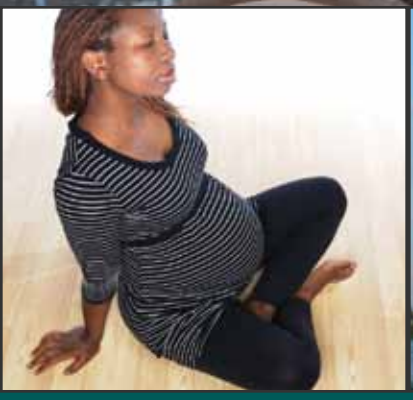

Early Exposures to Hazardous Chemicals/Pollution and Associations with Chronic Disease: *A Scoping Review*

Executive Summary

June 2011

A Report from the Canadian Environmental Law Association, the Ontario College of Family Physicians and the Environmental Health Institute of Canada

The complete report is available in English from www.cela.ca and www.healthyenvironmentforkids.ca.

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Ce document est également disponible en français au www.cela.ca et www.healthyenvironmentforkids.ca. Le rapport complet est également disponible en anglais au www.cela.ca et www.healthyenvironmentforkids.ca.

Foreword from CPCHE and OCDPA

In 2008, the Canadian Partnership for Children's Heath and Environment (CPCHE) and the Ontario Chronic Disease Prevention Alliance (OCDPA) – together comprising more than 35 organizations – embarked upon a multi-year collaboration, funded by the Ontario Trillium Foundation, to explore the known and suspected links between early environmental exposures and the later development of chronic disease. This collaboration was centred around the two networks' shared commitment to health promotion and a common concern about chronic diseases – specifically asthma, cancer, cardiovascular disease, diabetes and neurodegenerative disorders, among others – that are affecting large numbers of people. It was also based on a recognition that opportunities for prevention start early: during infancy and childhood, in the womb and even prior to conception.

The burden of chronic disease in Ontario and across the country is very high. In Ontario, about one in three people (all ages) have one or more chronic diseases. At least 60 percent of Ontario's health-care costs are related to chronic disease. Within the multiple determinants of health, it is understood that chronic diseases are typically complex conditions with multiple risk factors some of which can be the result of lifelong influences and circumstances. The social determinants of health are increasingly understood to be of paramount importance in contributing to the most common chronic diseases and their better-understood biomedical and behavioural risk factors. Adding to this complexity is the potential influence on chronic disease of environmental exposures, such as air pollution and other toxic substances, including the need to consider key differences between effects in adulthood versus during childhood or in the womb.

We know that, compared to adults, children are more exposed to toxic substances in their environment because of differences in size, intake and behaviour. They are also more vulnerable to adverse effects of toxic exposures. The flip side of this early vulnerability is that exposure reduction efforts specifically targeted at these formative years could have positive implications for lifelong health, particularly when combined with ongoing efforts to promote healthy eating and exercise, combat poverty and address other determinants of health.

The CPCHE and OCDPA partners are pleased to welcome this report, which has been prepared by the Canadian Environmental Law Association (CELA) in collaboration with experts in medicine and public health as a substantive contribution to our ongoing CPCHE-OCDPA collaboration. Applying the multiple determinants of health framework, the report

places the evidence about environmental risks in the broader context of existing knowledge about the multiple risk factors for several common chronic diseases. As such, it provides the two networks and the broader community with an evidence base from which to explore opportunities for prevention-oriented improvement in policy and practice.

The mutual sharing of expertise and perspectives between the chronic disease prevention and children's environmental health protection sectors, via this project, have resulted in new collaborations and a deeper understanding of the intrinsic linkages between our respective mandates and efforts. Fundamentally, the mandates of both networks include the prevention of chronic disease with a precautionary approach underpinning our collective health promotion efforts. We look forward to using these newly established connections and enhanced knowledge as we continue to work towards a healthier Ontario.

Erica Phipps
CPCHE Partnership Director
on behalf of CPCHE

Norman Giesbrecht and Chris Markham
OCDPA co-chairs
on behalf of OCDPA

Executive Summary

Project Scope and Report Overview

This report is a product of a network to network collaboration among groups involved with the Canadian Partnership for Children's Health and Environment and the Ontario Chronic Disease Prevention Alliance (CPCHE and OCDPA) to provide a baseline for further collaboration. The central focus is a scoping review of evidence for associations between early life environmental exposures and the later development of several of the most common chronic diseases.

Part One provides context about chronic disease and care in Canada's aging population, the reality of the multiple determinants of health, the primacy of the social determinants of health, the considerable breadth of environmental influences on health, the importance or early child development to lifelong health and the scope and complexity of multiple inter-relationships among all these health determinants.

Part Two introduces the Developmental Origins of Health and Disease (DOHaD) concept and the related and expanding field of epigenetics. It also discusses key issues that arise in evaluating evidence in complex environmental health issues. The main focus is review of the multiple risk factors for several common chronic diseases (cardiovascular disease, type 2 diabetes, several cancers, asthma, Alzheimer's disease and Parkinson's disease) and includes a detailed look at the evidence for links to environmental exposures. Evidence is reviewed for associations between health outcomes and both adult exposures and early life exposures, including in the womb.

Main Findings

Overall conclusions include the fact that chronic diseases and interrelated contributory factors are far more complex than is implied in, or amenable to response strategies focused solely on individual behavioural changes. In particular, there is a critical need to address poverty and the social determinants of health (SDOH) given the reality of biomedical and behavioural risk factors for various diseases arising from social and economic conditions. Environmental influences on health are multifaceted, involving multiple pollutants, exposure routes, on a scale ranging from macro to micro (e.g., from built environment features to the loading of floor dust with toxic substances), multiple interrelationships, and life course vulnerabilities. It is already well-established that the *in utero* and perinatal "environment" and maternal and early childhood circumstances play major roles in the risk of later life disease. Within this new paradigm for disease causation, the DOHaD concept and the related field of epigenetics, a rapidly expanding body of research indicates a role for early life exposure to environmental contaminants in this lifelong continuum of disease vulnerability. Because of the abundant complexity, not only is there a need for more research, but also to adjust assessments of the strenghth of evidence for associations between risk factors and health outcomes via tools such as the Bradford Hill criteria and hierarchical models of study designs. Given the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures, a broader approach to prevention is worthwhile. The following table provides a summary of early exposures (*in utero* or childhood) for which there is evidence of associations with prevalent chronic diseases addressed in this review.

Chronic Disease and Care in Canada's Aging Population

Canada has an aging population (currently 13% are aged 65 and over, predicted to rise to 25% by 2036) with high prevalence and in many cases rising incidence of many chronic diseases. 80% of those over 65 have one chronic disease, and, of those, 70% have two or more chronic diseases. More and more children are experiencing chronic diseases, or conditions that lead to chronic diseases. Low birth weight and preterm births are understood to be indicators of potential lifelong consequences (as discussed throughout this report) and incidence of preterm birth in Canada (excluding data from Ontario) has been rising steadily for 20 years.

Table 1: Summary of Early Exposures Associated with Prevalent Chronic Diseases or Conditions

NOTE: Important detail about strength of evidence is lost with this aggregation – see specific sections of this report for more detail

Cardiovascular disease (CVD)	• Lead, smoking, particulate air pollution, • Substances associated with cardiac birth defects • Substances associated with low birth weight • Endocrine disrupting substances affecting insulin signalling (BPA and phthalates), adult dev'mt of polycystic ovarian syndrome (BPA and other EDCs), lower testosterone levels in adults (BPA, phthalates, PCBs), and dysfunction in HPA-axis and stress response (lead).
Cardiac Birth Defects	• Ambient air pollution (specifically carbon monoxide and ozone), organic solvents in dyes, lacquers and paints (specifically halogenated hydrocarbons including trichloroethylene and dichloroethylene), chlorophenoxy herbicides, trihalomethanes, additional pesticides, ionizing radiation, lead, benzene, sulphur dioxide, ETS.
Low Birth Weight	• Air pollution – CACs (particularly sulphur dioxide and particulates), maternal smoking, ETS, PAHs, lead, mercury, arsenic, OC and OP pesticides, nitrates in drinking water, phthalates, BFRs, polyfluorinated compounds.
Obesogens	• Endocrine disrupting substances suspected as obesogenic (BPA, phthalates, organotins, PBDEs, polyfluoroalkyl compounds, OC pesticides, PCBs) • Human adenovirus 36, phytoestrogens, glycyrrhetinic acid (sweetener)
Type 2 Diabetes	• Prudent to assume that known continuum of common risk factors across CVD, metabolic syndrome and diabetes likely extends to early environmental exposures • Substances associated with low birth weight • Endocrine disrupting substances relevant to CVD • Suspected obesogens
Alzheimer's disease	• Prudent to assume that known continuum of common risk factors across CVD, metabolic syndrome, diabetes and Alzheimer's disease likely extends to early environmental exposures • Air pollution, lead
Parkinson's Disease	• If link to obesity confirmed, prudent to consider obesogens as environmental risk factors • Air pollution, certain pesticides (maneb and paraquat, OC pesticides)
Developmental Neurotoxicity	• Lead, mercury, arsenic, manganese, organic solvents, OP and OC pesticides, PAHs, ETS, PCBs, phthalates, BPA, dibutyltin, PBDEs, triclosan, artificial food colours and additives.
Cancer • Breast • Prostate • Testicular • Other Cancers	• Breast cancer: ionizing radiation, benzene and organic solvents, 1.3-butadiene, aromatic amines, BPA, phthalates, parabens, alkylphenols, PAHs, OC and triazine pesticides, PBDEs and other POPs, metals, tobacco and ETS, vinyl chloride, ethylene oxide. (See also Table 6.) • Prostate cancer: Synthetic hormones in food production, BPA • Testicular cancer: Maternal exposure to several POPs • Testicular Dysgenesis Syndrome: EDCs with anti-androgenic action (phthalates, some pesticides, BPA) • Other Cancers: particulate air pollution, radon, multiple pesticides, chlorination byproducts, cadmium, aromatic amines, PAHs, diesel exhaust, smoking and ETS, dioxin, ionizing radiation, vinyl chloride, some paints and solvents, cell phone use (see also Table 5)
Respiratory disease (asthma)	• Substances associated with low birth weight • Smoking and ETS, aeroallergens, indoor and outdoor air pollution including all the CACs (ozone, CO, PM_{10} and $PM_{2.5}$, nitrogen dioxide, sulphur dioxide, many different VOCs), multiple hazardous air pollutants (PAHs, aldehydes, acide vapours and aerosols, diesel exhaust), formaldehyde, VOCs, phthalates, aldehydes, isocyanates, anhydrides, cadmium, hexavalent chromium, manganese, nickel, benzene, dibutyl phthalate, dioxins, PCBs, metals (esp. lead), some pesticides, BPA, perfluorinated compounds

In Ontario, one in three people (of all ages) have one or more chronic diseases, and at least 60% of Ontario's health care costs are due to chronic diseases. In Canada, the prevalence of the most prominent chronic diseases is estimated to be in the multi-millions of affected individuals. Cost estimates are in the multi-billions of dollars with indirect costs, particularly of family caregivers, generally unrecognized.

There is strong and consistent evidence of socio-economic disparities in health, with significantly poorer health and shorter life expectancy for those living in poverty. The annual disease burden attributable to environmental exposures has been estimated from studying mortality, hospitalizations, patient-days spent in hospital, low birth weight, and serious congenital anomalies, for four major categories of diseases (respiratory, cardiovascular, cancer, and congenital affliction). Annual costs in Canada are conservatively estimated to be between $3.6 and $9.1 billion.

Understanding Environmental Exposures

Environmental exposures can include chemicals used in myriad products or released to the environment as various forms of pollution. Toxicants can be present in air, soil, dust, food, water, and consumer products, as well as simultaneously across all media. The reality of multiple exposures occurring across multiple media and often changing over time and by location creates major challenges in understanding relationships between environmental exposures and health outcomes.

Criteria air contaminants (CACs) in outdoor air pollution include coarse, fine and ultra-fine particulate matter (PM), carbon monoxide, oxides of sulphur and nitrogen, ammonia and volatile organic compounds (VOCs). Levels of these pollutants are highest in areas of high traffic volume, industrial activity, coal-fired electricity generation, and residential wood fuel combustion. Smaller contributions arise from many other activities. Lower volume, diverse outdoor air pollutants that are frequently more toxic at lower exposure levels are emitted from similar sources. For example, the largest sources of dioxin and furan (highly toxic persistent organic pollutants – POPs) emissions in Canada are from the incineration of municipal and medical waste.

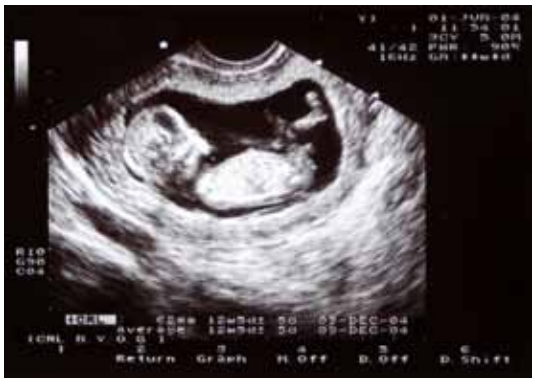
Soil pollution can result from legacy industrial site contamination or use of toxic metals (e.g. lead in paint and gasoline; arsenic as a wood preservative).

Indoor air pollution arises largely from consumer products, which are increasingly understood to partition into house dust, as well as products of combustion, biological allergens, and radon. Drinking water may contain disinfection byproducts, industrial effluents and pharmaceutical residues, biological contamination, as well as geological contaminants such as arsenic, or lead used in plumbing.

Food contamination depends on food type, processing, packaging, storage, and preparation methods, as well as fat content (lipophilic contaminants tend to be persistent and bioaccumulative, and are often highly toxic). A mother's body is a child's first environment, with many toxicants able to cross the placenta and to be expressed in breast milk.

Extensive evidence indicates that house dust contains more than 100 potentially toxic substances and allergens. House dust and PM in indoor air, from indoor and outdoor sources, are among the most important media for childhood exposures to lead, PBDEs, pesticides, polyaromatic hydrocarbons (PAHs), phthalates and other endocrine disrupting compounds (EDCs), arsenic, chromium, mould, endotoxin and bacteria.

Fetus and Child More Vulnerable



Infants and children are more exposed to environmental contaminants than adults because of their relatively larger absorptive surface areas, more rapid breathing, higher rate of ingestion, and hand to mouth exploratory behaviour. They are also more vulnerable to these exposures due to rapidly developing, still immature organs and body systems, including detoxification systems. Some children are genetically more susceptible to environmental insults, with lifelong implications.

Widespread Exposure of Uncertain Significance

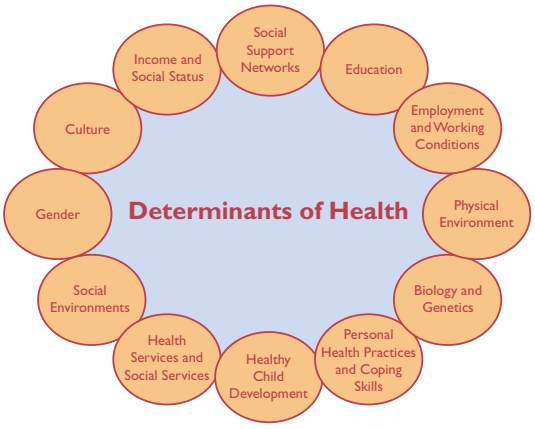
Human biomonitoring has revealed multiple chemicals in blood, urine, breast milk, and sometimes hair and nails, both in large population-based studies in Canada and the U.S., as well as in several smaller studies. Humans of all ages, from newborns to those entering their 8th decade, have retained legacy substances such as lead, mercury, PBDEs, PCBs, and organochlorine (OC) pesticides, as well as substances still being produced such as BPA, phthalates, perfluorinated compounds, acrylamide and perchlorate. The consequences of exposure to low levels of multiple substances are uncertain and the subject of extensive study.

The Multiple Determinants of Health

Many complex and dynamic factors combine, and often interact, to influence individual and population health. The Multiple Determinants of Health (MDOH) framework is useful but it can be limited in conveying the breadth of issues in the areas of social determinants of and environmental influences on health.

Application of the model in public health or health sciences focuses heavily on behavioural and biomedical risk factors, whereas quantitative and qualitative evidence from around the world points to crucial influences of the social determinants of health (SDOH) and early child development (ECD). There is also increasing evidence of the role environmental factors, such as exposure to pollution and toxic chemicals, play in the development and exacerbation of many chronic illnesses, but these have received limited attention in the SDOH and ECD literature.

Behavioural or modifiable risk factors include smoking and alcohol consumption, as well as exercise and eating habits, which commonly overlap with intermediate conditions known to be associated with chronic disease. Such intermediate conditions can include biomedical risk factors such as high blood pressure, high blood cholesterol, obesity, and high blood sugar. Chronic disease prevention strategies give priority to addressing the "big three" behavioural risk factors: unhealthy eating, physical inactivity and tobacco use/exposure. However, this focus belies the underlying importance of the SDOH, that is, the economic, social, and living conditions of daily life.



While behavioural choices or biomedical factors are individual, societal conditions are fundamentally influential. Although ill health is most prominent among the poorest of the poor, the World Health Organization confirms that health and illness follow a social gradient worldwide: at all levels of income, the lower the socioeconomic position, the worse is a person's health. In Canada, this gradient seems to disproportionately affect newcomers to Canada and Aboriginal communities. Inattention to the SDOH as primary determinants can undermine individual behavioural choices to achieve better health, including the ability to adopt such choices at all.

Environment is similar to income level or gender in being a cross-cutting determinant of health that interacts in many different ways with other determinants, especially the SDOH. Environmental determinants can encompass the entirety of indoor and outdoor circumstances of people's lives, with multiple media and routes of exposure that can vary widely according to activities occurring on a scale from individual to local to regional to global.

For example, some key issues are land use planning choices that result in a pervasively automobile-dependent lifestyle that in turn contributes to health-harming air pollution and climate change; a built environment that contributes to sedentary lifestyles and related overweight/obesity; and an increasingly mechanized, centralized and fossil fuel-dependent food production and marketing system that has altered the composition of food and is a major contributor to climate change and the glut of inexpensive sources of unhealthy food.

Many severe health impacts of climate change are expected to occur in coming decades when an unprecedented one quarter of the population will be over age 65 and, if current trends continue, the overwhelming majority if these seniors will be afflicted with at least one or more chronic diseases. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health- air, food, water and shelter.

Interacting Environmental and Social Risk Factors

There is evidence of more pronounced impacts of air pollution among poorer people, with higher pollution-related hospitalization and mortality rates. There is a greater likelihood that communities with low income and/or racial minorities to live near polluting industrial facilities, hazardous waste sites, or high traffic corridors. Poor quality housing can increase exposure to mould, other biological allergens, pesticides, lead, asbestos, and likely other contaminants. A 30-year retrospective analysis of population health and housing found that poor housing quality was related to higher levels of asthma, respiratory illness, obesity, diabetes, and lead poisoning, among other adverse health outcomes.

When nutrition is inadequate, children and the developing fetus are at greater risk from environmental exposures because deficiencies in protein, calcium or iron can enhance absorption of toxic substances such as lead. Cultural, as well as economic influences, affect intake of food-borne contaminants such as mercury and lipophillic POPs in fish; this occurs more often among Aboriginals, coastal community residents, and immigrant populations from Asia.

Combining both locational and nutrition issues, low income communities can also tend to have limited access to stores selling good quality food, greater access to fast food outlets, and an overall tendency to consume lower quality, energy dense foods due to greater affordability.

Smoking prevalence is twice as high among lowest income Canadians compared to the highest, but the Canadian Tobacco Use Monitoring Study shows a downward trend in most age groups, particularly in the percentage of children exposed at home to ETS.

Many early environmental exposures of concern originate in consumer products. These can include legacy components such as lead, PCBs, banned pesticides and flame retardants and newer components such as phthalates and BPA in plastics. These and many other contaminants are known to partition to house dust and can be at very high levels in older carpets. Such product-based indoor exposures are plausibly higher in the poor because of longer use of lower quality or second-hand goods, including older dust-laden carpets, and greater consumption of canned food affected by BPA-containing can liners. Exposure to lipophilic toxic substances will also be higher among those consuming a high fat diet.

Early Child Development

Early experiences fundamentally affect how the structure of the brain develops in early childhood, the evolution of emotional and social temperament and coping skills, abilities with language

and literacy, perception and cognition, and attitudes that may affect capacities for both physical activity and psychological health. Literature on early child development confirms a strong correlation between disadvantaged conditions in childhood and multiple aspects of poorer health later in life. There are long-term economic consequences of thwarted child development in terms of loss of human capital, poor health and insufficient community services.

There is a striking absence from the Canadian ECD literature of consideration of the developmental neurotoxicity of environmental contaminants. The fact that the otherwise exemplary and influential Canadian studies on this topic do not consider the evidence about the developmental neurotoxicity of environmental exposures, particularly the greater vulnerability *in utero*, illustrates a valuable reason for the collaboration behind this report; to review the evidence of environmental contributions to chronic diseases, and to put it into necessary context.

The Causal Puzzle

There is a tendency for research to be reductionist, focusing on multiple but separate environmental risk factors for chronic disease, i.e. individual pieces of the puzzle, rather than the causal puzzle itself. For example, understanding of the individual and combined effects of the domains of toxic substances, social environments, and nutrition is aided by recognition of how multiple factors can occur and interact within each domain as well as across two or all three, and that the relative importance of each can vary by circumstance. Understanding is hampered by large knowledge gaps about the health impacts and exposure circumstances of the many toxic substances to which children are exposed, as well as the potential for interactions.

The Developmental Origins of Health and Disease (DOHaD) and Epigenetics

The Developmental Origins of Health and Disease (DOHaD) explores the associations between adverse events during vulnerable, early life stages and later life patterns of health and disease, such as the relationship between maternal prenatal undernutrition, low birth weight and increased risks for metabolic syndrome, diabetes, cardiovascular disease, malignancies, osteoarthritis and dementia in adulthood.

Considerable evidence points to the *in utero* and perinatal environment as playing a major role in later life disease risk with epigenetic processes, or gene-environment interactions, as one important explanatory mechanism. “Environment” here is broadly defined to include maternal age, health status, nutrition, stress levels, etc. However, the similar concept of “windows of vulnerability” describes the greater vulnerability of the developing fetus or young child to environmental exposures during early life. Herein is a key nexus between the work of CPCHE and OCDPA.

Epigenetics processes likely underlie aspects of the toxicity of many environmental exposures of concern and are therefore highly relevant to understanding the evidence about early exposures to chemical substances and the development of chronic disease. The Bradford Hill criteria for causation provide useful signposts for judging the overall strength of an association and by extension, strength of a body of evidence. However, they are inadequate to the task of evaluating the complex and dynamic processes that contribute to disease in a multi-causal model.

Indeed, for environmental exposures that may fundamentally alter the life course via impacts on prenatal or perinatal development, a demand for epidemiological evidence to confirm the

existence of a chronic disease risk factor has significant implications. Application of the Bradford Hill criteria of analogy and plausibility could be more prudently applied to early environmental exposures in the context of recognizing that epidemiological evidence does not tend to become available until long after widespread exposure and often irreversible environmental contamination has occurred.

Early Exposures and Cardiovascular Disease

Despite a trend to dramatically decreasing rates of CVDs in Canada in past decades, the burden of CVD is expected to remain considerable, due to changing demographics and the prevalence of underlying risk factors. Heart disease and stroke, alongside cancer, remain the three leading causes of death and CVDs continue to be the leading cause of hospitalization in Canada.

Canadian and international research indicates that nine significant biomedical and behavioural risk factors account for the vast majority (90% or more) of the population attributable risks for myocardial infarction (heart attack) and stroke. These nine risk factors are abnormal lipids, smoking, high blood pressure, type 2 diabetes, abdominal obesity, psychosocial stress, limited or lacking consumption of fruits and vegetables, regular excess acohol consumption, and limited or lacking regular physical activity. However, a social determinants of health approach indicates also that material deprivation, along with psychosocial stress and the adoption of unhealthy coping behaviours are critical underlying risk factors to consider.

The DOHaD evidence indicates also that early life influences are highly significant and likely of greatest importance to those living in poverty in terms of nutritional factors (including inadequate fetal nutrition and nutritional imbalance) but also stress.

Although the nine traditional risk factors are considered to account for most of the CVD risk in a population and are thus crucial risk factors to control, there is increasingly clear evidence of impacts at a population level on CVD from environmental exposures such as particulate air pollution and lead (i.e., exposure among adults and perhaps due to lifelong exposure).

In addition to the CVD risk from low birth weight, congenital cardiac birth defects can also lead to later life CVD risk. These two outcomes are also associated with a wide variety of environmental exposures including air pollution and environmental tobacco smoke (ETS), certain solvents, pesticides and heavy metals. Additional early life exposures that may contribute to later life CVD risk including substances with endocrine disrupting potential, like BPA and lead.

Early Exposures and Diabetes

There is a high prevalence (6.2% among those ages one and older in 2006-07) and rising incidence of type 2 diabetes in Canada, within the context of a global pandemic of this disease. Rates of diabetes[1] are higher in Ontario compared to the Canadian national average and are distinctly higher among First Nations populations across Canada.

Obesity is a clearly linked, yet independent risk factor for type 2 diabetes. The dramatically rising obesity rates in Canada are, not surprisingly, paralleled by the increasing population statistics for diabetes. Excess food intake and insufficient physical activity on a population level are still viewed as important contributors to the secular trend to increasing obesity. However, experts indicate that several other risk factors, including exposure to endocrine disrupting chemicals, intrauterine environment and transgenerational factors, and social determinants of health, among others, provide plausible evidence of additional contributors to the global obesity pandemic.

1 90% of diabetes cases are Type 2 and the focus of this report. Henceforth, diabetes is intended to mean Type 2 diabetes.

Alongside genetic risk factors, there is considerable overlap among the economic, social and psychosocial risk factors for obesity, metabolic syndrome, diabetes and CVD. In addition, obesity and diabetes are themselves risk factors for other chronic diseases such as certain cancers, Alzheimer's disease, cognitive impairment, dementia, and CVD.

Evidence suggests that exposures to a broad range of environmental agents may disrupt insulin metabolism or alter biochemical activity in the pancreas, and be implicated in the onset of diabetes or of its related risk factors. Evidence is limited, largely cross-sectional in nature, and focussed on exposure during adulthood but has prompted studies in developing organisms that indicate endocrine disrupting compounds may act on genes during development in a manner that permanently affects the nature of adipose tissue and multiple metabolic processes in the body. These studies are instructive as to the possible associated diabetes risks from exposure to air pollution, lead, BPA, some phthalate metabolites, organophosphate (OP) pesticides and POPs (such as DDE, PCBs and dioxins).

The DOHaD framework and epigenetics contribute to understanding the role intrauterine conditions (e.g. fetal undernutrition or overnutrition; low birth weight, exposure to endocrine-disrupting substances) play in increasing risks for obesity and diabetes in later life.

The concept of endocrine-disrupting substances as "obesogens," was first described in 2006. Suspected obesogens are typically ubiquitous environmental chemicals that may act at very low levels of exposure and inappropriately influence the creation of fat cells and permanently affect the nature of adipose tissue, metabolic processes in the body and weight homeostasis. This body of evidence is largely accumulating from toxicological studies. Epidemiological studies are more limited and less consistent in their findings of obesogenic properties of environmental chemicals.

The list of possible obesogenic chemicals noted in recent reviews includes, DES, BPA, phthalates, organotins, PBDEs, polyfluoroalkyl chemicals, and POPs including OC pesticides and PCBs. Effects may occur by multiple mechanisms and may differ if exposure occurs *in utero* (during development) or during adulthood. The obesogen hypothesis proposes that the metabolic changes induced by environmental chemicals (i.e., altered fat differentiation or function and the initiation or misregulation of homeostatic controls) are superimposed on current trends of excess food intake and limited physical activity. This is an important area for further research, including a strong need for more compelling epidemiological data.

Early Exposures and Brain Impacts – Focus on Alzheimer's Disease and Parkinson Disease

Alzheimer's Disease (AD), and related dementias such as vascular dementia, as well as other neurodegenerative diseases such as Parkinson's Disease (PD) are considered part of a rapidly growing epidemic related to an aging population and the convergence of multiple risk factors. About 500,000 Canadians have dementia (about 63% is AD) and this number is predicted to be over 1.1 million in 2038. PD affects more than 100,000 people, a number predicted to double by 2050.

Advancing age is a key risk factor. The small proportion of AD associated with genetic risk factors typically manifests at an earlier age than other dementias of old age. Gender is a risk factor for AD in post-menopausal women. Strictly genetic risk factors account for about 5-10% of PD with the balance caused by complex gene-environment interactions that are not fully understood. Gender is a risk factor for PD with men having twice the risk as women. Research indicates that healthy brain aging results from a lifelong continuum beginning with healthy brain development and creation of brain reserve. Research indicates that healthy brain aging results from a lifelong process beginning with healthy brain development and creation of "brain reserve." Research into both AD and PD indicates that the timing and/or likelihood of their occurrence in old age results from a complex combination of lifelong influences ("multiple hits" and the "silent toxicity" or

latency of some risk factors), including epigenetic influences in the womb, that contribute to "brain reserve."

A continuum of common risk factors exists for obesity, metabolic syndrome, diabetes, CVD, AD and vascular dementia. Obesity may also be a risk factor for PD. Common risk factors include the same nine biomedical and behavioural risk factors noted for CVD as well as the additional risk factors noted for obesity and diabetes. Of particular importance among the common risk factors are those where circumstances contribute to inflammation and oxidative stress and thence to disrupted insulin signaling with some researchers calling AD "diabetes of the brain." Links to PD pathologies are more specific to effects of oxidative stress in the brain.

For environmental exposures in adults, insofar as a continuum is apparent whereby AD, and to a more limited extent PD, share common risk factors with other chronic diseases, the environmental exposures associated with these other conditions are also relevant. Recapping from the discussions about CVD and diabetes, these exposures include: air pollution, lead, BPA, phthalates, OP pesticides, and POPs.

Some adult exposures more directly implicated in AD include lead exposure (perhaps due to lifetime chronic exposure) and air pollution (also implicated in PD). Although there is less evidence, associations have been suggested with pesticides (PD via occupational exposure), PCBs and other POPs (AD, dementia/cognitive decline and PD), solvents (PD), and some additional metals (manganese, iron and copper with possible links to PD).

Likewise for early life exposures, the apparent continuum of several chronic conditions and diseases, including shared risk factors, is also relevant for AD and to some extent PD. Recapping early life exposures of concern in terms of being risk factors common to an apparent continuum of multiple chronic diseases, including AD, these exposures include: air pollution, organic solvents, chlorophenoxy herbicides, trihalomethanes, ionizing radiation, lead, ETS, mercury, OC and OP pesticides, nitrates in drinking water, arsenic, phthalates, BFRs, polyfluorinated compounds, BPA, phthalates, organotins, and PCBs.

Early life exposures for which there is more direct evidence of possible associations with later life neurodegeneration include air pollution (associations with AD, and to lesser extent PD) and lead (associations with AD).

Comparing the list of substances suspected in developmental neurotoxicity indicates considerable overlap with substance where evidence indicates associations with AD, PD or various conditions and diseases that may be co-morbid risk factors such as obesity, metabolic syndrome, diabetese and CVD.

Early Exposures and Cancer

Cancer represents a considerable chronic disease burden in Canada, having overtaken CVD as the leading cause of death. While cancer mortality is declining overall, it is predicted that nearly half of all Canadians will get cancer and approximately one in four will die from cancer. The most common cancers in Canada vary by gender and are breast, prostate, lung and colorectal cancers. Cancer agencies in Canada note increasing incidence in certain cancers (e.g. thyroid) and rising trends among adolescents and young adults, although cancer is still largely a disease of older adults.

Although influential work from the 1980s minimized the role of environmental factors in cancer causation, more recent research is seeking to correct that now outdated view. Genetic inheritance accounts for a small percent of cancers. Genetic polymorphisms may interact with environmental factors to influence human cancer causation. Additional processes affecting cancer susceptibility

such as cellular detoxification can be influenced by exogenous variables such as stress and nutrition, which are in turn affected by the broad SDOH.

There are many cancer risk factors, including the well known behavioural risk factors (smoking, diet, physical inactivity) along with others such as alcohol consumption, obesity, and social factors. A very large and growing body of evidence points also to multiple environmental and/or occupational exposures as known and/or suspected contributors to many different cancers, including those in highest prevalence.

Adding to the genetic mutation theories of cancer causation is expanding knowledge of the epigenetic mechanisms and events from the influence of external factors, including exposure to environmental contaminants. Epigenetic mechanisms are seen as central to understanding how cancers develop and progress. Furthermore, this knowledge indicates that these mechanisms are also centrally involved in early life events that can lead to later life cancer.

Molecular epidemiology, using biomarkers (such as cord blood levels of known carcinogens or their metabolites or cotinine from exposure to ETS), offers promise as an approach to detecting and preventing cancer development including those that result from early life exposures.

A wide range of chemical substances and physical agents are implicated in human carcinogenicity principally from studies of adults exposed occupationally or environmentally. The evidence for greater vulnerability of those exposed prenatally or in childhood to known or suspected carcinogens suggests two overall mechanisms: direct but delayed causation and increased sensitivity to later exposures.

There is evidence of early life exposure risk factors related to three highly prevalent cancers (breast, prostate and testicular cancers), which are a focus of this report.

For early life exposures and breast cancer, the greatest risks appear to come from large categories of substances suspected of endocrine disruption, either as xenoestrogens (i.e., foreign estrogens) or those with other endocrine disrupting properties. Substances of concern include POPs such as dioxins, PCBs, and most of the persistent OC pesticides such as DDT, its metabolite DDE, as well as dieldrin, aldrin, heptachlor and chlordane. Other less persistent xenoestrogenic substances, like BPA, are implicated on the basis of animal studies for increasing breast cancer risk. More limited evidence exists for links to breast cancer from exposure to alkylphenols, several metals, phthalates, parabens, UV filter components of sunscreens and the food additives bovine somatotropin (rBST) and zeranol.

Experts describe the potential for these substances to exert permanent epigenetic changes (during mammary gland development *in utero*) that alter later susceptibility, often before and during puberty, to other factors that can initiate breast cancer.

Based on occupational studies, some evidence for increased risks of prostate cancer, possibly via endocrine disruption mechanisms, implicates some pesticides, PCBs and cadmium. There is also evidence linking early life exposure to the synthetic hormone DES and to BPA to later prostate cancer via endocrine-disrupting modes of action.

Epidemiological and toxicological evidence supports the hypothesis that disruptions in sex hormones, occurring during fetal development, play a role in the current increasing incidence of testicular cancer, and of genital abnormalities in boys. Experts have suggested a broader range of risk factors, including environmental exposures, as being involved in the etiology of the developmental disorder called testicular dysgenesis syndrome (TDS) which they postulate is an indicator also of testicular cancer risk.

The TDS concept is a unifying hypothesis that invokes a common fetal origin of four effects on the male reproductive system, including the birth defects cryptorchidism (undescended testicles) and hypospadias (brith defect in the male urinary tract), poor semen quality and the later development of testicular cancer. Multiple animal studies have demonstrated these effects from endocrine

disrupting chemicals. Some pesticides, certain phthalates, perfluorochemicals and bisphenol A may all disrupt fetal testes development and are implicated in the development of TDS.

Early Exposures and Respiratory Disease

Although likely a large underestimate, prevalence of certain physician-diagnosed respiratory diseases in Canada is very high, most prominently asthma (2.74 million), chronic obstructive pulmonary disease (COPD) (>754,000), and lung cancer (>20,000). The focus in this report is on asthma due to high prevalence, evidence of associations with early environmental exposures (along with other risk factors), and because it is the most common chronic illness in children. Doctor-diagnosed asthma affects approximately 10% of Canadian children aged 2-7 years, almost quadruple the prevalence from 20 years earlier.

Asthma has been found to affect more male children (possibly because of smaller lung size, but fewer adult males (possibly because of larger lung size). While asthma may improve with puberty, some children go on to experience lifelong effects. The prevalence among adult women has been increasing, particularly in early to late middle age (35-64 years), and in adult men aged 35-44. Those with chemical hypersensitivity seem disproportionately affected by asthma, especially with onset during in adolescence (age 11-20 years).

There are complex host, genetic, and environmental risk factors for asthma with multiple interactions. Although the cause of asthma has not been fully elucidated, an immunological response to aeroallergens, resulting in inflammation of the lung airways has been noted.

Environmental factors modifying the epigenome in early life appear to play a crucial role in the susceptibility to asthma development. At least two windows of vulnerability for epigenetic changes are apparent. These include possible environmentally-induced changes *in utero* affecting how fetal genes are expressed, thus influencing later allergy and asthma risk. Then in early life, further epigenetic changes may occur if environmental factors modify a child's genome potentially causing and/or prolonging allergy or asthma.

Lung development begins in early pregnancy and continues to about age 18. It is vulnerable to developmental interruptions if there is exposure to environmental risk factors *in utero* or inhaled after birth. Greater exposure, compared to adults, occurs in infancy and early childhood for multiple physiological and behavioural reasons.

Potential mechanisms for how pollutant/chemical exposures can have a lifelong influence on lung structure and function include interference with factors in developmental processes in the lungs and the immune system that are highly conserved across species such as gene regulation, molecular signaling, and growth factors involved in branching morphogenesis and alveolarization. This evidence sits within the DOHaD model including evidence that lifelong lung function in both asthmatics and non-asthmatics is influenced by early life events such as low birth weight, undernutrition, and other factors.

There is evidence that interactions between genetic and environmental factors in infants and young children result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.

Multiple genes govern multiple aspects of the immune and respiratory systems, there is a great deal of heterogeneity among individuals, and variation also by gender and age. Epidemiological evidence reveals that genetic susceptibility for asthma or allergies onset can be influenced by multiple gene-environment and gene-gene interactions, as well as epigenetic mechanisms. For example, interactions between genetic and environmental factors in infants and young children

result in altered immune responses (dominance of the T_H2 phenotype), predisposing them to allergies, which in turn predisposes to asthma.

Evidence for associations between specific environmental risk factors and asthma are often inconsistent. Environmental risk factors related to asthma that are supported by considerable evidence include exposure to biological natural inhalants, childhood viral infections, ETS, other indoor and outdoor pollutants, socioeconomic status and stress, as well as to nutritional factors, gut colonization, and obesity (which influence immune system development).

Evidence indicates heightened risk of asthma onset in children when exposure to outdoor air pollution occurs in combination with high parental stress.

A wide range of outdoor air pollutants, such as CACs and many PAHs, acid vapours and aerosols, and diesel exhaust are associated with asthma onset and are triggers of asthma attacks.

Indoor air pollutants may overlap with outdoor and include products of combustion such as NO_2 and CO, formaldehyde, and numerous VOCs arising from consumer products such as cleaning agents, laundry, and personal care products.

Children are exposed to complex mixtures of pollutants indoors and out, and there are enormous challenges in assessing the health impacts of many co-exposures, as well as cumulative exposures. Nevertheless, there is evidence of association between preterm birth and air pollution, which in turn affects lung development. Air pollutants also impact the immune system, some skewing it towards T_H2 cell production.

Phthalates and BPA, well-known for their endocrine disrupting effects, have also been shown to heighten lung inflammation, and there is some evidence of immunotoxicity related to exposure to perfluorinated compounds.

Overall Conclusions

This report was one of several activities that fulfilled a vital objective for a larger project: to learn from each other across the CPCHE and OCDPA networks and to integrate each other's knowledge about risk factors for chronic disease. Despite its length, it only scopes a vast amount of research but now provides a foundation for further detailed work including analysis of related policy issues.

It revealed a number of truths about chronic disease prevention. The perspectives and approaches to population health prevention represented by the two networks (CPCHE and OCDPA) are similar in their great complexity. There is far more complexity involved than implied when chronic disease response strategies than is implied in or amenable to response strategies focused solely on individual behavioural changes.

The challenges to be faced over the next two to three decades in addressing chronic disease are sobering given the numbers of people predicted to be affected and estimates of costs. In multiple reports, dramatic language is used to frame these predictions such as the "rising tide" of dementia, the "perfect storm of risk factors" for CVD, the epidemic of obesity and diabetes and a related "economic tsunami" of health care costs, and "no breathing room" to capture the high numbers of illness and death and very high cost of air pollution. For cancer, the hard statistics (nearly half of Canadians will get cancer and about one in four will die from it) leave no need for the dramatic language.

These predictions and this language are used against the backdrop of an aging population. Within another 20 to 30 years, one quarter of Canada's population will be senior citizens (over the age of 65). If current trends continue, over 80% of those seniors will have one or more chronic disease. This disease burden will be disproportionately felt by those live in poverty. Many severe health impacts of climate change are expected to occur in coming decades. Similarly dramatic language, equally justified, arises. Climate change induced health impacts are predicted as a result of catastrophic weather events, extreme heat, increased vector-, food-, and water-borne illnesses and increased air and water pollution, which in turn are anticipated to affect the most fundamental determinants of health – air, food, water and shelter.

Because of the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures explored in this report, a broader approach to prevention is worthwhile. Equally important is a critical need to address the "causes of the causes," notably poverty and the SDOH given the reality of biomedical and behavioural risk factors for various diseases arising from social and economic conditions.

Environmental influences on health are similarly multifaceted, involving multiple pollutants, exposure routes, on a scale ranging from macro to micro (e.g., from built environment features to the loading of floor dust with toxic substances), multiple interrelationships, and life course vulnerabilities. Biomonitoring data indicates population-wide exposure to multiple contaminants, with levels higher in children and generally highest in breast-fed infants, with unknown consequences.

It is already well-established that the *in utero* and perinatal "environment" and maternal and early childhood circumstances play major roles in the risk of later life disease. Within this new paradigm for disease causation, the DOHaD concept and the related field of epigenetics, a rapidly expanding body of research indicates a role for early life exposure to environmental contaminants in this lifelong continuum of disease vulnerability.

Because of the abundant complexity, not only is there a need for more research, but also to adjust assessments of the strenghth of evidence for associations between risk factors and health outcomes via tools such as the Bradford Hill criteria and hierarchical models of study designs. Given the significant burden in terms of mortality, illness or hospitalization and attendant economic costs of chronic diseases, including the contribution from environmental exposures, a broader approach to prevention is worthwhile. Table 1 above provides a summary of early exposures (*in utero* or childhood) for which there is evidence of associations with prevalent chronic diseases addressed in this review. It is important to emphasize that important detail about strength of evidence (explored throughout this report) is not included in this table. Nevertheless, the multiple exposures noted indicate a priority list of substances of concern particularly those that repeat frequently across the table including air pollution (notably the CACs), lead, multiple pesticides, multiple POPs including PBDEs, phthalates and BPA.

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