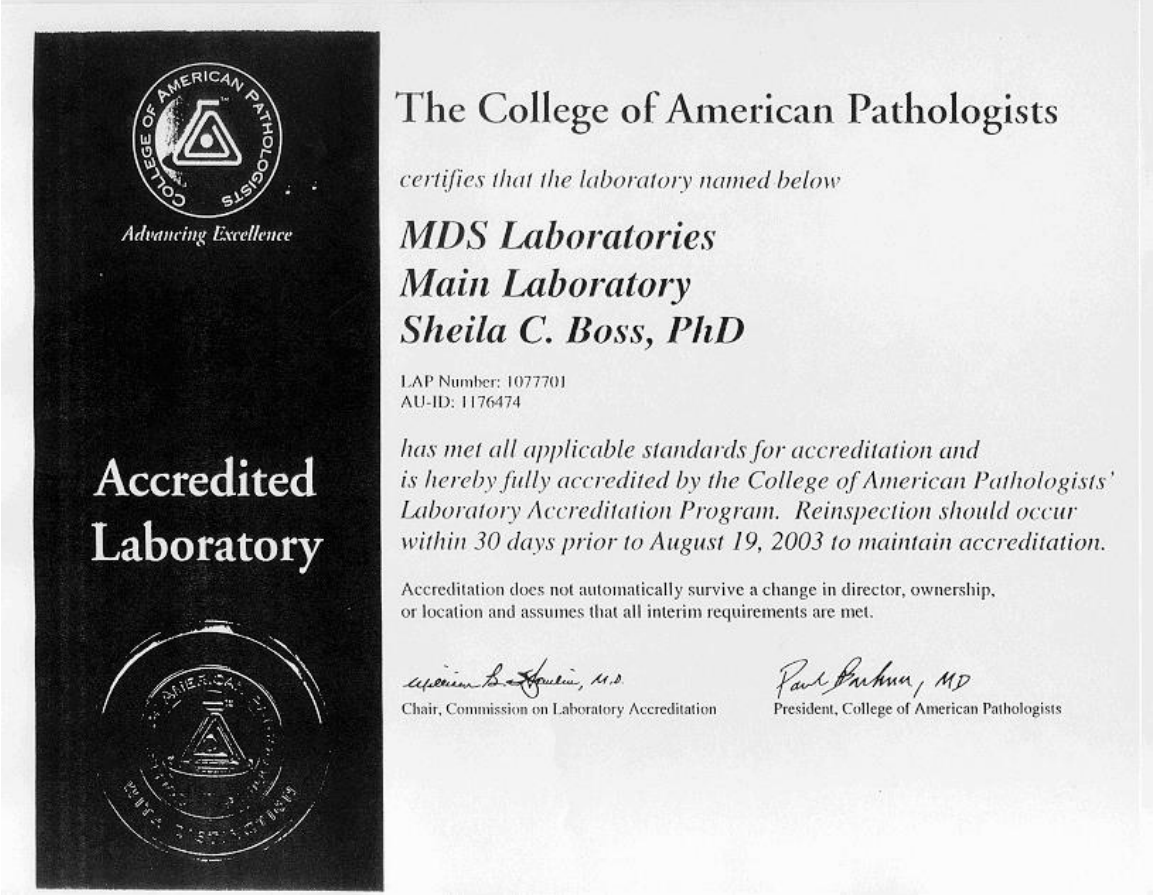
CLIA LABORATORY CERTIFICATE OF ACCREDITATION

Pursuant to Section 353 of the Public Health Service Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), Public Law 100-578, the above named laboratory located at the address shown hereon (and other locations registered under this certificate) is hereby authorized to accept human specimens for the purposes of performing laboratory examinations.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

Judith A. Yost, Director
Division of Laboratories and Acute Care Services
Survey and Certification Group
Center for Medicaid and State Operations

Appendix 10.8: MDS Licensure and Regulations



COLLEGE OF AMERICAN PATHOLOGISTS

Advancing Excellence

Accredited Laboratory

The College of American Pathologists

certifies that the laboratory named below

MDS Laboratories
Main Laboratory
Sheila C. Boss, PhD

LAP Number: 1077701
AU-ID: 1176474

has met all applicable standards for accreditation and is hereby fully accredited by the College of American Pathologists' Laboratory Accreditation Program. Reinspection should occur within 30 days prior to August 19, 2003 to maintain accreditation.

Accreditation does not automatically survive a change in director, ownership, or location and assumes that all interim requirements are met.

Chair, Commission on Laboratory Accreditation

President, College of American Pathologists

DEPARTMENT OF HEALTH & HUMAN SERVICES

Health Care Financing Administration

Laboratory: MDS LABORATORIES

Mailing Address: 100 INTERNATIONAL BOULEVARD
ETOBICOKE ONTARIO CANADA M9W6J6
FN

Laboratory Director: SHEILA BOSS

Physical Location: 100 INTERNATIONAL BOULEVARD
ETOBICOKE ONTARIO CANADA M9W6J6
FN

CLIA ID#: 99D0950529

Effective Date: January 20, 2001

Expiration Date: January 19, 2003

CLIA LABORATORY CERTIFICATE OF ACCREDITATION

Pursuant to Section 353 of the Public Health Service Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), Public Law 100-578, the above named laboratory located at the address shown hereon (and other locations registered under this certificate) is hereby authorized to accept human specimens for the purposes of performing laboratory examinations.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

Judith A. Yost, Director
Division of Laboratories and Acute Care Services
Survey and Certification Group
Center for Medicaid and State Operations

MDS Science Advancing Health

MDS Laboratory Services
100 International Blvd
Toronto, Ontario
Canada, M9W 6J6
Tel: 416 675-3661

Direct Tel: 416 675-6777 Ext. 2296
Fax: 416 675-4693
Email: sboss@mdsintl.com

Thursday, March 21st, 2002

TO WHOM IT MAY CONCERN:

I am writing at the request of Peter Catomeris, Director, Laboratory Services of MDS Pharma Services.

The International Reference Laboratory for MDS at 100 International Boulevard in Toronto maintains a Ministry of Health license, which permits MDS to perform clinical laboratory testing in the Province of Ontario.

The Ministry of Health License #5687, as you know, expires on March 15, 2002. Renewal application has been made to the Ministry of Health.

The inspection of the laboratory by the Ministry of Health took place on April 2nd to April 4th, 2001. Based on the inspection, no major deficiencies were noted and the license will continue. We will receive official notification and documentation shortly. Copies will be forwarded to you at that time.

I trust this information is supportive of your current initiatives and that you will let me know if there is further information we can supply.

Sincerely,

MDS LABORATORY SERVICES

Dr. Sheila Boss, Ph.D., FCACB
Laboratory Director

SB/ma

New York State Department of Health

PFI: 3595 Code: 9000A001 **Clinical Laboratory Permit** CLIA: 99

MDS Laboratories

100 International Blvd

Etobicoke Ontario M9W-6J6 CANADA

Director: Sheila C. Boss, Ph.D.

O

is hereby authorized to perform laboratory procedures at the above location in the fol
categories in accordance with Article 5, Title V, Section 575 of the Public Health La

Bacteriology
General
Clinical Chemistry
Endocrinology
Mycology
General
Oncology
Sera and Soluble Tumor Markers
Parasitology
General
Ther. Sub. Mon./Q.
Urinalysis
Urine Pregnancy T

Effective Date: July 1, 2001
Expiration Date: June 30, 2002

Subject to Rev
Permit Not Tr

STATE OF NEW YORK
DEPARTMENT OF HEALTH

POST CONSPICUOUSLY

COPY

Ontario

Ministry of Health and Long-Term Care

Laboratory and Specimen Collection Centre Licensing Act

Laboratory Licence or Renewal

Ministère de la Santé et des Soins de longue durée

Loi autorisant des laboratoires médicaux et des centres de prélèvements

Permis ou Renouvellement de permis de laboratoire

Under the *Laboratory and Specimen Collection Centre Licensing Act* and the regulations made thereunder and subject to the limitations thereof this
En vertu de la *Loi autorisant des laboratoires médicaux et des centres de prélèvements* et des règlements qui en découlent et sous réserves des restrictions qui sont stipulées, ce permis

- ☐ provisional/provisoire
- ☒ regular/ordinaire
- ☒ renewal/renouvelé

} licence authorizes the establishment, maintenance or operation of
autorise l'établissement, le maintien ou l'exploitation de

MDS Laboratories
(name of laboratory)/(nom du laboratoire)

100 International Blvd., Etobicoke
(address of laboratory)/(adresse du laboratoire)

to perform the following classes of tests:/pour exécuter les testes des catégories suivantes :

AS LISTED ON THE APPENDIX TO THIS LICENCE

Operator(s) of laboratory / Exploitant(s) du laboratoire: MDS Laboratories, A Division of MDS Inc.

Owner(s) of laboratory / Propriétaire(s) du laboratoire: MDS Inc.

This licence is issued subject to the following conditions:

1. That the person(s) named herein as operator(s) of the laboratory is (are) in fact the operator(s) of the laboratory.
2. That the person(s) named herein as owner's of the laboratory is (are) in fact owner(s) of the laboratory.
3. That the laboratory maintains at all times adequate laboratory staff who are qualified to perform the classes of tests specified in this licence.
4. That the laboratory remain situated at the address and location specified in this licence.

Ce permis est délivré sous réserves des conditions suivantes :

1) la ou les personnes nommées ci-dessus comme étant le ou les exploitants du laboratoire sont en fait les exploitants du laboratoire;
2) la ou les personnes nommées ci-dessus comme étant le ou les propriétaires du laboratoire sont en fait les propriétaires du laboratoire;
3) le personnel du laboratoire est toujours du personnel de laboratoire ayant les compétences voulues pour exécuter les catégories de tests désignées sur ce permis.
4) Le laboratoire se trouve bien à l'adresse et dans les locaux désignés sur le permis.

Date issued / Date d'émission: March 16, 2001

Expiry date / Date d'expiration: March 15, 2002

Licence number / Numéro du permis: 5687

D M Ogram

Director of Laboratory and Specimen Collection Centre Licensing
Directeur de la délivrance des permis aux laboratoires et aux centres de prélèvements

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