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Health Canada
Compilation of Research Abstracts
2019-2020

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INTRODUCTION

This document encompasses all in-house research including contracted social, physical and natural science activities toward generation of new knowledge conducted within Health Canada's Healthy Environments and Consumer Safety Branch (HECSB) in 2019-2020. In this context, research is defined as:

"*the systematic investigative process of inquiry, including development, testing and analysis, carried out in pursuance of the departmental mandate, in order to discover, interpret or analyse facts, events or behaviours, to develop and revise theories, or to make practical applications with the help of such facts, laws or theories designed to develop or contribute to knowledge.*"[1]

Such research includes:

- methods development,
- adaptation of methods should they be publishable and thereby making a contribution to scientific knowledge,
- monitoring, surveillance and testing to inform risk assessments and risk management options, or to characterise a situation and establish trends,
- clinical research,
- epidemiological studies, and
- new methods for data analysis, including non-laboratory based methods such as algorithms and data mining.

The importance of research within Health Canada and HECSB cannot be overstated: the various projects, collaborations, and expertise pursued by the Branch demonstrate its commitment to protecting the health and safety of Canadians.

This document should be viewed as a reference tool, a summary of the research projects being undertaken in the Branch. Developed to support Branch and Departmental programs and in particular research, risk assessment, management and policy communities, it has the potential to support broader collaboration and partnerships in addition to supporting the exchange and/or uptake of information to assist evidence-based decision making and policy objectives.

Attempts have been made to provide each project summary in non-technical language, and to include a short description of how the research relates to Health Canada's mandate. For ease of reference, the work has been grouped by Directorate within the Healthy Environments and Consumer Safety Branch as well as by Division.

[1] Definition developed by HECSB Research Governance Committee and approved by HECS Executive Committee, June 2013

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LEGEND

AAPHI	Addressing Air Pollution Horizontal Initiatives (formerly Clean Air Regulatory Agenda [CARA])
ADME	Absorption, distribution, metabolism, and excretion
AMAP	Arctic Monitoring and Assessment Programme
AQBAT	Air Quality Benefits Assessment Tool
AQHI	Air Quality Health Index
CCHS	Canadian Community Health Survey
CCIB	Climate Change and Innovation Bureau, SED
CCRPB	Consumer and Clinical Radiation Protection Bureau, ERHSD
CEPA	Canadian Environmental Protection Act
CHMS	Canadian Health Measures Survey
CHPSD	Consumer and Hazardous Product Safety Directorate
CIHR	Canadian Institutes of Health Research
CMP	Chemicals Management Plan under CEPA
CMP3	Third phase of the Chemicals Management Plan
CRA	Collaborative Research Agreement
CSSP	Canadian Safety and Security Program
DCL	Domestic Commerce List
DRDC	Defence Research and Development Canada
EHSRB	Environmental Health Science and Research Bureau, ERHSD
ERHSD	Environmental and Radioation Health Sciences Directorate
ESRAB	Existing Substances Risk Assessment Bureau, SED
F&DA	Food and Drugs Act
MOA	Memorandum of Agreement
MIREC	Maternal-Infant Research on Environmental Chemicals
NAM	New Approach Method/Methodology
NM	Nanomaterials
NSACB	New Substances Assessment and Control Bureau, SED
OECD	The Organisation for Economic Co-operation and Development
ORS	Office of Research and Surveillance, Tobacco Control, Controlled Substances and Cannabis Branch
PFAS	Per- and poly-fluoroalkylated substances

PI	Principal Investigator (or Principal Contact for the project)
PM	Particulate matter (PM2.5 = Fine particulate matter, < 2.5µm diameter; PM5 = particulate matter, <5µm diameter)
RAB	Risk Assessment Bureau, CHPSD
R-ICL	Revised In Commerce List
RPB	Radiation Protection Bureau, ERHSD
UFP	Ultrafine particles/particulate matter (<0.1 µm diameter)
SED	Safe Environments Directorate
SVOC	Semi-volatile organic compound
VOC	Volatile organic compound
WAQB	Water and Air Quality Bureau, SED
WHO	The World Health Organization

Environmental and Radiation Health Sciences Directorate (ERHSD)

Consumer and Clinical Radiation Protection Bureau (CCRPB)

Non-Ionizing Radiation Physical Sciences Division

Sound level determinations for the Wind Turbine Noise and Health Study

Health Canada's role with respect to wind power includes providing advice, upon request, on the measurement of noise and assessing its health impacts.The Department is aware of health-related complaints from individuals living in close proximity to wind turbine establishments and globally, wind energy development is an area of expansion, with research underway to support a broader evidence base on which international jurisdictions can base decisions. In collaboration with the Non-ionizing Radiation Health Sciences Division (NIRHSD), NIRPSD is conducting research to support increased specificity of sound levels (i.e., considering additional factors) based on observations from the Health Canada Wind Turbine Noise and Health Study. Subsequent to the initial yearly average sound level results released in 2014 (published in the *Journal of the Acoustical Society of America*), the ongoing data analysis pertains to the evaluation of measured and calculated sound levels from wind turbines in 10 minute intervals, including consideration of weather and wind turbine operational data. The analysis also includes new estimates of indoor sound pressure levels, assessment of infrasound, and potential impact on sleep. This work will support the Department in the provision of advice related to wind power development proposals, installations and operations and contribute to the global knowledge on wind turbine noise and health. (PI: Stephen Keith)

Modelling temperature elevation in the skin from millimeter wave radiofrequency fields

The growth of devices emitting radiofrequencies (RF) and emerging wireless broadband technology in the millimeter wave spectrum over the last few years has raised public concerns about possible associations between RF energy and adverse health outcomes. The Department's mandate regarding human exposure to RF electromagnetic energy from wireless devices includes carrying out research into possible health effects, monitoring the scientific literature related to such effects on an ongoing basis, and developing RF exposure guidelines, commonly referred to as Safety Code 6. Safety Code 6 sets recommended limits for safe human exposure to electromagnetic fields (EMF) in federally regulated industries and workplaces. The objective of this study is to model the potential increase in temperature in human skin from exposure to millimetre wave radiofrequency (RF) fields. Since millimeter wave RF fields are absorbed almost entirely within the uppermost layers of the skin and subcutaneous fat, numerical models are being developed to predict the rate of and/or steady-state increase in skin surface temperature taking into account both intensity and beam-diameter. The analytical model developed in this study can be used to assess frequency-dependent power density thresholds that would result in a defined tissue temperature increase. Alternatively this model can be used to estimate a maximum tissue temperature resulting from RF emitting devices based upon the radiation characteristics of the device.

The results of this research are intended to provide Health Canada, other levels of government and the broader scientific community with models that can be used to analyse thermal health effect limits for human exposure to millimeter wave. (PI: Greg Gajda; Mykola Zhuk; contact: Jonathan Paradis)

Non-Ionizing Radiation Health Sciences Division

Personal listening devices (PLDs) and impairment to hearing

Health Canada conducts research to assess the potential health risks from noise, including those from PLDs, as part of its role in administering the *Radiation Emitting Devices Act (REDA)*, which governs the radiation safety of products that are imported and sold in Canada, including products emitting acoustical radiation. It is well known that prolonged exposure to loud noise can cause noise induced hearing loss. Previously, Health Canada has assessed the typical volume setting on PLDs (e.g. MP3 players) used by students and correlated these findings to their self-reported and measured hearing status. These pilot studies have served as the rationale to conduct larger investigations. For the first time, national data was collected on hearing health among Canadians aged 3-79 as part of the Canadian Health Measures Survey (CHMS) (Cycles 3 and 4). This data included objectively measured hearing acuity in addition to self-reported exposures to loud workplace and leisure noise, and has led to publications on the prevalence of occupation-related hearing loss among Canadians. In 2019, Health Canada published a report on the prevalence of loud leisure noise exposure among Canadians, aged 6 to 79. Noise exposure from cumulative and specific sources of loud leisure noise activities, including PLDs, were estimated based on a common occupational limit (i.e. equivalent to or greater than 85 dBA for 40 hours or more per week). Health Canada will be undertaking a subsequent analysis to evaluate the impact of loud PLD usage and other loud leisure noise exposures on the hearing health of Canadians, aged 6 to 29. Collectively, these study findings will be used by Health Canada to estimate (characterize) the prevalence of noise-induced hearing loss among Canadians, including children/adolescents and young adults, from prolonged exposure to noisy devices (e.g. PLDs) capable of hazardously high volume levels. It will also help to inform policy makers, educators and health care professionals. (PI: Katya Feder)

Wind Turbine Noise and Health Study: Sleep Analysis

The Wind Turbine Noise and Health Study (WTNHS) (2012-2014) was conducted by Health Canada, in collaboration with Statistics Canada and other external experts, in order to better understand the effects of wind turbine noise (WTN) on human health and well-being. Measured endpoints included an automated blood pressure/heart rate assessment, hair cortisol concentrations and sleep actigraphy. In addition, self-reported data were collected during a face-to-face computer-assisted interview at participants' homes. While this study was completed and the preliminary results were announced in the fall of 2014, due to the volume of data collected, the publication of detailed results in peer reviewed scientific journals occurred throughout 2015-2019. A total of 14 journal articles have been published to date and additional analyses are ongoing. The current work from the WTNHS relates to a more detailed analysis of sleep actigraphy where, in the first analysis, sleep will be evaluated in 10-min time intervals that are time-synchronized to wind turbine operations; and, the second analysis will focus on determining the WTN sound pressure level that is associated with a 3% prevalence of self-reported high sleep disturbance, which is the sleep disturbance level on which the WHO currently bases its noise guidance. The results of this analysis will provide the most comprehensive assessment of self-reported sleep disturbance to date, and contribute to a global evidence base on which future decisions by Health Canada, other levels of government, and the broader scientific community, may be informed. . The

scientific results from these studies on WTN continue to inform legal proceedings related to wind turbine installations in Canada and around the world. (PI: David Michaud)

Indoor tanning equipment usage and injuries: Results from the Canadian Community Health Survey (CCHS)

The early onset of skin cancer has been associated with tanning equipment use, where increased use is correlated with increased risk. In 2014, Health Canada used the Canadian Community Health Survey (CCHS) to collect prevalence estimates of indoor tanning and associated injuries (to the eyes and skin). The survey found that 4.5% of Canadians used indoor UV tanning equipment in the past 12 months and usage was more prevalent among young females (aged 18-34). The majority of users indicated they used tanning equipment to develop a base tan. The current results from the 2019 CCHS represent a 5-year follow-up from the 2014 survey. As before, the rapid response component of the 2019 CCHS collected data on the use of tanning equipment in the previous 12 months, including reasons for use, frequency/duration of use, precautions taken, and adverse reactions or injuries providing a more robust estimate of the extent tanning equipment usage and injuries. The 2019 survey found that 3.0% of Canadians reported that they had used indoor tanning equipment in the past year, representing a 33% significant decline from usage prevalence in 2014. The majority of users were female and females aged 18-34 were significantly more prevalent users compared to females aged 45 or older. The prevalence of indoor tanning was higher among people without a university degree, however there were no differences in prevalence by household income or region. Most users indicated they used indoor tanning equipment within a tanning salon and the most common reason for usage continued to be for the development of a base tan. Over one third of all users reported undergoing more than 10 sessions in the past year. The information generated by this research will strengthen our knowledge base on trends in usage and user behaviour which is valuable for targeting communications to the public and developing evidence-based risk management decisions. (PI: Sami Qutob)

Handheld laser device usage and injuries: Results from the Canadian Community Health Survey (CCHS)

In 2014, Health Canada used the Canadian Community Health Survey (CCHS) to collect prevalence estimates of laser device usage and injuries in Canada. The survey found that 1.1% of Canadians reported an injury from a laser device. The majority of injuries were to the eye, with injuries also occurring in the skin, and often were the result of laser exposure from someone else's use of the device. Cosmetic treatments employing lasers were the most common cause of injuries. In 2019, Health Canada conducted a 5-year follow-up study using the CCHS, focusing on the prevalence of injuries from handheld laser devices in the previous 12 months, excluding cosmetic laser exposure. Factors such as the frequency and type of injury sustained, as well as whether the injury was the result of personal use or someone else's use was collected and analysed. The 2019 survey found that 12.4% Canadians reported using or being exposed to a handheld laser in the previous year. Laser pointers represented the majority of handheld lasers used in Canada. Youth between the ages of 12 to 17 made up almost a quarter of all users of these devices. Higher handheld laser device usage was found among those with university education and those within the higher income categories. Overall, very few Canadians reported discomfort or injury involving a handheld laser device in the past 12 months. A quarter of users indicated that they had intentionally directed the laser beam at their eyes or skin or those of someone else. Most respondents obtained their handheld lasers by some undisclosed means or purchased it from a retail store or online. Handheld lasers pose a potential hazard to the public, particularly to children,

who are unaware of the risks. This information was gathered to support efforts to monitor and address an emerging health concern regarding handheld laser devices. (PI: Sami Qutob)

Transcriptional benchmark dose modeling in a mouse skin model in response to UV radiation from a commercial sunbed

In 2016, the European Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) concluded that there is strong evidence that ultraviolet radiation (UVR) from tanning equipment usage is carcinogenic and the risk of developing cancer increases with both frequency and the age of the user. SCHEER also concluded that there is no safe limit for exposure to UVR from tanning equipment as there is no defined threshold for the development of adverse long-term health associated with exposure. This is due to the stochastic nature of cancer induction and the dose levels required for the production of a tan. There is also no established threshold level of UVR-irradiance or UVR-dose for long-term stochastic effects, such as cancer, from currently available data. More sensitive mechanistic studies and advanced analysis tools may provide more insight into the estimations of UVR exposure thresholds and possible adverse outcomes through transOMIC pathway analysis. A recent review of the scientific literature suggests that the application of Bench Mark Dose (BMD) modelling of transcriptional data offers significant advantages over traditional genomic bioinformatics approaches. In 2019, Health Canada conducted a study to use BMD modelling of transcriptomic responses in mouse skin using a broad-range of UVR doses emitted from a UV cosmetic tanning lamp. This work is the first of its kind to employ BMD modelling of transcriptomic response data in a live mouse model exposed to a biologically-relevant dose range of UVR emissions approximating a spectra of a typical UVR cosmetic tanning bed. This data will provide a point-of-departure assessment of molecular responses to UVR exposure to determine biologically-relevant thresholds of UVR responses that may preclude the occurrence of longer term pathophysiological consequences. (PI: Sami Qutob)

Ionizing Radiation Physical Sciences Division

Exposure characterization – Cone beam computed tomography x-ray

Cone beam computed tomography (CBCT) is a diagnostic X-ray imaging modality, used in dental and medical radiography, that produces 3-dimensional (3D) images of the volume of interest, which is similar to conventional computed tomography (CT). However, CBCT devices acquire X-ray images with a single, sometimes partial, rotation of a wide X-ray beam around the patient, as opposed to conventional CT devices which typically use numerous axial or helical rotations of a narrow X-ray fan-beam around the patient. In order to measure the radiation output of conventional CT devices, there are a number of different metrics that can be used. But the different methods used to generate/produce an image by CBCT devices can significantly impact the applicability and accuracy of the various metrics used to assess radiation output. This research study will investigate various CT radiation output metrics as applied to CBCT devices, including metrics proposed by industry/radiation protection organisations specifically for CBCT, to determine their ability/capacity to accurately measure the radiation output of the devices. Furthermore, the level of scattered radiation received by a patient with and without a lead apron will also be evaluated. As exposures to X-rays carries a risk of biological damage, which decreases as the level of exposure is reduced, this research will allow for more effective evaluation of the risks to patients from CBCT devices, including in comparison to other modalities of medical X-ray imaging. The results will also help to better inform regulatory and guidance initiatives for the devices. (PI: Graeme Wardlaw)

Ionizing Radiation Health Sciences Division

Assay development for biological dosimetry

In the case of a nuclear/radiological event it is imperative to quickly identify exposed individuals for the purpose of medical intervention, and to identify first responders who must be restricted from further exposure. Even for a lesser-scale event, many concerned members of the public will seek an assessment of their radiation exposure. The assessment of radiation dose is called dosimetry and when biological material is used for this dose assessment, it is termed biological dosimetry. This research involves the development of an imaging flow cytometry method for the cytokinesis-block micronucleus assay as a high throughput method for biological dosimetry. In addition, genomic, proteomic and metabolomic endpoints are being examined as new biomarkers for radiation damage to estimate the dose of ionizing radiation absorbed by an individual. This work is being conducted in support of emergency response and the National Biological Dosimetry Response Plan, which is linked to the Federal Nuclear Emergency Plan. (PI: Ruth Wilkins)

Biomarkers for exposure to low doses of ionizing radiation

Health Canada acts, on request, as the principal health advisor to other federal departments and agencies on occupational and public health matters related to radiation safety. CCRPB conducts research to support Health Canada's advice on radiation health impacts based on state-of-the-art science. Currently, it is assumed that the health risks resulting from radiation exposure are linearly proportional to dose without a threshold. However, the scientific knowledge emerging over the last decades clearly indicates that biological effects and the underpinning risk for human adverse health outcomes at doses below 50-100 mGy is uncertain. This includes radiation effects related to chronic and acute exposures, low and high doses and varied dose rates. There is also lack of clarity on the effects from different radiation qualities and how they impact different organs, tissues and induce cellular damage eventually leading to cancer and other adverse outcomes. It is widely recognised that more mechanistic research is needed to help address and reduce uncertainties at low doses. This study is investigating the biological effects of low-dose radiation; it exploits "omics" (e.g. proteomics, genomics) technology, a validated tool in biological research to generate new knowledge regarding the shape of the dose-response relationship; identifying key mechanistic pathways and threshold doses at which these pathways are activated and how they differ with radiation qualities and biological tissues. The results will feed into the related activities of developing of Adverse Outcome Pathway for ionizing radiation. A better understanding will provide a more biologically meaningful basis for reliable health risk estimation essential for a robust system of radiation protection. (PI: Vinita Chauhan)

Identification of biomarkers of radon gas exposure

Radon gas is a well-characterized human carcinogen. Studies have provided evidence of an association between residential radon and lung cancer risk, however, an understanding of the mechanistic basis of this relationship remains limited. Radon gas enters homes from different sources including: surrounding soil and rocks, and water supplies, where it can diffuse and accumulate to levels where it can pose a health risk. This study will examine how radon gas can affect blood and whether indicators of exposure, known as biomarkers, can be identified. The work will be conducted in partnership with members of the Canadian Partnership for Tomorrow Project (CPTP), a program that contains a repository of bio-banked

biological samples. Geographic mapping will be leveraged to help identify participants living in high and low radon risk zones. Blood samples will be taken from participants and then analyzed to identify associations between radon gas exposure and the presence of specific biomarkers. The outcomes of this work will provide an understanding of the types of bio-molecules that are released into the blood when individuals are living in high radon areas and the types of technologies that are sensitive to the detection of chronic-level exposures. New knowledge in this area will help direct future research at Health Canada and will inform current national/international standards. (PI: Vinita Chauhan (CCRPB); Michel Gauthier (RPB))

Environmental Health Science and Research Bureau (EHSRB)

Exposure and Biomonitoring Division

Development of non-targeted screening analysis approaches for identifying emerging metabolites and chemicals in human fluids as exposure biomarkers using high-resolution mass spectrometry

Over the past decade the sensitivity of biomonitoring approaches have been considerably improved as it relates to human exposure assessment of some targeted chemicals. However, there is still a gap between pre-selected targets and our capability of quantitatively determining unknown and new substances of emerging concern (also known as emerging substances) in human biofluids (e.g. urine, follicular fluids and blood). As a result, non-targeted approaches have gained much attention in risk assessment of human exposure to unknown and emerging chemical contaminants. The proposed four-year project plan, as a proof of concept study, is using high-resolution/high accuracy mass spectrometry to develop new non-targeted approach methods, which aims to identify metabolites of these chemicals and some parent compounds in human biofluids as potential biomarkers for assessment of human exposure to substances, including CMP priority chemicals and other emerging chemicals. Suspected, unknown, and emerging contaminants will be screened and identified based on accurate mass measurements with high-resolution mass spectrometry, fragmentation patterns, retention time with prediction models, and the structural similarity of known chemical groups. These newly developed approach methods will provide valuable screening information for metabolites and parent compounds as to the identification of potential emerging contaminants for future assessments under CMP; they will also generate meaningful knowledge regarding metabolites derived from emerging chemicals in human biofluids. The developed methods may be applied to analysis of samples collected in the Canadian Health Measures Study and Ontario Health Study and will also be beneficial to broader scientific communities. Method development and validation will include metabolites of selected CMP priority chemicals, but not necessarily limited to flame-retardants, BPA analogues, plasticizers, UV filters and stabilizers, their alternative or replacement chemicals, and mercapturic acids in various environmental samples and human biofluids such as urine, serum, plasma, and follicular fluids. (PI: Yong-Lai Feng)

Characterization of residential exposures to CMP metals and organics

Health Canada assesses potential exposures of the general population to chemical substances through all routes (inhalation, ingestion and contact on the skin) and all possible sources (including ambient and indoor air, food, soil, dust, and consumer products). As Canadians spend more than 90% of their time

indoors, there is an increasing demand for information on indoor environmental exposures. This research examines settled house dust samples collected from 1025 homes in 13 cities under the Canadian House Dust Study (CHDS), which was designed to provide a representative national baseline. This study focuses on metals, but also considers synthetic organic compounds including bisphenol A, pesticides, flame retardants, synthetic musks, bactericides, surfactants, and plasticizers. Metals enter the home by residents tracking in outside dirt and by infiltration of airborne particles which settle on hard surfaces, carpets and in crevices. In addition, metal and synthetic organic compounds in consumer products and building materials, such as plasticizers and drying agents in surface coatings, also accumulate in indoor particles as products deteriorate with age and wear. Nationally representative levels of contaminants will be reported as both concentrations and loadings to accommodate various approaches to estimating exposures. Correlations between house characteristics (such as house age, construction materials and environmental setting) and the chemical datasets will help to identify exposure sources and trends. The study focuses primarily on childhood exposures to house dust through normal hand-to-mouth ingestion behaviour. The study also looks at potential inhalation exposures by characterizing re-suspended dust in carpeted versus non-carpeted homes. Dust particles undergo physical and chemical transformations in the indoor environment, which may increase their bioaccessibility (solubility in the lung and gastrointestinal tract), and therefore metal bioaccessibility will be measured. This research supports Health Canada's risk assessment and management activities, with particular focus on mitigation of childhood residential exposures to chemical substances. (PI: Pat Rasmussen)

The impact of dissolution behaviour of metal oxide nanomaterials on toxicological response

Health Canada is responsible for assessment and management of risks associated with engineered nanomaterials (materials in a size range of 1-100 nanometers). The New Substances Assessment and Control Bureau (NSACB) has identified metal oxide nanomaterials as high priority for assessment under the CMP. The toxicological behavior of nanomaterials (NMs) is closely associated with their distinct physical-chemical properties. This research is investigating the influence of dissolution behaviour of NMs on their toxic potential. The term “dissolution behaviour” includes solubility as well as changes in suspension stability (e.g. size, agglomeration/aggregation, surface area, and surface charge) of NMs dispersed in different aqueous media. Although NM solubility has been recognized as one of the key properties that must be determined for accurate categorization of toxicological potential, standardized solubility test methods for nanomaterials are lacking. This study focuses on eight groups of metal oxides determined by NSACB to be in commerce in Canada (copper, nickel, zinc, titanium, iron, manganese, cerium and aluminum), many of which are used in consumer products to which Canadians are regularly exposed. The study investigates solubility of eight individual metal oxide NMs and determine the impact of solubility on their toxicity using toxicogenomics tools (to investigate the changes in the expression of all genes simultaneously). In addition, environmental releases of metal oxide and metallic NMs used in the automobile industry (e.g. iron oxides and platinum) will be investigated using road dust samples collected from the expressway network in the City of Toronto, providing a realistic exposure scenario. The results of the proposed research will inform HC risk assessments and will help HC meet its commitments associated with the Organisation for Economic Cooperation and Development (OECD) Working Party on Manufactured Nanomaterials (WPMN). (PI: Pat Rasmussen; Sabina Halappanavar)

Development of a high throughput chamber test method for the determination of semi-volatile organic compounds from consumer products

Consumer products are major indoor sources of many chemicals including semi-volatile organic compounds (SVOCs) such as plasticizers and flame retardants. SVOCs in these products can enter indoor environments through evaporation if they are not chemically bound to the polymer materials. The rate of evaporation, also called emission rate, is a critical piece of information in estimating SVOC levels indoors in order to assess human exposure to SVOCs from products. Due to relatively low vapour pressure and great tendency to be absorbed on surface materials, emission rates of SVOCs are difficult to measure using traditional environmental chamber tests. Further, when temperature increases, the emission rate also increases and desorption tendency decreases. The relationship between temperature and emission rates can be established through an empirical model. As a result, emission rates determined at higher temperatures in chambers can be extrapolated to the rate at ambient room temperature or any other desired temperature. Chamber tests at elevated temperatures can minimize the adsorption of SVOC to the chamber surface and reduce the duration of the tests. This project uses chamber tests at elevated temperatures to develop high-throughput methods to generate emission rates of selected bulk SVOCs, including plasticizers and flame retardants, and of SVOC-containing products. The emission rates are then used to predict levels of SVOCs in indoor air as a result of using SVOC-containing products indoors through available indoor air fate models. Prediction of SVOC levels in indoor air will support human exposure assessment and development of indoor air policies and guidelines. (PI: Jiping Zhu)

Multimedia exposure to replacement chemicals of emerging concern and selected CMP3 chemicals

Health Canada is responsible for the assessment and management of health risks to Canadians associated with exposure to chemicals in the environment. Several jurisdictions around the world have begun regulating the production, use and importation of various specific chemical compounds [e.g. bisphenol A (BPA), polybrominated diphenyl ether (PBDE) flame retardants, phthalates, parabens and triclosan] that have been shown to exhibit a range of health effects including endocrine disrupting properties. Consequently, many alternative chemicals have been introduced into the market as replacement chemicals; however, their exposure and potential health risks have not yet been assessed in Canada. The goal of this 4-year project is to generate Canadian exposure data for compounds including selected flame retardants, quaternary ammonium compounds, BPA analogues, alternative plasticizers, and alternatives to parabens and triclosan, in environmental and biological matrices, as well as children's products (baby bottles). Where unavailable, new analytical methods will be developed for quantitative analysis. This will be achieved by using archived specimens or new samples of dust, water, urine, serum, follicular amniotic fluid, and placental tissues collected from a variety of populations and residential homes across Canada. Furthermore, biological modeling of some of these chemicals will provide an insight into the relationship between the measured levels in different matrices and estimated daily exposure. The data generated will inform the risk assessment and/or risk management of those chemicals, and may be used to assess potential health outcomes. It can also be used to support the planning of future biomonitoring initiatives including the CHMS. (PI: Cariton Kubwabo)

Identification of unknown substances in e-cigarette refill fluids and vapors (CRA with ORS)

Electronic vaping products (EVPs), or e-cigarettes, are battery powered devices that are used to create an aerosol which is inhaled by the user. EVPs are used by hundreds of thousands of Canadians to obtain nicotine. An aerosol is created from a liquid, known as e-liquid, that is housed in a tank or cartridge and

usually consists of propylene glycol, glycerol, nicotine, and various flavorings. When used, the devices vaporize the e-liquid by way of a heating element or coil, housed in an atomizer. This vapor then quickly condenses into an aerosol that is inhaled. Many of the substances found in e-liquids, as part of a review conducted by Health Canada's Tobacco Control - Office of Research and Surveillance (ORS) are well-known harmful chemicals also found in tobacco. However, very little is known on the full composition of the thousands of e-liquid formulations available on the Canadian market. The objective of this study is to build Health Canada's capacity in the analysis of complex mixtures of e-liquids. The results of the open characterization will complement the existing body of knowledge on components of e-liquids. It will also support decision making and regulatory activities in providing TORS with data on the chemical composition of electronic cigarettes refill fluids and their aerosols, from products available in the Canadian market. (PI: Cariton Kubwabo)

Identification of biomarkers of exposure in users of tobacco and vaping products (CRA with ORS)

Electronic vaping products (EVPs), or e-cigarettes, are battery powered devices that are used to create an aerosol which is inhaled by the user. EVPs are used by hundreds of thousands of Canadians to obtain nicotine. An aerosol is created from a liquid, known as e-liquid, that is housed in a tank or cartridge and usually consists of propylene glycol, glycerol, nicotine, and various flavorings. When used, the devices vaporize the e-liquid by way of a heating element or coil, housed in an atomizer. This vapor then quickly condenses into an aerosol that is inhaled. Many of the substances found in e-liquids, as part of a review conducted by Health Canada's Tobacco Control - Office of Research and Surveillance are well-known harmful chemicals also found in tobacco. Once inhaled, these substances may metabolise in the body to form various metabolites that may be different from the parent compounds. The objective of this project is to develop Health Canada's capacity in predicting and analysing the potential metabolites (biomarkers) of substances contained in e-liquids. The results will be used for the monitoring of biomarkers in e-cigarette users and users of other emerging nicotine delivery vaping products. (PI: Cariton Kubwabo)

In vitro pharmacokinetics for high throughput data interpretation (Part 2)

Health Canada is responsible for assessing the risk to human health of thousands of substances present in the environment. The assessment of individual substances is tedious and unrealistic for a holistic risk assessment therefore, the use of high throughput screening (HTS), a combination of multiple signals from various sources and substances is increasing. Under a research project funded through the CMP, Health Canada researchers and regulatory scientists are collaboratively investigating the utility of integrating *in vitro* toxicity tools for human health risk assessment. The generation of pharmacokinetic parameters is crucial to the interpretation of the HTS data and the estimation of levels of human exposure that will provide a better basis for informed decision on a chemical's potential for toxicity. The aim of this project is to conduct *in vitro* experiments in order to generate required pharmacokinetic parameters for a series of chemical classes such as complex phenols, glycols, plasticizers, perfluorinated compounds and flame retardants identified by risk assessors. The work is being performed by an external company and results will be used by Health Canada scientists to develop case studies on the application of *in vitro* HTS data for regulatory purposes. (PI: Andy Nong)

In Vitro to *In Vivo* Extrapolation (IVIVE) toxicokinetics of CMP chemicals

Advances in toxicity testing have led to a rise in *in vitro* and high-throughput approaches to predict potential biological effects following chemical exposures. The challenge remains to relate these screening results with exposure guidance values based on actual animal or human effects. To address this challenge, new exposure and *in-silico* methods were developed to help interpret and extrapolate the *in vitro* measures. The latest development in translating the *in vitro* measures has been the use of drug metabolism pharmacokinetic tests, also known as *in vitro* toxicokinetics (TK), to generate critical data for computer models to incorporate when predicting the fate of a chemical *in vivo* based on *in vitro* toxicity assays concentrations (*in vitro* to *in vivo* extrapolation – IVIVE). However, current *in vitro* TK studies and models used to extrapolate the concentrations observed from *in vitro* toxicity tests are made on basic assumptions that are not necessarily true *in vivo* for all environmental chemicals. Other biological processes such as gut absorption and metabolic activation have yet to be accounted for in past modeling efforts. The resulting omission may result in misinterpreting human dose exposures based on *in vitro* measures. The goal of this research is to develop better *in vitro* toxicokinetic data and consistent biological extrapolation models to predict realistic doses *in vivo* where potential toxicological effects would be anticipated based on measures from high throughput *in vitro* assay toxicity database. These tests and models will explore the largest family of substances recently used as replacements to plasticizers, flame retardants and perfluorinated chemicals that are identified on the Health Canada CMP priority list and found in the US Environmental Protection Agency ToxCast™ program. This effort will help Health Canada develop tools and supporting data to predict toxicity of chemicals for high throughput risk assessments with IVIVE and help identify chemicals to be considered safe or alternatively trigger additional testing for the health of Canadians. (PI: Andy Nong)

Designing cost-effective drinking water surveys in the 21-st century: Optimizing target analytes, site selection, sampling and analytical methods

Sampling, shipping and analysis are the most common causes of high cost for drinking water surveys. Drinking water is an active media; therefore, specific sampling protocols are essential for some water contaminants and require well-trained personnel to obtain consistent results. Shipping is usually costly as significant volumes may be required to analyse trace levels of contaminants and different analytical methods are applied to determine various types of water contaminants, resulting in a variety of sample collection and processing requirements and sometimes various analytical laboratories. Over the years, Health Canada has conducted multiple targeted surveys and two national surveys on drinking water to generate data used for the development of Guidelines for Canadian Drinking Water Quality. The results have also been used to conduct human health risk assessments. The main objective of this project is to determine cost effective ways to design and perform future drinking water surveys. Specific areas for optimization include the selection of the sampling sites, classes of contaminants, sample volume, on-site sample concentration techniques, as well as analytical methods. The in-house expertise developed at Health Canada will be used to aggregate the knowledge generated over the years in drinking water sampling and analysis, and new emerging analytical tools explored to reduce the analytical methods-to-contaminants ratio. The ultimate goal is to reduce the cost of future surveys while improving data quantity/quality as required to fulfil Health Canada's mandate to protect and improve the health of Canadians. (PI: Anca-Maria Tugulea)

Derivation of biomonitoring equivalents for organics and inorganics for interpreting biomonitoring data to support chemical risk assessment

Biomonitoring can provide valuable data on the presence of trace levels of chemicals in human blood, urine or breast milk. Determining the presence of a chemical, however, is not enough to establish the potential risk to human health. A biomonitoring equivalent (BE) is the concentration of a chemical in human tissue or fluid that corresponds to an allowable exposure guidance value, such as a reference dose (RfD) or tolerable daily intake (TDI), that is considered safe. BEs are an integral part of the hazard and risk characterization and resulting data are used to inform the health risk assessment for many chemicals. As a part of the third phase of the CMP, risk assessments of inorganic chemical groups are being conducted. The overall research objective is to derive biomonitoring equivalents (BE) for metals to interpret biomonitoring data in support of the chemical risk assessments. BEs for additional chemicals were also generated for corresponding biomonitoring data as a part of a CHMS Biobank project. Risk assessments for the latest metals began in FY 2018/2019 and open access scientific publications have been released since then. (PI: Andy Nong)

Uptake rates of silicone based personal sampling devices – Proof of principle

The Chemicals Management Plan (CMP) aims to assess the risks to human health posed by thousands of chemicals but only a fraction of these chemicals have known human exposure data. It has been evident from previous assessment cycles that changes to priority setting paradigm must be made in order to assess chemicals more effectively and to identify potential triggers for future assessments. There has been extensive work in the environmental analysis and biomonitoring front, but personal exposure has been overlooked. Unlike biomonitoring, personal exposure can provide dosimetry data. The use of personal passive sampling devices (PSDs) are limited to those compounds that can be measured at environmental concentrations but often require longer sampling periods, thus limiting the practical wear time or number of subjects that can be monitored. In recent years, there has been a growing interest in using silicone PSDs for monitoring indoor air and water. In a study carried out at Oregon State University, a wide range of chemicals absorbed on silicone wristbands (SWs) worn by 22 participants were identified. However, the main limitation in the published work was the lack of uptake rate values, the constant contact between SW and skin, surfaces and clothing. Without the uptake rate, the concentration found in the SW cannot be translated to the environmental concentration or exposure estimation, which restricts the use of these data for risk assessment. Our project aims to fill current data gaps in the determination of uptake rates in different sorbent materials: silicone (use as wristbands, SW); and new material developed at North Caroline State University (CIPS). In addition, silicone wristbands will be deployed during firefighters training exercises in order to assess their exposure to polycyclic aromatic hydrocarbons (PAHs). (PI: Rocio Aranda-Rodriguez)

In vitro toxicokinetics for data interpretation (CRA with ESRAB/WAQB)

Health Canada has been exploring the use of new approach methodologies to evaluate health risks from chemicals. This study develops computer models and applications to help interpret and relate new testing data and approaches into population daily exposure levels for regulatory purposes. An abundance of toxicity data known as high throughput screening is now available thanks to large international testing initiatives. These tests screen thousands of chemicals over various biological responses measured in cells, tissues or even small organisms. As a joint effort between Health Canada and the US Environmental Protection Agency, additional experimental chemical kinetic information, also known as *in vitro* toxicokinetics, are generated to aid with the computer models to predict exposure

levels. Web applications that combine all this knowledge and help predict the potential harm from chemicals are also being designed for regulatory end users. By investigating different categories of environmental chemicals, case studies are being prepared to address key elements and considerations in the use of computer application with high throughput screening data to predict and evaluate health concerns. Eventually, the computing research will provide a better basis for informed decision making to prioritize and evaluate chemicals from potential health risks in the next cycle of Health Canada Chemicals Management Plan. (PI: Andy Nong)

Analysis of vaping product aerosols (CRA with ORS)

Electronic vaping products are battery powered devices that are used to generate aerosols for users to inhale. Aerosols are produced from e-liquids, which are housed in a tank or cartridge and usually consist of propylene glycol, glycerol, nicotine, and various flavorings. Chemical composition and profile of these aerosols is highly dependent on the type of electronic cigarette refill (e-liquid) used as well as the operating conditions (temperature, wattage, etc.) of vaping devices. Previous studies have identified that some chemicals in e-liquids and aerosols may have potentially negative health effects on users of these products. Studies on the use of these devices at very high operating temperatures or under other extreme conditions have also identified those chemicals that are known to have significant health effects on human. This project is developing methods to measure carbonyls present in the aerosols produced from vaping devices currently available on the Canadian market, and investigate the transformation of e-liquids during the vaping process through open characterization of transformation products in vaping aerosols produced from various components of e-liquids. The project focuses specifically on the relationship between device parameters and the generation of aldehydes. The project will also generate a dataset relating carbonyl generation to vaping product devices, settings, and vaping conditions. The data generated in this project will be provided to the Office of Research and Surveillance (ORS), Controlled Substances and Cannabis Branch, to support decision making on the relative harm of vaping products to inform future regulatory and policy directions. The conditions determined from this project will potentially serve as a standardized method that the ORS can utilize in the testing of a wide variety of vaping products on the Canadian market. (PI: Yong-Lai Feng)

Phase identification of metal oxide nanopowders purchased from on-line distributors (CRA with NSCAB)

Health Canada is responsible for assessing and managing risks associated with engineered nanomaterials (materials in a size range of 1-100 nanometers). As part of their risk assessment activities, New Substances Assessment and Control Bureau (NSACB) purchased commercially available metal oxide nanopowders to characterize their physical-chemical and toxicological properties. For metal oxide nanomaterials, identifying the mineral phase and crystallinity is critical for their risk assessment because distinct phases exhibit different solubility and toxicity. Mineral phase identification is usually achieved using powder X-ray diffraction (XRD). This research assists NSACB in their physical-chemical characterization of eight groups of metal oxides (Cu, Ni, Ce, Al, Fe, Mn, Ti and Zn) to complement on-going toxicological studies on the same nanomaterials. The goal is to use powder X-Ray diffraction to identify the mineral phases (crystalline and amorphous) of several nanoforms of each of the priority metal oxides, and estimate crystallite size based on XRD spectral features. By confirming mineral phases, purity and particle size of these nanomaterials, the results of the proposed research will bring to completion the full physical-chemical characterization of the initial 54 nanopowders listed for

investigation by NSACB and add value to the toxicological investigations conducted on these nanomaterials. (PI: Suzanne Beauchemin; Pat Rasmussen)

Endocrine disrupting chemicals: Towards responsible replacements - Determination of organophosphate esters (OPEs) and their metabolites in breast milk, food and water samples

Health Canada has a mandate to regulate chemicals to which Canadians are exposed. Several chemicals that have been banned from the Canadian marketplace due to their toxicity, have been replaced by alternate chemicals for which there is limited knowledge. Health Canada is collaborating on a CIHR Team Grant project to investigate the exposure and hazards of substances used as replacements for polybrominated diphenyl ethers (PBDEs) flame retardants. PBDEs, initially used in home furnishings, were removed from commerce in 2008 in Canada due to their persistence in the environment and their tendency to accumulate in human and animal tissues. Manufacturers are increasingly using organophosphate esters (OPEs) as a replacement to PBDEs to ensure that their products continue to meet the flammability standards in a variety of home furnishings, fabrics, clothing, electronics, and motor vehicles. Health Canada's Biomonitoring Laboratory has developed and validated analytical methods for OPEs and their metabolites in food, water and breast milk.This study examined dietary exposures to OPE flame retardants and plasticizers as well as other chemicals in 3 locations: 1) Montreal, Canada (urban developed world), 2) Pretoria, South Africa (urban less developed), and 3) the Vhembe region of Limpopo province of South Africa (rural, poorly developed). The data will support epidemiological analysis and contribute to the dietary assessment of exposure to these chemicals. This dataset is the first assessment of breast milk that allows comparison between the levels of these substances in Canada and in less developed countries, using identical sample collection and analytical methods. (PI: Cariton Kubwabo; in collaboration with McGill University)

Hazard Identification Division

Assessment of the performance and predictiveness of an optimized *in vitro* developmental neurotoxicity assay using proven developmental neurotoxicants and negative controls

Many *in vitro* assays have been proposed for Developmental Neurotoxicity Testing (DNT). However, the reliability and reproducibility of these assays will need to be properly validated before they can be used to inform chemical health risk assessments by Health Canada and other regulatory agencies. Cerebellar Granule Cells (CGCs) harvested from rat pup brains are a popular experimental *in vitro* model used to study neurodevelopment and neurotoxicity. CGCs are easy to grow and can recapitulate neuron differentiation and maturation processes observed *in vivo*. Genes associated with CGCs neuro development have been identified and used to screen chemicals for potential developmental neurotoxicity. Unfortunately, replication of these findings at Health Canada proved challenging, as gene expression measurement protocols were often poorly described, quality controls infrequently reported and CGCs themselves presented significant batch-to-batch variability. In spite of these issues, a reliable *in vitro* DNT protocol based on commercially-sourced CGCs and reagents was optimized and a subset of developmentally-regulated genes presenting reproducible expression patterns across different laboratories was identified. Promising preliminary results suggest that proven developmental neurotoxicants can be differentiated from non-neurotoxic controls based on the expression of this subset of key genes involved in neuron differentiation and maturation. The complete and transparent description of a reliable *in vitro* DNT assay using well-characterised CGCs and neurodevelopmental

biomarker genes will facilitate future investigations and inter-laboratory comparisons. Further validation of this CGC-based assay may lead to its inclusion in a yet-to-be-determined battery of *in vitro* DNT assays that will support the screening and prioritization of potential developmental neurotoxicants. (PI: Guillaume Pelletier)

Assessment of the carcinogenic potential of CMP-chemicals through the application and investigation of the Syrian Hamster Embryo Cell Transformation Assay (SHE-CTA)

The Organisation for Economic Co-operation and Development (OECD), including Canada, and the European Centre for the Validation of Alternative Methods (ECVAM), are international agencies collaborating to set standards to be used by industries worldwide to identify toxic chemicals. Among evaluated cell transformation assays, the "Syrian Hamster Embryo Cell Transformation Assay" (SHE-CTA), was found to be the most accurate CTA to identify chemicals with the ability to induce cancer. In contrast to other tests, the SHE-CTA detects both the chemicals that induce cancer by damaging DNA and those that do not damage DNA (which are difficult to identify). Some OECD-member countries raised concerns that the molecular mechanisms in the SHE-CTA may not be relevant to those in humans. Nevertheless, the advantages of this test, and its consideration in proposed chemical testing strategies by the U.S. Environmental Protection Agency's (Office of Chemical Safety and Pollution Prevention), may influence companies to generate SHE-CTA data, which will also eventually be submitted for review by Health Canada. The initial research plan involved the development of the SHE-CTA in the laboratory to: (1) gain expertise in conducting this assay and test priority chemicals, (2) investigate mechanisms of cell transformation, and (3) identify endpoints that can improve this assay. The chronology of DNA changes were demonstrated starting from normal cells up to the time at which they become potential cancer cells. Based on these findings, methods to improve the assay can be suggested and tested. Collectively, these *in vitro* data will assist HC in the development of chemical testing strategies, in strengthening predictions of chemicals that can increase the risk of developing cancers, and in providing alternatives to reduce dependence on *in vivo* rodent cancer bioassays. (PI: Daniel Desaulniers)

Developing *in vitro* screening methods for metabolic disruptors in adipocytes

Evidence from animal and human studies suggests that exposure to commercial chemicals is associated with adverse health outcomes including diabetes, cardiovascular disease, endocrine cancers and obesity which are afflicting the human population in the developed world. The fat tissue and the fat cells are not only responsible for storage of excess caloric consumption but also potently influence the metabolism of the entire organism via the secretion into the blood stream of hormones and other factors that affect the function of other organs. It is hypothesised that one of the ways by which the fat tissue affects cardiovascular disease, high blood pressure and diabetes is through an imbalance in the factors secreted by this tissue. This makes the fat tissue a likely target for chemical effects. A hormone known to contribute to cardiovascular and metabolic disease, including diabetes, is the stress hormone cortisol. Increased cortisol level is associated with increased mid body fat accumulation and an increase in cardiovascular disease and type 2 diabetes. It has been postulated that chronic exposure to cortisol leads to a change in the metabolic function of the fat cells. As previously shown in cell models, chemicals such as bisphenols and flame retardants can act similarly to the stress hormone in fat cell formation. However, it is unclear whether the resulting fat cell is healthy or contributes to disease through imbalanced secretion of soluble factors and hormones. To date, there is limited information and no high content or validated screening method for the functionality of the fat cells exposed to

chemicals. This project is working to develop a screening method which can both identify substances that drive fat cell formation and determine if they contribute to metabolic disease. (PI: Ella Atlas)

Development and validation of rapid methods to assess endocrine toxicity

There are growing concerns that exposures to commercial chemicals cause harm by interfering with the hormonal control of growth and development of the brain, reproductive tract and lead to metabolic and stress-related problems. Developing rapid methods to identify chemicals posing these hazards is a critical need for safety assessment. Building on experience gained in previous studies, the current project seeks to 1) develop rapid methods to detect chemical toxicity to thyroid hormone signalling (very important to early brain development) and 2) identify, characterize and develop assays for the enzymes that are inhibited by some organophosphate flame retardants (OPFR) leading to toxicity to the ovary and adrenal gland. Separate assays based on molecular targets of thyroid hormone disruptors will be refined and further validated using a robust list of substances known or suspected of interfering with TH signalling. High-throughput assays based on these molecules will be developed into protocols fit for toxicity test guideline development through the Organization of Economic Cooperation and Development (OECD). Secondly, innovative methods will be employed to identify molecules that react with the flame retardant molecules. Early results show that these are enzymes involved in cholesterol metabolism. Assays for these enzymes are currently being developed and these will be used to compare the potency across all phosphate flame retardants that are used in Canada. These studies will help inform risk assessment activities and support assessment and minimization of the risks of chemical use. (PI: Mike Wade)

Direct comparison of the sub-acute toxicities of Bisphenol A, F and S using a standardized OECD exposure protocol

Bisphenol F (BPF) and bisphenol S (BPS) are bisphenol A (BPA) substitutes prioritized for measurement in the cycles 7 and 8 of the Canadian Health Measures Survey (CHMS). BPF and BPS both present structural similarities to BPA and their levels in environmental and human samples are increasing. Information on BPF and BPS toxicities is much more limited than for BPA, making it difficult to properly evaluate the potential health consequences of BPA substitution by BPF and BPS. In this study, the toxicities of BPA, BPF and BPS were directly compared when administered to rats over a wide dose range according to a regulatory toxicology protocol based on OECD 407 Guidelines (Repeated Dose 28-Day Oral Toxicity Study in Rodents). Given the relatively limited effects of BPA on the parameters prescribed by the OECD 407 Guidelines, perturbations of endocrine functions were further investigated. Based on published information on the *in vivo* and *in vitro* toxicities of BPA, BPF and BPS, additional serum hormone levels were measured, while the expression of specific genes involved in their biosynthesis and degradation will be assessed in the liver. By directly comparing the *in vivo* toxicities of BPA, BPF and BPS, this project will allow a better assessment of the potential human health risks associated with the substitution of BPA by BPF and BPS. It will also contribute to a better interpretation of CHMS biomonitoring data. (PI: Guillaume Pelletier)

The role of stress and stress reactivity in mediating impacts of air pollutants on the brain and lungs

Health Canada is responsible for assessing the health risks associated with exposure to air pollution. Even at the relatively low average pollutant levels typically experienced in Canada, exposure to air pollution is associated with increased risk of neurological and mental health disorders (e.g. cognitive

decline, dementia, depression). However, underlying mechanisms are unclear. Stress may be a central unifying mechanism. Health Canada research has shown experimentally that inhaled ambient particulate matter and ozone provoke a stress response, causing the release of stress hormones that impact biological systems throughout the body. The brain is highly sensitive to stress, and chronic stress exerts profound biochemical and structural effects on the brain that contribute to local and systemic disease processes. This study investigates the role of stress responses in mediating impacts of pollutant inhalation on the brain and lungs. *In vivo* and *in vitro* models are used to examine biological pathways that link pollutant effects in the lungs and blood to the brain, and in turn feedback to impact the lungs and other organs. In collaboration with researchers at the University of British Columbia, stress biomarkers are assessed in a human diesel exhaust chamber study to extend laboratory findings to humans. Knowledge gained will be used to explore stress hormone involvement in associations between air pollution and brain development in a birth cohort in collaboration with researchers at ISGlobal (Barcelona, Spain). By linking results from experimental models to humans, this project will support the causal basis of epidemiological associations and inform effective risk assessment and management strategies. (PI: Errol Thomson)

A test system for the exposure of lung cells to microplastics under conditions that model real-life human exposures (CRA with WAQB)

Health Canada is responsible for assessing risks to health posed by inhaled pollutants. The environmental prevalence of microplastics has raised questions about potential toxicity. As inhalation is a potential route of exposure, tools that realistically model human inhalation exposures are needed. Traditional toxicity testing of inhaled contaminants involves exposure of animals; growing interest in moving away from animal models (due to ethical concerns, uncertain relevance to humans, high cost) has prompted development of devices that expose human cells and tissue samples to airborne test materials. Air-liquid interface (ALI) exposures mimic lung conditions: cells/tissues more closely resemble lung cells/tissues compared to conventional submerged cell cultures, and exposures occur by air. This study aims to establish an ALI exposure system that enables reproducible testing of microplastics and other airborne contaminants under conditions that model real-life human exposures. Human cells grown at the air-liquid interface are exposed to contaminants carried by a stream of air, as occurs in the lungs. Exposure conditions are optimised through real-time monitoring of particle characteristics and cellular deposition of airborne microplastics in the nano- and micro- size ranges. Established conditions and protocols maintain cell viability during exposure to air, thereby ensuring that toxic and inflammatory responses are specific to test agents. The system will provide an innovative approach to assess effects of inhaled contaminants (e.g. complex mixtures of gaseous and particulate air pollutants, combustion emissions, traffic-related pollutants, secondary organic aerosols, metals, nanoparticles, microplastics, vaping products, etc.) without animal exposures. Importantly, this will provide Health Canada with the capacity to assess health-relevant biological responses in human cells to the actual atmospheres to which people are exposed, rather than using extracts or simplified model materials, thereby more closely modeling human lung toxicity and improving hazard identification and mechanistic studies in support of regulatory needs. (PI: Errol Thomson)

Screening of replacement chemicals of emerging concern and selected CMP3 chemicals through *in vitro* assays for endocrine toxicity (CIHR Team Project)

Scientific and public concern mount about the potential health impacts due to widespread use of chemicals suspected of causing endocrine disruption. Regulatory action and/or consumer pressure have

caused a reduction in the use of a number of suspected endocrine disruptors including pentabromodiphenyl ethers (PBDE; flame retardants), bisphenol A (BPA) and diethylhexyl phthalate (DEHP). In response, a large number of chemicals have been introduced into the marketplace as substitutes; some of which may pose similar risks due to structural or functional similarities. In this study, chemicals used as replacements for PBDE, BPA and DEHP are screened with *in vitro* assays to determine effects on thyroid hormone or steroid hormone production. Results will inform the potential hazards of use of these replacements and help identify less toxic alternatives. (PI: Mike Wade)

Mechanistic Studies Division

GeneTox21 – An integrated platform for *in vitro* genetic toxicity assessment and regulatory evaluation of new and existing substances

Genetic damage is associated with numerous human diseases, and chemical screening programs routinely assess a chemical's ability to damage DNA (i.e., genetic toxicity). Traditional assessment tools (i.e., bioassays) are laborious and not conducive to high-throughput (HT), high-content chemical screening using tools that employ cultured cells (i.e., *in vitro* bioassays). Physical manifestation of genetic damage (e.g., mutations and chromosome damage) requires cellular replication; thus, no *in vitro* genetic toxicity assay can truly be considered HT. Even the most rapid assays require 24+ hours from cell exposure to data acquisition; consequently, no *in vitro*, HT, multi-endpoint system for genetic toxicity screening has been established. However, HT scoring technologies (e.g., flow cytometry) can be employed to increase the throughput and precision of some traditional *in vitro* genetic toxicity assays. Assays using such newer scoring technologies can be considered higher throughput in comparison with the traditional approach (e.g., manual microscopy). This project aims to establish an integrated, multi-assay, higher throughput platform for the assessment of chemically-induced genetic toxicity. The system includes multi-measurement, per-cell assays for an array of effects (i.e., MicroFlow® and MultiFlow™ tools), the high-throughput CometChip® assay for DNA breaks, a miniaturized version of the Salmonella fluctuation test (i.e., Ames II), a gene expression profiling assay for cellular responses to DNA damage, and high-throughput microscopy for per-cell *in situ* imaging. The performance of the higher throughput system is being evaluated by analysis of 35 reference compounds and 20 data-poor compounds prioritized for regulatory screening. The overall performance of the assay is being evaluated; it will subsequently be deployed for routine generation of genetic toxicity profiles for prioritized substances. The platform, termed GeneTox21, will be internationally promoted to encourage its adoption for routine genetic toxicity assessment of new and existing substances. (PI: Paul White)

Refining and deploying a quantitative framework for the analysis and regulatory interpretation of genetic toxicity dose-response data

Genetic damage is associated with numerous human diseases, and chemical screening programs routinely assess genetic toxicity. The results of genetic toxicity tests have traditionally been evaluated using qualitative binning (i.e., yes or no) that merely identifies DNA-damaging agents. However, there is increasing interest in quantitative analyses of genetic toxicity test results, and the use of chemical-specific potency values (i.e., Point-of-Departure or PoD metrics) to determine human exposure limits and assess the likelihood of adverse health effects. Earlier work determined the most suitable PoD metric for routine analyses of genetic toxicity test data and developed a preliminary approach to determine human exposure limits that correspond with negligible likelihood of adverse effect. This

research study addresses issues that hinder routine use of PoD metrics, such as the Benchmark Dose (BMD), to assess the likelihood of chemically-induced genetic effects. More specifically, the project uses dose-response data collected from the scientific literature to determine test-specific Critical Effect Size (CES) values. These values, which are also known as Benchmark Response (BMR) values, are required to determine the dose associated with a toxicologically meaningful response; and moreover, to determine the exposure limit associated with minimal risk of adverse human health effects. Analyses of published data is also being used to empirically-determine values for the uncertainty factors used to interpret experimental toxicity assessment data for human health risk assessment. Related analyses of published test data are being used to compare regulatory assessments based on genetic toxicity data with those based on carcinogenicity data (i.e., case studies). The results obtained will be used to develop a framework for routine quantitative use of genetic toxicity data for regulatory evaluations of new and existing chemicals. Interactions with stakeholders will permit an evaluation of the proposed framework, and international promotion of quantitative methods for regulatory evaluations of genotoxic chemicals. (PI: Paul White)

Development of pathogenicity test methods for assessing the hazard of microorganisms used in biotechnology

Microorganisms routinely used in biotechnology for industrial (e.g., biofuel production), consumer (e.g., cleaning products), or emerging applications (e.g., synthetic biology) can be related to those capable of causing infections in humans. Some of these pathogenicity traits found in strains could be a serious problem for risk management. Therefore, it is critical that reliable pathogenicity testing protocols are established to ensure that risk assessments are carried out with the best available data. This project will develop clear, stepwise methods to test the effects of new microorganisms intended for biotechnology applications. Standardized pathogenicity laboratory methods for opportunistic pathogens do not currently exist, but are urgently needed in order to reduce the regulatory burden associated with non-standardized industry submissions. Methods will enable regulators to guide the biotechnology industry when they notify Health Canada of new microorganisms to be imported into or manufactured in Canada. Additionally, with rapidly advancing knowledge and technology, there is an opportunity and need for developing more sensitive and rapid models. These new methods are essential since although current test models can identify highly infectious microorganisms, they create uncertain results for less infectious microorganisms that can only cause disease in those with suppressed immunity (e.g. young, elderly or those with chronic illnesses). Development of such models would ensure risk assessments take into consideration the most sensitive people in our population. Furthermore, they involve 3-dimensional mammalian cell cultures to detect multiple toxicity indicators that occur during infection, which could eventually eliminate the need for animal testing. The methodology will be investigated to track living microorganisms within biotechnology products composed of microbial mixtures, which is currently unavailable. Ultimately, microbial test methods and new laboratory models will greatly advance science-based decision-making for regulators/evaluators, and ultimately result in safer biotechnology products available to the consumer. (PI: Azam Tayabali)

Relative toxic potency of silica and titanium dioxide nanoparticle variants

Manufactured nanomaterials (NMs) provide challenges in hazard identification and risk evaluation due to lack of reliable physico-chemical and toxicity data, creating a difficulty for government agencies to establish effective safety evaluation guidelines. Furthermore, engineered NMs are reaching the market through consumer products and applications such as paints, sealants and cosmetics, there are also new

reports suggesting that these NMs are found in ambient atmospheres and consequently can have public health implications. The project is designed to address the needs of the risk assessment process for NMs, specifically nanosilica and nanotitanium dioxide, which exhibit the potential to reach the atmosphere and may potentially be harmful to human health and environment. Understanding the toxicity of NMs can also help understand the health outcomes due to components of air pollutants that are in nano size range. In this work, Health Canada investigators, in collaboration with academic and Environment and Climate Change Canada partners, are probing toxicity characteristics of these NMs with varying physical and chemical properties. Composition, size and surface coating characteristics of these NMs are being assessed along with toxicity in lung epithelial cells and macrophages, and in cells from biopsy samples from healthy and pulmonary diseases (e.g. cystic fibrosis). Toxicity of nanoparticles after atmospheric transformation under simulated experimental atmospheres will be examined as well. The information obtained from this work will advance our understanding on the health consequences of exposure to NMs, in providing toxicity information to contribute to the risk assessment of these materials (e.g. NSACB), and also can assist in the design of less toxic NMs. (PI: Premkumari Kumarathasan)

An integrated testing strategy to assess somatic and germ cell mutations using the OECD's transgenic rodent test guideline TG 488 and the MutaMouse model

Health Canada contributes to the development and standardization of internationally accepted test guidelines (TGs) for the Organisation for Economic Cooperation and Development (OECD). TGs are routinely used for assessing the safety of chemicals before they come on the market. HC has played a fundamental role in developing TG 488 (Transgenic Rodent Mutation Assay) for evaluating the induction of mutations (i.e., changes in the DNA sequence) in germ cells (sperm and eggs) or in somatic cells (all other cell types in the body). Mutations in germ cells may be transmitted to offspring resulting in heritable genetic effects that impact both the individual and population; mutations in somatic cells increase the risk that an individual will develop cancer. Despite these distinct implications, regulatory testing is done almost exclusively in somatic cells. A significant hurdle is the need for a second set of animals for germ cell testing, because of the duration of spermatogenesis, the process producing sperm. Previous work suggests that it may be possible to use germ cells from testes, rather than sperm, and a single time-point for analyzing mutations in somatic and germ cells. However, there is uncertainty regarding the optimal time-point, and more data are needed before recommendations can be made to update TG 488. Work conducted under this project has generated critical data that has recently lead the OECD to update TF 488 on the recommended design for germ cell mutagenicity. This is also impacting testing in somatic tissues because it proposes a single time-point that enables the analysis of somatic and germ cell mutations with comparable sensitivity. Additional work is being conducted to support the suitability of this single time-point for mutagenicity testing in both somatic tissues and germ cells. This integrated approach will significantly reduce the number of animals that are needed for testing. (PI: Francesco Marchetti)

Development of methodology for home dust microbiome analysis towards Canadian exposure assessments of biotechnology microbes

Health Canada assesses and manages risks of biotechnology microorganisms under CEPA. The scope of management includes microorganisms on the Domestic Substance List (DSL) that are contained as active ingredients in some types of microbe-based cleaning products (MBCPs). These products are used as alternatives, or additives, to chemicals-based cleaners and likely contribute to the biomass found in

house dust. The exposure patterns of MBCPs in home environments are unknown and without this information, risk cannot be accurately evaluated. In recent years, initiatives have taken place to analyze Canadian house dust ((Canadian House Dust Survey and Canadian Healthy Infant Longitudinal Development (CHILD) birth cohort study)) and these initiatives have helped provide an understanding of Canadian house dust composition. This project examines metagenomic DNA extracted from dust samples from Canadian homes in order to inform the assessment of MBCPs derived from biotechnology microbes. Metagenomic DNA analysis is necessary because microbial cultivation methods can only support the growth of a fraction of microbial flora. The overall objectives are to develop methodology for estimation of DSL microbial presence in house dust and provide insight into the microbial content of homes where MBCPs are used, versus those homes where chemicals-based cleaning products are used. (PI: Phil Shwed)

Dermal absorption testing of existing and new priority chemicals under the Chemicals Management Plan

Several substances identified as priorities for further action under the third phase of the CMP are present in personal-care products, cosmetics, paints, or household cleaning products. For these substances, skin is the primary exposure route. The objective of this project is to evaluate the dermal absorption potential of prioritised substances, to inform and refine related exposure scenarios. Potential health impacts associated with the exposures are not being investigated in this study. The study was conducted in two phases. In the first phase (2016-17 fiscal year), one chemical (CAS RN 81-48-1 (an anthroquinone)), a chemical present in skin products was assessed for its capacity to be absorbed through the skin. In the second phase (2017-18 fiscal year), six individual parabens were tested, namely iso-propylparaben (CAS RN 4191-73-5), iso-butylparaben (CAS RN 4247-02-3), methylparaben (CAS RN 99-76-3), ethylparaben (CAS RN 120-47-8), propylparaben (CAS RN 94-13-3) and butylparaben (CAS RN 94-26-8). In 2018-19, two additional priority chemicals Citral (CAS RN 5392-40-5) and Alpha-pinene (CAS RN 80-56-8) were tested. The data concerning chemical-specific dermal absorption for many chemicals are not available. The project is generating dermal absorption data required to set the absorption rates for some substances that are highly prevalent in consumer products. (PI: Sabina Halappanavar)

Use of gene expression profiles to facilitate read-across for 24 priority PFAS (CRA with WAQB)

Per- and poly-fluoroalkylated substances (PFAS) are a large class of man-made chemicals that are ubiquitously found in the environment due to their wide variety of industrial and commercial uses, their persistence and their high mobility. There are concerns for PFAS exposure through environmental media (e.g., water, soil, foods) to cause potential adverse health effects including liver and kidney toxicity, increased cholesterol levels and delays in mammary gland development. Although there is a growing body of knowledge on PFOS (perfluorooctanesulfonic acid) and PFOA (perfluorooctanoic acid) toxicity, there is little known about the many other PFAS. Health Canada has identified toxicity testing for PFAS as a research priority. To date, >3,000 PFAS have been identified; it is recognized that not all PFAS can be tested to develop health-based values. Therefore, Health Canada compiled a list of 24 PFAS that best represent variability in chemical composition across PFAS and importantly, have been found in Canadian drinking water or have analytical methods for detection in drinking water. Acquiring information on data poor substances for risk assessment has been challenging for regulatory agencies worldwide, including Health Canada, due to the cost and length of traditional toxicological research. In an effort to accelerate the pace of risk assessments, the international toxicology and risk assessment communities are investing in case studies to demonstrate the utility of new approach methodologies (NAMs) that are cost/time

effective in chemical evaluations. This research employs gene expression profiling in human liver cells in culture to facilitate assessment of various PFAS. Objectives include: 1) applying gene expression data to acquire mode of action information on PFAS and to facilitate read-across for human health risk assessment; 2) to explore how PFAS behave in mixtures; 3) to use the data as a case-study for the use of NAMs in risk assessment. (PI: Carole Yauk; Ella Atlas)

Evaluation of dermal decontamination to reduce firefighters' exposures to combustion-derived PAHs (polycyclic aromatic hydrocarbons) (Ottawa Fire Services, Canadian Forces Fire Marshall, Ottawa Professional Firefighters Association, Association des pompiers de Montréal, International Association of Firefighters, and Institut de protection contre les incendies du Québec)

Firefighters face serious risks on the job, including heat, physical and mental stress, as well as exposure to a toxic environment both in and around fires. In recent years, statistics have shown that these exposures have taken their toll on firefighters. For example, it has been shown that firefighters have an increased cancer risk compared to the general population. Previous studies have shown skin to be a major route of exposure. Skin cleaning wipes are the most practical and suggested method for dermal decontamination for firefighters yet little research has been done to assess if this is effective, and whether or not different types of wipes or other skin cleaning methods (e.g., soap and water) are better at removing dermally-deposited contaminants. This project is specifically designed to collect the necessary information to make sound, evidence-based decisions on how to optimally protect firefighters from dermal exposure to combustion emissions. An intervention study at training fire events in Ottawa has been designed to assess the effectiveness of the use of skin cleaning protocols. Exposures to PAHs are measured and compared between participants following current decontamination protocols (i.e., the control group), and those who add an additional dermal decontamination step using skin cleaning wipes or a wash cloth with soap and water (i.e., the intervention groups). These research activities are conducted at training fires, where exposures are relatively uniform across the participants. Ultimately, the research will contribute to a greater understanding of the effectiveness of skin cleaning procedures and furthermore, whether different protocols are superior to others in removing hazardous contaminants deposited on the skin. The results will be used to develop new protocols, or modify existing practices, to minimize dermal absorption of contaminants among firefighters. (PI: Paul White; Jules Blais [University of Ottawa])

Development of methods for identification and hazard assessment of biotechnology-related microorganisms: Assessment of virulence of opportunistic human pathogens in microbial mixtures (CRA with NSACB)

Microorganisms formulated as heterogeneous mixtures are most often notified to regulators as individual microorganisms (i.e., one notification per microorganism). Currently, there is considerable uncertainty in our understanding of how pathogens may express virulence in these mixtures compared to how they exist in homogeneous cultures. Towards clarifying the effect of mixtures on pathogenicity, this project aims to establish a systematic approach for testing the virulence of several known pathogens as they exist in homogeneous cultures compared to a component within a mixture of microorganisms. This approach could possibly be applied to any type of heterogeneous microbial mixture being considered for commercial biotechnology applications. (PI: Azam Tayabali)

Portable automated biosensing of potential dual-use biological threats to critical water systems (DRDC-CSSP)

New genetic engineering and synthetic biology technologies are generating unknown threats that need to be assessed and countered. The project aims to advance a biological sensor to detect specific bacteria (*Bacillus* species) commonly used in biotechnology applications, but that could be manipulated to function as agents of bioterrorism. These bacteria are termed 'dual-use' because of their capacity to be used for both beneficial and malicious activities. The proposed device is envisaged to be physically linked to water systems (e.g., potable water supplies, dams, pipelines, treatment plants, and recreational sites), and repeatedly (i.e., daily) concentrate and sample bacteria without user intervention for 30-60 days. Besides developing the automated portable device, the project aims to provide fundamental knowledge on the pathogenic potential of bacteria used in biotechnology applications. This is done by developing a functional, immune cell -based method to mimic an infectious mechanism shared by close relatives of the known biological threat, Bacillus anthracis, which is the etiological agent of anthrax. Bacillus anthracis infects specific white blood cells called macrophages, so this capacity will be assessed with biotechnology Bacillus strains that are either closely or distantly related. Furthermore, this project will investigate whether biotechnology-related Bacillus species can be detected in natural surface waters using both molecular methods and a unique existing bacterial identification system for biotechnology strains used in Canada. Ultimately, the project aims to develop an innovative biological sensor for automated detection of potential dual-use Bacillus strains, and generate important information on the pathogenic potential and environmental occurrence of biotechnology-related Bacillus species that are close relatives to known human pathogens. (PI: Azam Tayabali)

Evaluation of *in vitro* methodologies to resolve the differences in toxicity characteristics of newly synthesized nanosilica particle (SiNP) variants optimally to assist read-across in risk assessment of nanoparticles (CRA with NSACB)

Cellular respiration is a critical aspect of cell health and thus functioning of mitochondria, the power-house of the cell, can be of importance in terms of toxicity testing of nanosilica particles (SiNPs). Typically, *in vitro* cell viability assays incorporate assessment of mitochondrial performance. Previous observations indicated subcellular localization of SiNPs in the mitochondria by transmission electron microscopy (TEM) analyses and others have reported mitochondrial oxidative stress in response to nanoparticle exposure. The objectives of this work are to examine subcellular localization of a newly synthesized set of pristine and surface-modified SiNP variants in macrophages by TEM, and to assess the impact of size and surface modification on internalization of SiNPs. A further aim of this study is to conduct oxidative stress analyses by following mitochondrial protein changes after exposure to nonporous SiNPs. These findings can support OECD test guideline development, provide a mechanistic basis to rank and prioritize SiNPs that are on the Domestic Substances List (DSL) for further toxicological testing as well as support the activities on risk assessment of these materials by NSACB. (PI: Premkumari Kumarathasan)

Development and application of fit-for-purpose, Adverse Outcome Pathway-based testing strategies to enhance hazard and risk assessment of chemicals causing genomic damage

The *Canadian Environmental Protection Act* requires the evaluation of the health effects of chemicals that are in the Canadian marketplace. However, conventional toxicology tests are time consuming,

expensive, and require large numbers of animals. Health Canada (HC) regulators are in urgent need of new tests to meet legislated mandates. New methods proposed to identify toxicological hazards are based on measuring a chemical's ability to disrupt critical biological processes. Genomics is a powerful tool to identify biological changes because it surveys effects across all of the genes in tissues/cells following a challenge. The use human cells in culture offers considerable advantages including increased throughput, reduced animal use, and cost savings. The need to modernize regulatory toxicology tests by making greater use of human cells in culture (instead of animals) and genomic methodologies has been emphasized internationally, but practical examples of use in human health risk assessment are required. This project works toward the unifying purpose of providing genomic solutions to support Canadian regulatory sciences and the challenges/needs noted above. The overarching objective of the project is to develop and implement practical genomic methods in human cells in culture for hazard identification and risk assessment of environmental chemicals in the area of genetic toxicology (damage to DNA). This project harnesses the Adverse Outcome Pathways (AOP) knowledgebase towards its objectives; AOPs catalogue cellular perturbations that are associated with detrimental health outcomes following chemical exposures. The project will build expert-informed AOPs to develop testing strategies implementing state-of-the-science genomic methods to predict genetic diseases like cancer. The methods, data, and analytical tools will be made publicly available to enable widespread use of the technologies/approaches. Case studies applying the modern test strategies will be applied to evaluate the effectiveness of the proposed approaches, assess feasibility to regulatory adoption, and provide data for human health risk assessment. (PI: Carole Yauk)

Development and application of novel Next Generation Sequencing approaches for mutagenicity testing in the 21st century

The *Canadian Environmental Protection Act* mandates that chemicals that come into commerce must be tested for the ability to induce mutations (changes in DNA sequence). Mutations occur at each cell division either because of random errors or because of exposure to a toxic agent. When mutations happen in tissues, they may generate cancer. When mutations happen in sperm or eggs, they can be transmitted to the offspring and result in a variety of genetic diseases. Existing mutagenicity tests have limitations. Specifically, they measure mutations in a single gene (the human genome has ~20,000 genes) or use genetically modified laboratory rodents where mutations are measured in a bacterial gene. Also, these methods are not suited for studying transmitted mutations in the offspring because they would require large numbers of animals. Recently, significant improvements in DNA sequencing technologies enabled the identification of mutations over the entire genome. We are using these methodologies to analyze the genomes from human families to identify environmental exposures that increase the number of transmitted mutations to future generations. In addition, we are evaluating a new sequencing approach as a replacement of existing methods for mutation testing. This new method allows the analysis of mutations in many genes in parallel without the need for genetically modified rodents, and, it provides information on the mechanism of mutation induction. Lastly, we are using computational approaches to analyze induced mutations to identify patterns that are specific to each chemical and that are associated with genetic diseases such as cancer. Overall, this project will generate foundational data to modernize and improve regulatory testing for mutagenicity. This project is linked to Health Canada's priority of effectively and efficiently assessing the potential adverse health effects of chemicals and is expected to provide regulatory knowledge to help prevent cancer and other genetic diseases. (PI: Francesco Marchetti)

Development of an Integrated Analysis Tool for Genotoxicity Assessment (IATGA) (CRA with NSACB)

Genetic damage is associated with a variety of human diseases; routine toxicological screening of chemicals in commerce requires identification of substances that can damage genetic material (i.e., genetic toxicity assessment). A related CMP-funded project is developing an efficient, effective, high(er) throughput genetic toxicity assessment platform based on analysis of cultured cells; the platform is known as GeneTox21. Compound screening using the GeneTox21 platform generates large amounts of complex data; the regulatory utility of the data depends on the user's (e.g., clients and stakeholders) ability to organize, browse, analyse, display and interpret the information in an intuitive and user-friendly fashion. A recent research endeavour established an innovative, user-friendly bioinformatic tool known as DREAM-TK; the tool allows users to browse, analyse and interpret complex toxicological test results. DREAM-TK constitutes a foundation for the development of a related tool for efficient interpretation of test results generated using the GeneTox21 platform; a tool to facilitate essential interpretation of genetic toxicity screening data in a regulatory context. This work is building on the DREAM-TK paradigm, and developing a bioinformatic platform to browse, visualise, analyze, and interpret GeneTox21 results; the tool being delevlooped is called the *Integrated Analysis Tool for Genotoxicity Assessment* or IATGA. Work conducted to date has built a *beta* test version of IATGA; interactions with regulatory group have highlighted avenues for improving functionality. Bioinformtic tools such as IATGA are essential for effective and efficient chemical safety assessments based on simultaneous interpretation of results generated using several (geno)toxicity assessment tools. (PI: Paul White)

Systematic characterisation and preliminary validation of genomics-guided non-animal test models (*in vitro*/*ex vivo*) and methods for nanomaterial safety assessment

Broadly defined, nanomaterials (NMs) are a novel class of man-made substances that exhibit a size range of 1-100 nanometers (one nanometer is one billionth of a meter). While their nano size-associated physical and chemical properties make them attractive for various industrial and consumer product applications, the same properties can complicate their safety assessments. Health Canada (HC) is responsible for regulating products containing NMs in Canada however, an effective risk assessment strategy and appropriate tools for evaluating NM-induced toxicity are not available. While the 'gold standard' for evaluating toxicity of substances involves testing in animals, owing to their time and resource intensiveness, animal-reliant methods are not optimal for NM testing. Thus, the overarching objective of the proposal is to identify and optimise animal alternatives (involving cells derived from animal or human tissues) that are already in development at HC and in other organisations internationally, and demonstrate their relevance and sensitivity to assess NM-induced responses in animal tissues. The optimised tools will be used to generate toxicological data for the effective risk assessment of NMs at HC. The study is conducted in collaboration with New Substances Assessment and Control Bureau of HC, and the results will enhance HC's ability to assess and manage the risks of adverse effects from exposure to NMs in products and the environment. (PI: Sabina Halappanavar)

MAPLE: The Microplastics Air Pollution Laboratory and Exposure Project: Developing methods to detect, quantify, and characterize airborne microplastics (CRA with WAQB)

Microplastics are small particles of plastic measuring less than five millimeters in length. With growing concern on their ecological and human health impacts, the Government of Canada is leading international efforts to protect the environment from microplastic plastic pollution. In support of *Canada's Plastics Science Agenda*, the government has prioritized research on: a) the detection,

quantification, and characterization of plastics in the environment; and b) Impacts on wildlife, human health, and the environment. Very few studies have purported to measure microplastics concentrations in air, and there is a need to develop rigorous scientific protocols to strengthen future efforts. No studies to date have investigated the impact that exposure to airborne microplastics has on human health. The purpose of this study is to develop and optimise sample collection, and subsequent microscopic and analytical methods to detect, quantify and characterise different types of microplastics in both indoor and outdoor samples. As Canadians spend approximately 90% of their time indoors, data on both indoor and outdoor microplastic exposures will be required to understand their sources, pathways, fate, and distribution; and to identify and prioritize specific microplastic categories or mixtures for future research, risk assessment/management. (PI: Sabina Halappanavar)

In vitro toxicity screening of nanoforms of zinc oxide (CRA with NSACB)

Engineered nanomaterials (NMs) including nanoforms of zinc oxides (ZnO) are incorporated into various consumer products. Nano zinc oxide, for instance, has wide ranging applications in paints, coatings, building materials, antibacterial agents, sunscreens, moisturizers, food packaging, etc. These NMs thus can have human health implications and furthermore are problematic in terms of hazard identification and risk evaluation due to lack of reliable physico-chemical and toxicity data, creating a challenge for government agencies towards establishing effective hazard evaluation guidelines. The recent data gap analysis of nanoscale forms of substances on the domestic substances list (DSL) of the New Substances Assessment and Control Bureau (NSACB) of Health Canada has identified the nano ZnO (CAS RN 1314-13-2) as one of the 53 nanomaterials in commerce in Canada under the CMP that requires information to help tailor assessment and management approaches. This work is designed to conduct *in vitro* cytotoxicity screening of nano-zinc oxide forms in two types of lung cells to determine their relative toxicities, using various toxicity testing approaches. The toxicity endpoints for cytotoxicity assessment will include cellular viability, metabolic activity, membrane integrity, oxidative stress and inflammatory status. In addition, association between nano ZnO potencies and their physico-chemical properties is also studied and toxicity mechanisms will be explored to support risk assessment processes by NSACB. (PI: Premkumari Kumarathasan; Azam Tayabali).

Population Studies Division

Air Health Trend Indicator (AHTI): Development and updates

The Air Health Trend Indicator (AHTI) provides information on how the health risks associated with exposure to ambient air pollution change over time. The AHTI measures day-to-day changes in non-accidental deaths including those due to heart, circulatory and respiratory conditions a few days after exposure to two major air pollutants, ground-level ozone and fine particulate matters (PM2.5). The tool is based on 22-24 major urban cities across Canada, accounting for geographical differences in air pollution levels, climate and health risks with reports and updates posted on Environment and Climate Change Canada's website, and accessible to all Canadians since 2011. The AHTI will be extended in five areas: study period, number of cities, health outcomes, subpopulation, and perspective on short-term exposure. More recent health data for 2013-2015 has been added to the study as well as additional cities in order to obtain more reliable and less biased estimates of public health risks. In addition to mortality, daily hospitalizations are now being monitored, which amounts to approximately 10x the daily mortality, allowing researchers to obtain more information on specific causes of hospitalization. Subpopulation groups, such as the elderly (>65 years) will be studied by age and biological sex as these

subgroups are expected to be more vulnerable to air pollution. Finally, exposure to air pollution can be short-term or long-term without consensus on the definition. Setting clear and fixed definitions depending on study purpose will let researchers determine the effects of short-term pollution exposures. As an on-going study, new advanced statistical models are being developed further to understand deaths and hospitalizations attributable to two air pollutants concomitantly, to estimate combined health risk. This multi-response with multi-pollutant model development will be the main extension for the fourth update of the AHTI. (PI: Hwashin Shin)

An intervention study on the effectiveness of the Air Quality Health Index (AQHI) advice in a panel of patients with implanted cardioverter defibrillators in Toronto

The AQHI is a risk communication tool intended to provide information to the public on current and forecasted air quality conditions. Although the AQHI has been used extensively for several years, little research has been done to characterize the benefits that may be achieved by following AQHI advice. This project involves conducting a panel epidemiological study in a randomized cross-over design to examine the actual effectiveness of the AQHI as an intervention in reducing cardiovascular risks. Eighteen patients who had an implantable cardioverter defibrillator (ICD) and who lived and worked in the Toronto area were followed for a maximum of ten weeks in the summer and fall months of 2016 or 2017. Their blood pressure, pulse rate and oxygen saturation, before and after a 30-minute outdoor walk were collected. Hourly ambient ozone, nitrogen dioxide, fine particulate matter ($PM_{2.5}$), sulphur dioxide and carbon monoxide concentrations were collected, and the AQHI calculated. On days when the AQHI was ≥ level 5, half of study participants were randomly assigned to exercising indoors. Participants' daily exposure to air pollutants was estimated using Geographic Information System according to their residential postal codes. The results show that air pollution in Toronto was significantly associated with adverse changes in cardiovascular measurements in patients with ICD, and advice to reduce exposure to air pollution based on AQHI levels may help reduce adverse cardiovascular measurements. The results also show that daily mild exercise over 70 days may benefit cardiovascular function in this cohort of ICD patients. The significance of this study is that an objective clinical observation was used to test the effectiveness of a risk communications tool in a vulnerable population. The results may be used for patients and health professional outreach activities. (PI: Ling Liu; Dave Stieb)

Systematic Meta-Analysis and Review Tools (SMART) in support of science assessments

Science assessments involve the review of large amounts of research data with a view to evaluating the existence of a causal relationship between the exposure and response in question. Like the assessment process, systematic reviews formalize the review process by identifying, determining the relevance of, critically appraising, and extracting data from relevant literature according to a standard protocol. In a meta-analysis, results from individual studies are quantitatively pooled to provide an overall quantitative estimate of the magnitude of association between an exposure and response. Systematic reviews and meta-analyses provide a powerful summary of the weight of evidence which may be particularly informative in assessing the existence of a causal association. In this study, a standard protocol, data management and analysis tools were developed, and as a test case, these tools were applied to evidence from 86 studies linking short-term nitrogen dioxide (NO_2) exposure to ischemic heart disease (IHD) morbidity, and 76 studies of long-term exposure and mortality. Pooling results across these studies showed that short term NO_2 exposure was significantly associated with IHD morbidity, while long term exposure was significantly associated with mortality from all causes as well as specific causes including cardiovascular disease, respiratory disease and lung cancer. The evidence

was considered sufficient to infer a likely causal relationship between short term NO_2 exposure and IHD morbidity, while the evidence was considered suggestive of, but not sufficient to infer, a causal relationship between long term NO_2 exposure and mortality. The results highlight the need for additional research to understand physiological mechanisms through which NO_2 contributes to both morbidity and mortality, and to evaluate the role of confounding factors such as other air pollutants, noise and stress. The synthesis tools should prove valuable in future risk assessments. (PI: Dave Stieb)

The Air Quality Benefits Assessment Tool (AQBAT) - Update

AQBAT is a computer application developed by Health Canada which is designed to estimate the human health impacts of changes in Canada's ambient air quality. It is used to estimate the benefits (positive impacts) or damages (negative impacts) of proposed regulatory initiatives related to outdoor air quality as mandated by the Treasury Board Cabinet Directive on Regulatory Management (when developing new regulations that affect air quality, Treasury Board requires that Health Canada quantify the human health and associated economic benefits of estimated changes in air quality). AQBAT consists of a Microsoft Excel application file which enables the user to define, run, examine and save the inputs and outputs for specific scenarios combining pollutants, health endpoints, geographic areas and scenario years; it contains historical and projected population data, pollutant concentration data, annual baseline health endpoint occurrence rates, and Health Canada endorsed concentration-response functions and health endpoint valuations; and it utilizes the @Risk add-in software to perform Monte Carlo simulations, which allow the user to examine the effects of uncertainties on estimated health impacts. AQBAT is a knowledge translation tool in that it applies findings from research studies of the health effects of air pollution to develop concentration-response functions and economic valuation estimates used in quantifying health impacts and their economic value. AQBAT has been applied to numerous regulatory and non-regulatory scenarios including impacts of vehicle electrification, impacts of wildfire smoke, assessment of climate change impacts, and Human Health Risk Assessments for Diesel Exhaust and Biodiesel. Ongoing updating of data, parameters and methodology is required to ensure that assessments of regulatory initiatives reflect the most current science such that they most effectively protect the health of Canadians and do not impose unwarranted costs to society. Version 3 of AQBAT was released in 2019. (PI: Dave Stieb)

National Biomonitoring Program under the Canadian Health Measures Survey (CHMS) – Cycles 5-6 (2016-2019) and cycles 7-8 (2021-2024)

The National Biomonitoring Program is conducted as a component of the Canadian Health Measures Survey (CHMS), which is a national survey led by Statistics Canada, in partnership with Health Canada and the Public Health Agency of Canada. Through personal interviews and the collection of physical measurements, this ongoing survey provides nationally-representative data on indicators of environmental exposures, chronic and infectious diseases, fitness, and nutritional status. The physical measurements include biomonitoring, the measurement of environmental chemicals or their metabolites in blood, urine and/or hair samples. Health Canada's Population Studies Division is responsible for the National Biomonitoring Program that encompasses the planning, collection, quality control, reporting and dissemination, as well as analysis and interpretation of national biomonitoring data. The program establishes baseline concentrations and trends for environmental chemicals of concern in Canadians and help meet the regulatory and public health data needs. Key milestones for the national biomonitoring program during FY 2019-2020 included: 1) publication of the Fifth Report of Human Biomonitoring of Environmental Chemicals in Canada that included data for 99 environmental

chemicals (e.g. alternate plasticizers, pesticides, and VOCs) collected from approximately 5,800 Canadians aged 3–79 years in cycle 5 (2016-17); 2) Completion of sample collection for CHMS Cycle 6 (2018-2019); 3) Publication of two key papers: an updated evaluation of the CHMS biomonitoring data in risk context and the first-ever regional-scale analysis of the data comparing concentrations of several chemicals in Ontario, Quebec and the rest of Canada; 4) Organization and chairing of the Second Meeting of the International Biomonitoring Network in August 2019; 5) Refinement of analytical methods for certain chemicals prioritized for biomonitoring in cycle 7; 6) Initiation of analysis of the CHMS biobank samples during the CHMS gap year (Jan - Dec 2020) to meet near-term data needs of stakeholders; and 7) Completion of data analysis to identify demographic, environmental and lifestyle factors associated with the blood concentrations of lead and benzene. (PI: Annie St-Amand)

Regional analysis of CHMS biomonitoring data

The Canadian Health Measures Survey (CHMS), an ongoing national health survey conducted in two-year cycles, collects extensive data on blood and urinary concentration of environmental chemicals that are used to assess chemical exposures in Canadians. Although the data collected is only nationally representative within each cycle of CHMS, combining data from multiple cycles of the CHMS allows calculation of chemical concentrations that are representative at the regional level for the 5 different CHMS regions, Atlantic, Quebec, Ontario, Prairies, and British Columbia. The aim of this ongoing project is to develop statistically robust estimates of concentrations of chemicals at the regional level and secondarily, to explore opportunities for calculation of valid estimates at smaller geographical scales. In the first-ever regional analysis of CHMS data published in FY 2019-2020, blood and/or urinary concentrations of several environmental chemicals for the provinces of Quebec and Ontario, as well as the entire CHMS (representing Canada) minus Quebec, and the entire CHMS minus Ontario were compared. The analysis showed several regional differences in exposures to chemicals and helped assessment of contributing factors. Continued regional-scale assessments under this project will involve additional CHMS regions (e.g. British Columbia), and help relating exposures to regional or point sources of pollutants and/or sociodemographic or lifestyle factors unique to a region. Ultimately, these data may contribute to a regional-scale prioritization of control measures to reduce chemical exposures in Canadians. (PI: Annie St-Amand)

Long-term exposure to ambient air pollution and effects on cardiovascular, respiratory and neurological health in an older population: The Canadian Longitudinal Study on Aging

The Canadian Longitudinal Study on Aging (CLSA) is a population based national study which will follow the health, lifestyle, social and economic transitions, and trajectories of 50,000 Canadians, aged 45 to 85 years old, at three-year intervals for 20 years. Health Canada's goal is to collaborate with the CLSA over the many years of follow-up to study the effects of ambient air pollution on healthy aging. The current proposal is to measure change in cognitive function measures and the incidence of cardiac, pulmonary and neurologic disease during six-years of follow-up, associated with the average neighbourhood concentrations of ozone (O_3), nitrogen dioxide (NO_2), and fine particulate matter ($PM_{2.5}$), during a six year period. Exposure will be estimated by satellite monitoring, Environment and Climate Change Canada's National Air Pollution Surveillance Program (NAPS) ground monitors and land-use regression techniques, where appropriate. Traffic-related air pollution will be estimated by the proximity of residence to roadways. This project has already received AAPHI funding (2016-2019) for the first three year follow-up. This project aims to update the data linkage (air pollution and climate variables to the CLSA data base) and data analysis to include another three years of follow up for a total of six years. A

longitudinal study will help clarify the health effects of air quality among the elderly, and build the foundation necessary to continue this legacy study over a twenty year period. A secondary aim is to determine if susceptible subgroups exist through stratifying results by gender, education, income, rural versus urban locations and the presence (at the time of study inception) of chronic comorbid conditions including diabetes, cardiovascular disease, and chronic obstructive lung disease. This study will be unique and provide some of the most definitive information available on the relationship between air quality and cognitive function in Canada. (PI: Bob Dales)

Long-term exposure to industrial air pollution emissions and the incidence of childhood asthma: A population-based birth cohort study

Industrial emissions are important sources of ambient air pollution, and contribute to local and regional air pollutant concentrations. However, information on the health impact of Canadian industrial emissions is still limited. Asthma is the most common childhood chronic disease in Canada. In this study, Health Canada collaborated with the Quebec Public Health Agency and University of Montreal and constructed a Quebec population-based birth cohort from administrative health databases in order to study childhood asthma incidence. Researchers analysed ambient levels coming from industrial emissions of $PM_{2.5}$, sulfur dioxide and nitrogen dioxide, using a pollutant dispersion modeling technique that incorporates meteorology and land uses. The ambient pollutant levels were linked to children's residence to estimate their long-term exposure to industrial emission-related air pollutants. Then, regression models were developed to study the risk of asthma incidence associated with exposure to air pollutants, adjusting for socioeconomic status and environmental tobacco smoke. The models were also adjusted for road traffic emissions and regional particulate pollution to reduce exposure misclassification. The results demonstrate that exposure to air pollutants from industrial emissions was significantly associated with asthma onset in children. The results from this study will contribute to the weight of evidence for establishing concentration-response curves for long-term exposure to industrial pollution. Risk functions from this project will help estimate costs/benefits of decreased asthma incidence associated with actions to reduce industrial air pollutant emissions. (PI: Ling Liu)

Maternal-Infant Research on Environmental Chemicals (MIREC) research platform

The Maternal-Infant Research on Environmental Chemicals (MIREC) Research Platform encompasses the original MIREC Study of Canadian pregnant women and the follow-up studies of some of their infants (MIREC-Infant Development: MIREC-ID) and young children (MIREC-Child Development at age 3: MIREC-CD3 and MIREC- Early Childhood Biomonitoring and Neurodevelopment: MIREC-CD Plus) and is designed to obtain pan-Canadian data on maternal and fetal/early life exposure to priority environmental chemicals and potential adverse health effects on the pregnancy, and newborn and infant/childhood growth and development. For the original MIREC Study, co-led by Health Canada researchers, approximately 2,000 women were recruited in the 1st trimester of pregnancy from 10 cities across Canada and followed through to delivery. Questionnaires administered during pregnancy and post-delivery collected information on occupation, lifestyle, medical history, environmental exposures and diet. Information on the pregnancy and the infant were collected from medical charts. Maternal blood, urine, hair and milk as well as cord blood and infant meconium were collected and analyzed for numerous environmental chemicals and nutrients. Subsequent follow-up studies of the infants and young children were designed to examine the potential association between prenatal exposure to various chemicals and the risk of adverse effects on infant growth, and potential markers of reproductive toxicity (MIREC-ID), child behaviour (MIREC-CD3) and neurodevelopment (MIREC-CD Plus).

Child blood and urine samples were analyzed to address gaps in data for young children on several metals/elements and non-persistent chemicals (phthalates, phenols, pyrethroids) (MIREC-CD Plus). The Platform also includes the MIREC Biobank of biospecimens collected for future research on the health of mothers and their children. The project continues to generate new knowledge on early life cumulative exposure to endocrine disrupting chemicals and potential health risks in vulnerable populations of pregnant women, fetuses, infants, and young children that contributes to risk assessment and management of chemicals. (PI: Tye Arbuckle)

MIREC ENDO: pubertal timing, endocrine and metabolic function

This new longitudinal component of the Maternal-Infant Research on Environmental Chemicals (MIREC) Research Platform will study the metabolic health of MIREC mothers over time and the pubertal growth and development and metabolic health of the MIREC children. The results of this study will address critical information gaps for Health Canada on the potential role of early life and childhood exposures to endocrine disrupting chemicals on children's metabolic function, growth (e.g., obesity) and the onset and progression of puberty, as well as whether maternal health status and chemical exposures during pregnancy have any long-term health impacts on the women. To do this, researchers will collect and analyze additional biospecimens for hormones and chemicals, conduct clinical health assessments of mothers and children and collect questionnaire-based data from the cohort at key ages relevant to pubertal onset, namely 7-9 years of age, 10-12 years of age, 13-15 years of age and from the MIREC mothers. In addition, 1st trimester maternal urine samples from the MIREC Biobank will be analysed for a number of emerging chemicals including organophosphate flame retardants, glyphosate, and bisphenol analogues. This study is designed to incorporate sex- and gender-based analysis. The project will result in new analytical methods for emerging chemicals and generate new knowledge on cumulative exposure to chemical mixtures and potential health effects in vulnerable populations through various critical life stages that will support risk assessment and risk management policies. (PI: Tye Arbuckle)

Northern Contaminants Program (NCP)

The Northern Contaminants Program (NCP) was established in response to concerns about human exposure to elevated levels of contaminants in wildlife species that are important to the traditional diets of northern indigenous people. The program's main objective is to work towards reducing and, where possible, eliminating contaminants in traditional/country foods, while providing information that assists individuals and communities in making informed decisions about their food use. Biomonitoring and health outcome studies continue to be undertaken to characterize human exposures to, and the health impacts of, environmental chemicals in the northern population. In 2018-2019, four human health project proposals were funded to address exposure to contaminants and links to country foods and nutritional status in multiple northern regions (Yukon, NWT, Nunavik) and the development and evaluation of health communication tools. Along with colleagues in the Health Products and Food Branch (HPFB), staff from the Population Studies Division is leading the human health component of the NCP. The NCP currently provides Canada's main contribution to the contaminants component of the Arctic Monitoring Assessment Programme (AMAP) under the Arctic Council. A Human Health Assessment Group (HHAG) was established under AMAP, through which trend monitoring and assessment of implications and impacts of pollutants on the health of Arctic residents is undertaken. (PI: Cheryl Khoury)

Oxidative stress, inflammation, and cardiovascular changes associated with oxidative potential of ambient coarse, fine and ultrafine particulate matter

Particulate Matter (PM) in ambient air is a complex mixture of various sizes and constituents. Oxidative stress/inflammation is thought to be an important pathway leading to PM-associated disease status. This has led to a hypothesis that oxidative potential (OP) may be an integral property of PM that initiates oxidative stress/inflammation in the body. Health Canada is conducting a study to investigate how OP and chemical constituents of coarse, fine and ultrafine PM may influence oxidative stress/inflammation and cardiovascular measurements. Investigators completed a clinical study in which healthy volunteer participants were exposed to size fractions in an environment-controlled facility, and PM mass and constituents used for these exposures were determined. The particles came from a Toronto downtown street and information was collected about traffic types and counts during exposures. Before and after an exposure, cardiovascular measurements were collected including blood pressure and heart rate variability, as well as blood and urinary samples, which were evaluated for biomarkers for oxidative stress and inflammation. Investigators measured OP of the PM mass and metal contents, and are analyzing associations of OP and PM constituents with changes of cardiovascular fuction and blood cells in participants. This study complements Health Canada's epidemiological studies on OP and particulate metal components, and helps verify epidemiological findings. Since PM sizes and constituents are related to various emission sources, knowledge on PM's chemical constituents, OP and adverse effects on human health may help identify toxic PM emission sources and prioritize source control strategies. (PI: Ling Liu)

The influence of air pollution on potentially fatal cardiac arrhythmias in Ontario, Canada

On days with higher levels of air pollution, cardiac morbidity and mortality are increased. Exactly how air pollution affects the heart is unknown. Perhaps air pollution may interrupt the normal heath rhythm. People that are at risk for life threatening cardiac arrhythmias often have a device implanted under the skin of their chest which will detect an abnormal heart beat and electrically shock the heart if needed to bring it back to a normal rhythm. The device is called an implanted cardio defibrillator (ICD). To investigate the influence of daily changes in air pollution in Ontario, Canada on the frequency of discharges from ICDs, researchers compared ambient air pollution concentrations on the day of an ICD discharge to other days in the same month and year when no discharges occurred. Among 10.320 patients with ICDs, air pollution levels were similar on days when cardiac arrhythmias occurred and did not occur. The levels of air pollution seen in the study did not appear to be a risk factor for potentially fatal cardiac arrhythmias in patients with ICDs. (PI: Bob Dales)

DEET usage study

DEET is the common name for N,N-Diethyl-m-toluamide, an active ingredient in personal insect repellents approved by Health Canada for use by children and adults. DEET helps protect against mosquito, blackfly and tick bites. The purpose of this study is to generate biomonitoring data from DEET used by children in a camp setting. Following parental consent, about 125 children aged 7 to 13 years participating in overnight camps and who are already planning to use DEET were recruited. Urine samples were gathered over the course of one 24-hour day in the camp setting and analysed to determine the amount of DEET and two metabolites in the body. The study, which complements other studies by Health Canada that measure chemical exposures in children from typical use, will provide a better understanding of Canadian children’s exposure to DEET and inform any future recommendations. (PI: Jennifer Gibson; Kim Irwin)

Exposure to ambient air pollutants and the onset of dementia: An administrative cohort study in Quebec

Effects of air pollutants are related to oxidative stress which have been linked to the pathogenesis of dementia including Alzheimer's and associated diseases. Health Canada collaborated with the Quebec Public Health Agency and the University of Montreal to assess the Quebec population's risk of developing dementia following long-term exposure to air pollutants. The dementia risk of living near major roads was also assessed for the island of Montreal. A cohort of adults aged 65 years and older starting in 2000 and ending in 2012 in the province of Québec, Canada was created, using linked medico-administrative databases in which new cases of dementia were defined. Annual residential levels of nitrogen dioxide and fine particles ($PM_{2.5}$) were estimated for each year of follow-up using estimates based on satellite images and ground air monitoring data. Dementia risks for the annual pollutant exposure level at each residential address were assessed using statistical modeling techniques adjusting for age and sex. Models also were adjusted for the calendar year, neighbourhood socioeconomic conditions and tobacco smoking. Statistical results reveal that increased exposure to nitrogen dioxide and $PM_{2.5}$ and decreased distance between homes and major roads were associated with increased risk of developing dementia. The results of this study will add to the weight of evidence for Canadian population's long-term exposure to air pollution and associated adverse health impact. (PI: Rick Burnett; Ling Liu)

Assessment of associations between exposure to air pollutants and the onset of chronic diseases in Quebec

Studies show associations between long-term exposure to regional fine particulate matter ($PM_{2.5}$) and the onset of hypertension and type 1 and type 2 diabetes. However no study has assessed associations with $PM_{2.5}$ from local industrial point sources which may be large contributors of $PM_{2.5}$ pollution in some communities. Health Canada collaborated with Quebec Public Health Agency, University of Montreal and University of Toronto and studied the associations between exposure to $PM_{2.5}$ from regional and industrial sources and risks of hypertension and diabetes incidences in population-based cohorts of adults in Quebec, Canada. A population-based open cohort was created for adults aged >20 years without hypertension or diabetes from the province of Quebec. The population was followed from 2000 to 2015 with new cases of hypertension and diabetes recorded. Industrial emission data were from the National Pollutant Release Inventory, and participants' yearly exposure to industrial emission-related air pollutants in ambient air were estimated using a CALPUFF dispersion modeling technique. Satellite estimates were used for regional air pollution levels. All pollution data were linked to participants' residential locations. Cox proportional-hazards models were used to estimate the associations between long-term exposure and disease incidence, with age as time axis (with stratification by sex), adjusting for area social and material deprivation and calendar year. Models included splines for time varying PM2.5 levels. Results show that residential exposure to PM2.5 from regional and industrial sources both appear to be independently associated with incident hypertension and diabetes. The results of this study will add to the weight of evidence for Canadian population's long-term exposure to air pollution and potential associated adverse health impacts. (PI: Rick Burnett; Ling Liu)

The association between air pollution and the degree of difficulty controlling sleep disordered breathing by positive airway pressure therapy (Ottawa Hospital Research Institute)

Obstructive sleep apnea has been shown to be linked to heart disease, hypertension, diabetes and depression. Sleep disordered breathing (OSA), which is characterized by abnormal or insufficient breathing in sleep causing sleep fragmentation and a reduction in blood oxygen level, has been associated with oxidative stress and inflammatory biomarkers. Positive airway pressure (PAP) treatment which helps keep the windpipe open during sleep is the treatment of choice for OSA. However, adherence with PAP treatment is low and multiple factors may affect PAP usage including environmental considerations. OSA and air pollution have been linked to increased cardiovascular diseases and mortality and may lead to symptoms of nervous system inflammation, including sensory discomfort and fatigue, the latter being a common manifestation of poor quality sleep. However, the association between pollution and OSA is still poorly understood and current evidence is very limited, though some human and animal studies have demonstrated that air pollution has an effect on OSA. Indoor air pollution, especially particulate matter which is small enough to be deposited in the upper airways of the respiratory tract, may potentially cause irritation and inflammation of the upper airways, reduce airway patency and consequently may lead to OSA development or worsening of existing OSA symptoms. This study aims to establish the concentration-response function for OSA by comparing day-to-day and night-to-night changes in air pollution with night-to-night changes in control of sleep apnea as measured by data from individuals'' CPAP machines. The results of this study will allow researchers to determine if air pollution aggravates sleep apnea and to what degree. This will help Federal evaluators determine the burden of illness/disease due to air pollution in the Canadian population, will be useful for determining the total economic impact of air pollution, and in the end, help with decisions about air quality standards. (PI: Bob Dales; Dr Tetyana Kendzerska [Ottawa Hospital Research Institute])

Chronic disease and air pollution: disease trajectory and intervention (ROUTE) Study

Over the past decade, there has been mounting evidence linking low levels of ambient air pollution to a higher risk of premature mortality around the world. However, important questions remain - the exact mechanism and pathways, whereby the accumulation of air pollution exposures elicits premature death, requires more precise elucidation. Because health is a dynamic state, encompassing successive episodes of good and poor health states, this information is crucial for supporting health guidance, as well as for estimating the burden of air pollution. Health Canada is conducting a study to investigate the important role of exposure to air pollution in affecting individuals' health trajectories, and how this unfolds along different physiological pathways. A better understanding of the ways in which air pollution shapes health trajectories will help identify key pathways of public health significance and inform public polices. The second objective of the ROUTE Study is to further evaluate the effectiveness of some widely-implemented or potential individual- and policy-level interventions in reducing air health effects. Air pollution has major public health and economic consequences, but considerable uncertainty exists concerning which actions can be taken to reduce its effects. To achieve the two objectives, the ROUTE Study will draw on Big Data sources, and use state-of-the-art causal inference methodologies. Results of this study will fill important gaps in air health research and support policy decisions and public actions on mitigating air pollution effects in Canada and elsewhere. (PI: Hong Chen)

The association between pregnancy exposure to air pollution and autism in children

Autism Spectrum Disorder (ASD) is a complex developmental disorder, characterized by difficulties in social communication and interaction that can persist throughout life. In Canada, the Public Health

Agency of Canada released a report of the National Autism Spectrum Disorder Surveillance System, focusing on prevalence and incidence in children (5-17) from six provinces and one territory. With limited studies on the association between air pollution and childhood ASD in Canada, Health Canada is undertaking an epidemiological research study to investigate negative effects of maternal exposure to various air pollutants during pregnancy on ASD in children aged five or under; a vulnerable Canadian subpopulation in Ontario. In contrast, positive effects of neighbourhood green space and walkability are also examined. This study associates children with ASD and their mothers based on key linkages and then estimates the association between maternal exposure to air pollution and ASD in children based on a matched case-control design with a matching ratio of 1:5. Evaluation during the perinatal period is essential since it is the period of critical brain development during which an environmental exposure can influence neurodevelopment. Study findings will help to understand potential causation or prevention of the occurrence of ASD in children and thus reduce burden of societal and family related health care and costs. (PI: Hwashin Shin)

AQHI updates by expanding temporal and spatial coverages

Health Canada has a mandate to assess health risks of sources and components of air pollution, identifying specific vulnerable populations, and helping Canadians maintain and improve their health. The Air Quality Health Index (AQHI) is an important daily communication tool to provide guidance to the public on protecting their health from the adverse health effect of short-term exposure to outdoor air pollution. The AQHI, which sums the individual risks associated with three major air pollutants, ground-level ozone, nitrogen dioxide (NO2) and fine particulate matter (PM2.5), is in need of updates in four areas: 1) improved modelling, 2) extension of study areas, 3) reflection of more recent study periods, and 4) additional health outcomes. First, the current AQHI is based on three single pollutant models for the three air pollutants individually, which could result in under- or over-estimates depending on their correlations. It is desirable to fully represent the effect of their combined exposures on health, accounting for the interactions among the three air pollutants. Second, while the AQHI is designed for national usage, it is based on urban areas only, due to air pollution data availability so expanding to rural areas and more urban locations is desirable. In terms of time periods, the tool is based on data for 1991-2000. Recognizing that the Canadian demographic profile, air quality profile, and medical care have changed since 2000, the exposure-health outcome relationship over time may have changed and thus expansion to recent years (2001-2015) is necessary. Finally, the AHQI considers mortality but will now be extended to hospitalization. Overall, this study is intended to provide new information to support prediction of adverse health effects related to the three air pollutants studied. (PI: Hwashin Shin)

Impact of temporal variation of industrial emissions of air pollutants on asthma incidence in children of Quebec - An approach to accountability study

Industrial emissions contribute to local and regional air pollutant concentrations. In Quebec, significant reduction in industrial air pollutant emissions has been observed over the past decades, because of plant closures and government regulatory actions. Such reductions offer an opportunity to evaluate the potential emission reduction-associated health benefits. Health Canada is collaborating with the Quebec Public Health Agency (INSPQ) and the University of Toronto to conduct a study on the associations between changes over time in exposure to ambient fine particulate matter (PM2.5), nitrogen dioxide and sulphur dioxide emitted from industrial sources and childhood asthma incidence in Quebec. A birth cohort for children who resided in Quebec in 2002-2015 has been created to study asthma incidence. The POLYPHEMUS platform, that has the components of dispersion and chemical transport models, will

be used to estimate ambient air pollutant concentrations resulting from industry and transportation sectors. Yearly changes in exposure to ambient pollutants emitted from industrial sectors in each small area will be estimated using a combination of Gaussian and chemical transport models for this period. The associations between industry emission-related concentrations of ambient pollutants and childhood asthma onset will be studied using first difference/fixed-effects regressions. Specific industrial sectors petroleum refineries, metal smelters and pulp and paper mills will be studied separately. Using the concentration-response relationship generated from this study, modelling of potential health benefits of policy scenarios may be carried out targeting emissions from various industrial sectors. This project contributes to the evidence regarding the impact of government regulatory/non-regulatory actions on industrial emissions on children's lung health. Concentration-response functions produced from this project may help estimate the costs/benefits of reducing industrial emissions, and set priorities in air quality management actions on specific industrial sectors. (PI: Ling Liu)

Associations between blood volatile organic compounds, and changes in hematologic and biochemical profiles, in a population-based study

Health Canada is responsible for the assessment and management of health risks to Canadians associated with exposure to air pollutants in the environment. In this study, Health Canada assessed the influence of volatile organic compound (VOC) exposure on hematological and serum biochemical parameters in the Canadian population. Associations between VOCs and hematogical profiles, serum tests reflecting liver and kidney function and glucose metabolism are not well known. Using generalized linear mixed models adjusting for age, sex, smoking, alcohol consumption, BMI, education and household income, the association between selected VOCs and hematogical profiles, serum tests reflecting liver and kidney function and glucose metabolism were tested in 3,950 participants of the Canadian Health Measures Survey. This study provides evidence that exposure to VOCs, at levels found in the Canadian population, may influence blood cell counts and indicators of liver and kidney function. Renal hyperfiltration is postulated to be one mechanism explaining the inverse association between serum VOC and creatinine concentrations. (PI: Sabit Cakmak)

The Association between air pollution and hospitalization for patients with systemic lupus erythematosus in Chile: A daily time series analysis

Health Canada is responsible for the assessment and management of health risks to Canadians associated with exposure to air pollutants in the environment. In this study, Health Canada and collaborators in Chile assessed the risk associated with air pollutants and systemic lupus erythematosus (SLE). SLE, characterized by humoral and cellular immune system dysregulation, loss of self-tolerance and production of auto-antibodies to self-antigens with chronic inflammation and damage to multiple organs, can be debilitating and even fatal, but its association with air pollution is not well known. Using ambient air pollution (Ozone, nitrogen dioxide, sulfur dioxide, carbon monoxide and particulate matter) and climate data from seven air monitoring stations distributed in the seven urban centres in Santiago, Chile, along with daily patient hospitalization data from 2001 to 2012, an association between ambient air pollution and daily hospital admissions for SLE were tested. Our findings suggest that acute increases in air pollution may be one risk factor for hospitalization of patients with a primary diagnosis of SLE. (PI: Sabit Cakmak)

Factors influencing volatile organic compounds in Canadian homes

Health Canada is responsible for the assessment and management of health risks to Canadians associated with exposure to products and chemicals in the environment. Volatile organic compounds (VOCs), are a group of carbon-based chemicals which evaporate into the air at room temperature, can be odourless and have multifaceted dissipation times. Several VOCs have been associated with adverse human health effects (including irritation of mucosal surfaces, headaches and cancer) and have many possible residential indoor sources. This study analyzed data from a Canadian cross-sectional population based study, the Canadian Health Measures Survey (2009-2011) in order to determine the housing characteristics (such as having an attached garage or completing home renovations) and occupant behaviours (such as opening windows and personal care product use) that influence residential exposure to VOCs. Results of the research illustrated that households with someone smoking daily contained higher levels of smoking related VOCs while houses over 50 years old, had higher levels of most VOCs tested. Homes with attached garages revealed higher levels of traffic-related VOCs than those without and residences with recent renovations or paints/stains, new carpets or recent candle burning had higher concentrations of various VOCs when compared with homes without. Several modifiable risk factors for exposure were evident suggesting that population exposure to VOCs is, to a large part, under the control of individual residents, unlike exposure to ambient air pollution. The results of this study contribute to the growing body of evidence regarding common VOCs levels found in Canadian residences and suggests potential approaches regarding how Canadians can control their VOC exposure while at home. (PI: Sabit Cakmak)

Effect modifiers of the associations between traffic exposure and cardiovascular, respiratory and neurological disease-related mortality in a long-term Canadian cohort

National health and population-level data are considered in risk assessments carried out by Health Canada and other federal Government Departments and Agencies. The Canadian Census–Tax–Mortality Cohort comprises 3.5 million respondents, with detailed individual and household characteristics, and includes mortality information up to 2016 including respiratory diseases, cardiovascular complications, ischemic heart disease, cerebrovascular disease, neurological diseases including Alzheimer's and Parkinson's, and chronic obstructive pulmonary disease (COPD), and diseases with known associations to traffic exposures. In this study, national traffic density data will be linked to the cohort to examine the association between traffic density and mortality due to cardiovascular, respiratory, diabetes and neurological disease causes. An assessment will then be carried out as to whether certain individual or environmental factors render individuals more or less susceptible to the adverse effects of traffic density. The factors to be investigated will include socioeconomic and sociodemographic status, weather, and the amount of neighborhood green space (vegetation). The relationship between traffic exposure and health is present within the context of a changing, warming climate, where high seasonal average temperatures and urban heat islands, urban or metropolitan areas that reach significantly warmer temperatures than surrounding rural areas, may provide additional burdens on health that disproportionately affect certain socioeconomic groups. People can be additionally stressed by limited access to green space due to urban design; socioeconomic and sociodemographic characteristics, long term seasonal average temperatures, urban heat islands, and residential greenness may modify the association between traffic exposure and mortality. The results will allow for more accurate traffic-related risk estimates for socio-economic and sociodemographic sub -populations by taking into account the complex interactions between health and exposure to traffic, socioeconomic and sociodemographic factors or characteristics (age, sex, family education and income, employment status, visible minorities, immigrants), weather, microclimates, and green space. (PI: Sabit Cakmak)

Analyses of non-linear concentration-response functions for short term exposure to air

Health Canada has an interest in understanding the negative health impacts of air pollution concentration levels on human health. Traditional methods of risk assessment for outdoor air pollution have generally assumed a risk model that is a linear in shape. Many of the risk models included in the Air Quality Benefits Assessment Tool (AQBAT) make this assumption. However, new evidence is emerging that relationships between outdoor concentrations of air pollutants and health may not all be best characterized by linear risk models. In this study, new elaborated non-linear risk models have been used to assess relationships between short-term exposure and health impact. Data obtained from emergency department visits for cardiac problems and exposure to nitrogen dioxide, and respiratory diseases and ambient ozone exposure are used to develop the models. Concentration-response curves developed for a series of lagged exposures are summarized as one common parametric function. The constructed function is applied to represent risk along concentration. The study is generating knowledge on air health effects represented as concentration-response curves, and is developing a methodology to generate non-linear functions to represent the impact of air pollution on human health. (PI: Mieczysław Szyszkowicz).

Interaction between gene variants and air pollution in AQHI panel studies participants

Research is needed to improve our understanding of the biological mechanisms of the health effects of air pollution, specifically for associations at low pollution concentrations observed in Canada. Research is also needed to better characterise and reduce health risks of air pollution for Canadians, especially vulnerable groups. This research study addresses Health Canada's mandate regarding factors mediating vulnerability to adverse effects of air pollution, with implications for regulatory decision-making and health messaging. Recent studies have suggested that common, heritable, genetic differences may influence susceptibility of individuals to health effects of air pollution. Specifically, genes involved in responses to oxidative stress have been investigated as possible factors that alter sensitivity to air pollution. From 2013 to 2015 saliva DNA samples were collected from 176 participants in the Air Quality Health Index (AQHI) Panel Studies. Study participants also provided 10 weeks of daily and weekly health data (lung and cardiovascular function tests, symptoms, activities). To this point, all samples have been analyzed and study participants have been characterized with respect to the presence of 23 gene variants, and assigned an overall gene score reflecting the combined presence of multiple variants. In the next phase, analysis of health measure data will determine whether the health effects of air pollution differ between individuals with or without these gene variants, thereby evaluating the importance of oxidative stress as a mechanism for air pollution effects; and determine whether the morbidity data support the mortality-based AQHI formula (public information tool). These findings may provide important biological information about how even very low pollution levels can affect health and suggest possible mechanistic links between air pollution and health effects. This information could be useful for future development of interventions or messaging to protect individuals who have a genetic susceptibility to the effects of air pollution mediated oxidative stress. (PI: Dave Stieb)

Longitudinal effects of air pollution, aeroallergens and urban environment features in the Toronto Child Health Evaluation Questionnaire (TCHEQ) cohort

Health Canada has an interest in better understanding the multiple sources of exposure that characterize diverse features of urban environments. The Toronto Child Health Evaluation Questionnaire

(TCHEQ) study established a cohort of 5,619 grades one and two (aged 5 to 9) Toronto school children in 2006, collecting detailed data on the child's and parents' health, sociodemographic characteristics and exposures in the home environment. There are few other Canadian cohorts of children of this size. In the original study, the prevalence of asthma was associated with nitrogen dioxide in those children with other allergic disease such as hay fever and eczema. In the previous round of CARA funding, TCHEQ participants were linked to Ontario health care utilization data housed at the Institute of Clinical Evaluative Sciences (ICES) to determine the incidence of new cases of asthma and other allergic disease 10 years after the original study, and to examine their associations with air pollution. To date, analyses have revealed that exposures to oxidant air pollutants (ozone and nitrogen dioxide), but not fine particulate matter, were associated with an increased risk of incident asthma and eczema. In this phase of the study, analyses will examine the incidence of allergic disease in association with oxidative potential and aeroallergens (pollen and spores), link the cohort to other outcomes including early childhood development, and conduct updated linkage to health care data 15 years after the original study. A better understanding of longitudinal effects of air pollution and aeroallergens and the ability to control exposure sources supports Health Canada's efforts related to regulatory decision-making and health messaging. (PI: Dave Stieb)

Development of a national forest fire smoke PM2.5 exposure model

Forest fire smoke is increasingly recognized as an important source of exposure to air pollution, which is likely to increase in importance as a result of climate change. There is also an increasing weight of evidence linking air pollution from forest fire smoke to adverse health effects, although gaps remain. Studies conducted using large national health databases are powerful tools to address these gaps, but they require national exposure data. New national studies and exposure data can also directly inform public communication such as the Air Quality Health Index, and national assessments of mortality and morbidity attributable to forest fire smoke. This study will build a national forest fire smoke exposure model based on fine particle concentrations from ground monitors, forest classification, remotely sensed fires, meteorology, and elevation. The model will build on an existing model for British Columbia which has provided exposure data for epidemiological studies and served as a basis for the BC Asthma Monitoring System (BCAMS). Model data will be made available for linkage to epidemiological studies. (PI: Dave Stieb)

Radiation Protection Bureau (RPB)

Radiation Health Assessment Division

Medical countermeasures for lung deposition (CSSP)

Health Canada has a mandate to protect the population from risks due to radiation. During a radiological or nuclear emergency, first responders and the public may be internally contaminated by radionuclides via inhalation. This study aims to evaluate the effectiveness and/or applicability of specific measures to counter a large deposition of these contaminants. There are two types of contaminants being studied in this research project: (1) Inhaled insoluble radioactive materials that remain in the lungs for a prolonged time period and are not removed easily. This component investigates the application of approved drugs

or their combination for effective removal of inhaled insoluble materials from the lungs, using an animal model; and (2) Inhaled soluble radioactive materials that are currently treated using decorporation agents, such as DTPA-Zn. For these, the treatment efficacy is compromised due to the rapid clearance of the drug from the body. This component investigates the application of nanoparticles to slow down the clearance of the drug so to improve the removal efficacy, using an animal model. Results of this project will support the preparedness and response to radiological and nuclear emergencies, in both guideline development and medical countermeasures preparedness. (PI: Chunsheng Li; Canadian Nuclear Laboratories)

Monitoring of radioactivity in caribou and beluga in response to the Fukushima accident (Northern Contaminants Program)

Health Canada has a mandate to protect the population from risks due to radiation. Following the 2011 accident at the Fukushima Daiichi nuclear power station in Japan, concerns in northern communities were expressed regarding the safety of caribou and beluga whales as food sources. Historically, studies following the Chernobyl accident in 1986 had shown that radioactivity in some northern Canadian caribou increased, although the animals were still considered safe to eat. Using samples provided through the Northern Contaminants Program, radionuclides are being measured in samples of caribou, beluga, and beluga prey species collected before the Fukushima accident, shortly afterwards, and several years later, after the radioactive contamination had crossed the Pacific Ocean. The results of the comparison of some of the samples before the accident and shortly afterwards have been published. To date, no increase has been observed in any of the species and levels are expected to remain well below established guidelines for radioactivity in food. (PI: Trevor Stocki)

Survey of Cs-137 in bird species harvested across Canada

Health Canada has a mandate to protect the population from risks due to radiation. A historic data set containing unpublished measurements of Cs-137 radioactivity in 238 pooled samples of pectoral muscle from 1892 birds representing 37 species, was analyzed in order to determine if birds were contaminated due to global weapons fallout and/or the Chernobyl accident; to understand baseline cesium levels in birds across the country; and, to ensure the birds were safe to eat. Current work is leveraging this data set to improve capabilities to assess the impacts of release of radionuclides on country food chains. Samples were obtained from 173 locations across Canada (including locations in the Arctic); mostly in the fall hunting seasons between 1989 and 1995. Each of these composite samples was then measured by gamma spectrometry. Various methods of correlating measurements with environmental Cs-137 levels and species' habits were explored in order to determine environmental radiological transfer factors for six different foraging groups. All of the Cs-137 measurements in the samples were very low; therefore, there was no evidence of a human health risk. (PI: Trevor Stocki; Birgit Braune [ECCC])

Radon research – Review of equilibrium factors for dose assessment

Exposure to indoor radon is the leading cause of lung cancer among non-smokers, and the second-leading cause among smokers. Radon enters a home as radon gas and quickly decays through a series of short-lived radioisotopes.. Breathing in the radon gas actually contributes relatively little to the radiation dose to the lung. It is the inhalation of the short-lived radon decay products that delivers most of the dose that, ultimately, can lead to lung cancer. The same radon gas concentrations can have different decay product concentrations under different environmental conditions, which are accounted for in

dose assessment using an equilibrium factor. Equilibrium factors are often estimated; however, in this study, published measurements from more than 20 countries are reviewed, encompassing indoor and outdoor residential, public, and occupational environments. In the indoor residential environment, equilibrium factor values are shown to be significantly higher in poorly ventilated houses and in homes with smokers. In some occupational environments (mines, caves, and thermal spas), there was a range of equilibrium factors, suggesting that location-, environment-, and operation-specific values are more appropriate than an average for assessing exposure for these workers. This information is valuable for identifying populations at higher risk from radon exposure and for targeting radon reduction programs, including the National Radon Program. (PI: Jing Chen; Naomi Harley)

Pilot Study in Chelsea, Quebec to investigate levels of radon and radionuclides in water

Long-term exposure to indoor radon is the leading cause of lung cancer among non-smokers, and the second-leading cause among smokers. Health Canada's radon (Rn) guideline recommends corrective actions when the indoor radon in air level is above 200 Bq/m^3. The total indoor radon concentration of a given home is generally a function of the contribution from the surrounding soil. However, radon from private well water sources can outgas into the home and become a significant source of radon in indoor air. Elevated radon levels in water are more prevalent in deep drilled wells than surface wells. The issue of radon and uranium in drinking water in Chelsea, Quebec is a recognized health risk that is being addressed by the provincial and municipal health authorities. This study measured the levels of radon in air and water in homes in Chelsea, Quebec with results suggesting that soil-borne radon is the main contributor for radon in indoor air in the study cohort. Results also suggested that water-born radon contribution was less than expected but could still increase radon in air on specific floors given water usage. In order to assess whether water treatment systems posed a potential exposure hazard by concentrating natural radionuclides, gamma emissions from water filters were also measured. Although, in some cases, dose rates were much higher than gamma background, no significant occupant exposure scenario was encountered. Further analysis primarily identified short-lived decay products from the uranium chain. Overall, the findings of this pilot project will help improve Health Canada's guidance about radiological risk management from radon in water sources to the public. (PI: Mathieu Brossard [RORB, Quebec]; Veronique Juneau [Municipality of Chelsea, Planning and Sustainable Development Division]; Deepti Bijlani [RPB])

Radon research – Assessment of radon mitigation strategies in the Canadian environment

Exposure to indoor radon is the leading cause of lung cancer among non-smokers, and the second-leading cause among smokers. Radon enters a home as radon gas and quickly decays through a series of short-lived radioisotopes. Health Canada and the National Research Council's (NRC) Ventilation and Indoor Air Quality Group of the Construction Portfolio collaborate closely on radon mitigation studies. Ongoing work focuses on evaluating the performance of full vertical passive stack mitigation systems in specialized testing facilities and in homes ("field studies"). Preliminary results, including field studies conducted in the National Capital Region, indicate that these are effective radon reduction solutions under test conditions. In this study, field studies will be conducted in different regions in Canada to investigate the impacts of different climatic factors (e.g., indoor and outdoor temperature, relative humidity, air pressure), geographic conditions and construction patterns on the performance of the systems. Testing will be conducted in both the summer and winter seasons. This research supports national radon mitigation guidance and standards and will inform future revisions to the National

Building Code. (PI: Zhou Liang Grace [National Research Council] Michel Gauthier [RPB]; Adelene Gaw [RPB])

Residential radon testing in the town of St. Lawrence, Newfoundland

Radon gas is a human health risk, as long-term exposure through inhalation is the second leading cause of lung cancer after smoking. Radon in the mining occupational environment and radon in residential indoor air have both been studied worldwide. St. Lawrence is a town located on the Burin Peninsula of Newfoundland and Labrador and was a centre for commercial fluorspar mining in the early 1930s.The town has a well-recognized history for an increased incidence of lung cancer among fluorspar miners that alerted health officials to a possible cancer risk. It was discovered that air in the mines contained radon gas in concentrations at very high levels. In the first ever survey of indoor radon levels in Canada in the late 1970s, indoor radon levels were found to be high in the homes in this community. The provincial government of Newfoundland and Labrador approved plans to re-open the fluorspar mining operations in light of a new vein of fluorspar being discovered which makes mining viable once again. Health Canada and the Town of St. Lawrence conducted extensive indoor radon testing in 2017-18 to create a baseline; measurements will be repeated in approximately 2 years' time to see if there are significant changes after mining operations resume. This study will serve as a model for other mining communities to raise public awareness and encourage radon testing and mitigation. The study further supports the National Radon Program's mandate to promote targeted radon risk awareness and reduction measures in radon-prone and potentially vulnerable populations. (PI: Lance Richardson-Prager [RORB-Atlantic]; Allison Denning [RORB-Atlantic]; Michel Gauthier [RPB])

A comparative study of radon levels in federal buildings and in residential homes in Canada

Long-term exposure to indoor radon is the leading cause of lung cancer among non-smokers, and the second-leading cause among smokers. While radon exists everywhere, people are exposed to different levels depending on geography, building construction, ventilation, and occupancy patterns. Health Canada's National Radon Program has led three large-scale indoor radon surveys to characterize the concentrations in Canadian buildings, including one for federal government workplaces and two for private residences. In 2018-19, the data from these and other surveys were combined in order to generate information about Canadians' exposure to radon in different indoor environments. While most of the indoor environments that were measured were below the Canadian guideline (200 becquerels per cubic meter), concentrations in 7% of homes exceeded this level compared to only 2% of workplaces. Furthermore, analysis showed that average indoor radon concentrations in homes are 2-5 times higher than in schools and workplaces. Given that Canadians aged 15 y and older spend more than 70% of their time indoors, at home (Statistics Canada, 2015), where average radon concentrations are highest, it has been estimated that exposure at home constitutes more than 90% of the risk of radon-induced lung cancer. Results of this work underscore the important role of homeowners in protecting themselves and their families, and clearly demonstrate that radon education and awareness in Canada should prioritize efforts to support residential testing and remediation. (PI: Jeff Whyte, Contact: Jing Chen)

Domestic radon exposure and childhood leukemia: a population-based study in Canada

Long-term exposure to radon gas is recognized as an important cause of lung cancer. This study examines the possibility, first raised using a data set collected in the 1970s, or a possible link between

average radon concentrations in the home and the incidence of childhood leukemia and lymphoma in Canada. Following the launch of the National Radon Program in 2007, Health Canada completed a long-term radon survey in 33 census metropolitan areas (CMAs), which covers about 70% of the Canadian population. Data obtained was examined alongside leukemia and lymphoma incidence rates among children (0 - 14 years of age) in the past decade (2006-2015), exploring linkages between city-level average radon concentrations and leukemia and lymphoma incidence rates in 33 major Canadian cities. Analyses were conducted for 6 subtypes of leukemia and lymphoma. Estimated exposures of red bone marrow to domestic radon were low and no associations were found between radon exposure at home and an increased risk for developing leukemia among children under 15 years of age living in the CMAs. These result add to the body of evidence indicating no significant correlation between radon exposure and leukemia. (PI: Jing Chen; Lin Xie)

Longitudinal analyses of nuclear energy workers in the National Dose Registry (CANDU Owners Group's low dose Strategic Research and Development program)

Radiation is a recognized carcinogen, however, there are many uncertainties about the nature of the dose-response relationship at lower levels. Radiation can also influence the risk of other adverse health outcomes. This study will make use of the updated record linkage of workers in the Canadian National Dose Registry to national mortality and cancer incidence data in order to characterize associations between low levels of radiation exposure and different causes of death, and low levels of exposure and different types of cancer incidence. Modelling efforts will evaluate the impact of exposure latencies and differential exposure-response relationships by age and sex, and life table methods will be used to estimate the impacts of ionizing radiation on life expectancy. Results will add to the body of evidence that underpins national and international recommendations for radation risk assessment and risk management. (PI: Paul Villeneuve (Carleton University); Lydia Zablotska (University of California, San Francisco); Rachel Lane (Canadian Nuclear Safety Commission); Minh Do (Carleton University and the Ontario Occupational Cancer Research Center); Susana Abraham Cottagirl (Carleton University); and Tim Prendergast (HC)).

A cost effectiveness analysis of interventions to reduce residential radon exposure in Canada

The inhalation of radon poses a risk to human health and long-term exposure to radon is the second leading cause of lung cancer, after smoking. This study estimated the incremental cost effectiveness ratios for the 2012 populations in Canada, each province/territory, and 17 census metropolitan areas, for practical radon mitigation scenarios to reduce residential radon exposures. Sixteen intervention scenarios compare radon mitigation implemented at differing rates in new and existing housing relative to preventive measures installed at construction, using three different radon mitigation thresholds. A period life-table analysis, a secondary data analysis, was conducted using data derived from two recent Canadian radon surveys, along with Canadian mortality and quality of life data. Analyses adopted a lifetime horizon and a discount rate of 1.5%. Results of the study indicate that reducing radon ingress in new construction is cost effective across Canada, and expanding the intervention to also include the mitigating of high radon levels in existing housing is cost effective where regional radon levels are high. This information on the cost per unit health benefit estimated to result from an intervention will be used to prioritize strategies for reducing the burden of radon-induced lung cancer in Canada. (PI: Janet Gaskin, NRC: Jeff Whyte, University of Ottawa: Doug Coyle, Nicholas Birkett, Daniel Krewksi)

An assessment of uncertainty using two different modelling techniques to estimate the cost effectiveness of mitigating radon in existing housing in Canada

Long-term exposure to radon gasis the second leading cause of lung cancer, after smoking. In Canada, it was estimated for 2016 that 34% of lung cancer deaths attributed to radon in women and 27% in men occurred in non-smokers. A previous analysis demonstrated that mitigation of high radon levels in existing housing in addition to reducing radon ingress in new housing is only cost effective where regional radon levels are high, therefore it was important to assess the sensitivity of the cost effectiveness estimate to parameter uncertainty. The cost-utility analysis is a secondary analysis that incorporates many different published datasets to model the costs and the benefits of a health intervention. This analysis was focussed on evaluating the uncertainty associated with the estimates of cost effectiveness of interventions to reduce residential radon in existing housing only, according to the choice of model used, the rate of radon testing and mitigation in existing housing, the renewal rate of the housing stock, and the distribution of the number of residents per dwelling. The results showed that the cost effectiveness would improve at increased rates of testing and mitigation of existing housing. The estimates were not sensitive to the choice of model used, nor to the housing renewal rate, nor to the increase in one person households and decrease in two person households reported recently for Canada. Based on the study findings, recommendations to home owners to test andmitigate high radon concentrations in existing housing are strengthened and policy options and communication of these results to the public will be explored to encourage homeowners and thereby increase the rates of radon testing and mitigation. (PI: Janet Gaskin, NRC: Jeff Whyte, University of Ottawa: Doug Coyle)

A better understanding of radon dosimetry through indoor aerosol characterisation and computational simulation

Radon is the second leading cause of lung cancer, after smoking. Although the guideline for radon exposure in homes is provided in concentration of radon gas, it is actually the short-lived radon progenies that deposit most of the energy that contributes to the radiation dose. The majority of the radon progenies attach to particulate matter; depositing in the lung, and are therefore dependent upon particle concentration and their relative size distribution. In this study, measurements of indoor aerosol characteristics relevant to radon dosimetry, such as radon progeny concentration, equilibrium factor, unattached fraction, and radon progeny particle-size-distribution will be carried out. These characteristic parameters will be used in conjunction with a radon dosimetry computational simulation tool to calculate radiation dose to lung. The knowledge generated from this project will improve our ability to assess residential radon dose and associated risk. (PI: Baki Sadi)

Development of an adverse outcome pathway (AOP) relevant to uranium induced kidney toxicity

Uranium is a naturally occurring radioactive element as well as a heavy metal. Biological and health effects of uranium have been attributed to both its radiological and chemical toxicity. While the majority of the published studies indicate uranium toxicity is primarily due to chemical damage to the kidney, other *in vitro* and *in vivo* experiments show genotoxic effects that could be attributed to both chemical and radiological toxicity. Due to potential occupational exposure in the uranium-based nuclear fuel cycle, environmental exposure from mining and other industrial activities and chronic exposure through drinking water, especially in communities served by underground well-water, adverse health effects of uranium is a concern to risk assessors and regulators in both radiological and chemical communities. The objective of this project is to define an adverse outcome pathway (AOP) relevant to uranium-induced

kidney toxicity for submission to the Organization for Economic Co-operation and Development (OECD) Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). (PI: Baki Sadi)

Emergency dosimetry (International Committee on Radiological Protection)

Nuclear and radiological emergencies are relatively rare but, when they occur, emergency workers, first responders and the general public may receive significant external and internal exposures from a range of radionuclides. Radiological assessment and protective actions need to be implemented promptly to mitigate the impact on human health. A methodology for the quantitative description of exposures is among the essential elements of emergency management systems. The current dosimetry system recommended by the International Commission on Radiological Protection (ICRP) focuses on situations where doses and associated radiological risks are low and the primary objectives are to optimize protection against stochastic health effects and to demonstrate compliance with regulatory requirements; such system needs to be expanded to address the requirements for emergency situations. The goal of this research study is to develop reference methodologies and datasets that would expand the current ICRP dosimetry system for performing radiological assessments in emergency exposure situations. An expanded dosimetry system will consider both stochastic effects and harmful tissue reactions, situation-specific conditions, such as contamination of wounds, thyroid blocking, decorporation treatment, individual- or group-specific characteristics (e.g. iodine-deficient diet in the affected region). Standard estimates of effective dose will be complemented by more detailed individualised assessments of absorbed doses/absorbed dose rates in organ and tissues of individuals of various ages. (PI: Chunsheng Li; ICRP Task Group 112).

National Radon Program behavioural study

The National Radon Program (NRP) has an extensive outreach program to motivate Canadians to take action to protect themselves from radon-induced lung cancer. This year, the NRP initiated a behaviour intervention trial to assess the whether a behaviourally-informed intervention – specifically, a postcard with straightforward messaging – led to a significant incremental increase in awareness and in test kit purchases. Separate treatment and control groups were drawn from areas where there was little grassroots radon activity, which was assumed to correspond to limited radon awareness in the community, and where there was a high level of activity, corresponding to higher pre-existing radon awareness levels. All communities in the trial had previously been identified as having an elevated risk of high residential radon levels (based on the Cross Canada Radon Survey and other data). Influence was assessed by comparing website traffic and test kit purchases between groups who received the postcard and those who did not. Anecdotal evidence was also collected. Findings indicate that the behaviourally informed postcard increased awareness of radon and, further, increased awareness more within high grassroots communities compared to low grassroots communities. The study also found that receiving the postcard increased the likelihood that people would purchase a radon test kit, and that this increase was higher in communities with more pre-existing grassroots activity compared to those with less. While the study showed an increase in test kit purchases among those who received the postcard, absolute numbers were still quite small, indicating that behaviourally-informed postcards on their own are not an effective solution to the challenge of increasing Canadian radon testing and mitigation rates. This early study shows promise for using behavioural science to assess and improve the effectiveness of radon action campaigns. (PI: Jane Howe (Deloitte Canada); Kelley Bush, Katelyn Penstone)

Radiation Surveillance Division

Fixed point surveillance network

Health Canada operates a network of 80 Fixed Point Surveillance (FPS) spectroscopic Sodium Iodide (NaI) detectors measuring, in real-time, airborne radiation. The detectors are distributed across the country to provide population representative radiation risk assessments with enhanced monitoring around Canadian nuclear power plants in support of emergency management and response. Data collected by the FPS network is used to assess radiation dose levels, which are subsequently made available to Canadians through the Health Canada public website. The networks can also be used to assist decision-making during a nuclear emergency to ensure the health and safety of Canadians. Real-time FPS monitoring data is automatically transmitted to the International Atomic Energy Agency's (IAEA) International Radiation Monitoring Information System (IRMIS) to help fulfil Canada's obligations under the Convention on Early Notification of a Nuclear Accident. The data is also posted automatically on the European Radiation Data Exchange Platform (EURDEP) for public consumption alongside data from over 5500 monitoring stations in 39 countries. The amount of data automatically transferred to these systems on an annual basis represents approximately 2.5 million data points. (PI: Kurt Ungar; Eric Pellerin)

Health Canada's Total Diet Study

Ingestion of excessive amounts of contaminants, including radioactive elements, through the food supply can be detrimental for the health of consumers. Every year, the National Monitoring Section (NMS) participates in Health Canada's Total Diet Study program. The program analyzes a wide range of food products present in a typical Canadian diet, to estimate levels of exposure that Canadians accumulate through the food supply. NMS is responsible for analyzing the samples for radioactive elements and ensuring that the levels found in foods remain safely within acceptable national and international guidelines. The results of Health Canada's Total Diet Study help ensure food available to Canadians remains safely within acceptable national and international guidelines. (PI: JF Mercier; Robert Dabeka [HPFB])

The Canadian Radiological Monitoring Network (CRMN)

The Canadian Radiological Monitoring Network (CRMN) comprises 26 sampling stations distributed across Canada that routinely send environmental samples to the National Monitoring Section of the Radiation Protection Bureau. These samples are analyzed for radionuclides that may adversely impact the health and well-being of Canadians. Sample matrices include airborne particulates collected by filters, precipitation (rain or snow), drinking water, and milk. The detection techniques employed to identify and quantify radionuclides of interest are gamma spectrometry, alpha spectrometry, gas proportional counting, liquid scintillation counting, and inductively-coupled mass spectrometry. The CRMN additionally operates 12 sampling stations, predominantly concentrated about the Gentilly and Pt. Lepreau nuclear power generating stations, to collect water-vapour samples for assessment of tritium content, which is used as a metric to assess reactor leakage. Continuous and comprehensive monitoring provides a current and accurate determination of background radioactivity in Canada, and enables early detection and rapid response in the event of a national or international incident with radiological consequence. (PI: JF Mercier)

The Comprehensive Nuclear Test-Ban Treaty radionuclide stations and radionuclide laboratory monitoring

The Comprehensive Nuclear Test-Ban Treaty (CTBT) was adopted by the United Nations General Assembly in 1996 and serves as an effective nuclear non-proliferation and disarmament measure. The treaty has a comprehensive verification regime to ensure that no nuclear explosion goes undetected. The verification regime consists of the International Monitoring System (IMS) and International Data Centre (IDC), a consultation and clarification process, on-site inspections and confidence building measures. The IMS consists of stations and laboratories located throughout the world which use one of four technologies to collect data: 1) Seismic monitoring, 2) Infrasound monitoring, 3) Hydroacoustic monitoring, and 4) Radionuclide monitoring. As part of the IMS, Health Canada manages four radionuclide stations and one radionuclide laboratory. This year was highlighted by the development work associated with the addition of Noble Gas analysis capabilities to the Health Canada CTBT radioisotope laboratory to align with evolving CTBT requirements. The laboratory entered a testing a calibration phase that should culminate in the fall of 2019-2020 with the certification visit by CTBTO authorities initially scheduled for the Fall of 2020 to early 2021. (PI: Kurt Ungar)

Identification of a chemical fingerprint linking the undeclared 2017 release of 106Ru to advanced nuclear fuel reprocessing

Safeguarding the well-being of Canadians with respect to environmental radioactivity is underpinned by the nation-wide monitoring and measurement activities of the Radiation Surveillance Division (RSD). The reality that these efforts unfold in a global context was made very apparent in the fall of 2017 with the undeclared release and detection of ruthenium-106 (106Ru) across Europe that prompted an international effort to ascertain the circumstances of the event. The RSD has used its expertise in air transport modelling, in collaboration with Environment and Climate Change Canada's (ECCC) Canadian Meteorological Centre (CMC), to contribute to an internationally led effort to narrow possible geographic locations of origin. However, there had been no direct empirical evidence to address the nature of the release. This was due to the absence of radiological and chemical signatures in the sample matrices, considering that such signatures encode the history and circumstances of the radioactive contaminant. In limiting cases such as this, the RSD has introduced novel methodology, namely, the use of selected chemical transformations, to elucidate the chemical nature of the radioactive contaminant as part of a nuclear forensic investigation. Through this work, the RSD has revealed a clear chemical fingerprint that irrefutably links the 106Ru release to very specific nuclear fuel reprocessing activity. The information generated from this more than two-year endeavor was shared with key Federal stakeholders and was instrumental in supporting Canadian diplomatic efforts, including meetings hosted by the International Atomic Energy Agency and with the G7 Nuclear Safety and Security Group. This work was recently completed and culminated in a publication in the journal Proceedings of the National Academy of Sciences of the United States. It serves, by example, as a valuable addition to the field of nuclear forensics, and marks the Radiation Protection Bureau as a global leader and innovator with respect to the characterization of environmental radioactivity. PI: Michael Cooke

Radioactivity monitoring and assessment in the Canadian Arctic: participation in an international research project of the Arctic Monitoring and Assessment Programme (AMAP) 2023

Access to reliable and up-to-date information is essential for the development of science-based decision-making regarding ongoing changes in the Arctic and their global implications. Related AMAP

summary reports have therefore been developed specifically for policy-makers, summarizing the main findings of the assessment. Since 2019, an international team of experts (Canada (Health Canada) joined the team as one of the Arctic countries) has been conducting an assessment of Arctic radioactivity issues. The information contained in this study will be fully referenced, and is based on peer-reviewed and published research and monitoring results since 2014. The updated radioactivity assessment will include new radioactivity data, effects of radon on human health, and data on radionuclides dumped or transferred into the Arctic. It will also introduce Health Canada research on the impact of climate change on the transportation of natural radionuclides in the Arctic. These studies will improve Health Canada's ability to estimate the increased Pb-210 and Po-210 activity level in the Arctic region due to northern contaminants, and to model atmospheric radionuclide transportation that is crucial to assess radiation dose to humans. PI: Weihua Zhang

Development of a reference dosimeter for separating the neutron contribution from the other cosmic ray components

The Radiation Protection Bureau (RPB) has a long-standing commitment to protect and promote the health of Canadians from ionizing radiation exposure in daily living and working environments. For almost two decades, RPB has been operating a Fixed Point Surveillance (FPS) network for monitoring radiation exposure and the associated health risks arising from man-made sources and naturally occurring radiation materials. The network is comprised of more than seventy 3"x3" sodium iodide (NaI) gamma spectroscopic dosimeters distributed across Canada and the recorded energy spectrum below 3MeV has been used for radiation identification and dose estimations. The FPS network's potential as a cosmic dose monitoring system has recently been explored by using the recorded count rate above 3MeV. The observed counts at various FPS locations were found to correlate well with the theoretical cosmic doses in which the geographical and solar cycle effects were included. The result suggested that the FPS network can be used to monitor not only terrestrial radiation but also cosmic radiation if well calibrated. To become a cosmic ray dose monitoring system, the FPS network has to be experimentally calibrated by a reference dosimeter. For this purpose, Tissue Equivalent Proportional Counter (TEPC) is proposed as a reference dosimeter to calibrate the recorded FPS cosmic ray count rate to H*(10) dose rate. TEPC has been widely used for cosmic ray dose estimation at high altitude (e.g at commercial aviation level or international space station) and is capable of separating the neutron contribution from the other cosmic ray components. As a reference dosimeter, the TEPC instrument itself has to be calibrated; conducted in various exposure scenarios (gamma, neutron, mixed field, high energy neutron field etc.). The calibrated TEPC instrument will then be used to perform side-by-side measurement with our FPS detectors to calibrate the count rates. A boat survey may be also involved to conduct comparison/calibration among multiple types of detectors. PI: Weihua Zhang

National Dosimetry Services Division

Measuring workload with paired detectors

Linear accelerator workloads for each available photon energy are important quantities to know for radiation safety considerations. This research study explores a technique to measure the workload using paired detectors. The signals from the two detectors can give sufficient information to separate the signal contributions from 6 and 18 MV photon fields and combined with a signal-per-monitor-unit calibration factor yields the number of monitor units delivered for each energy. CR-39NTD is a neutron detector chosen for its ability to discriminate between 6 MV and 18 MV radiation fields. TLD-100 is a

detector responsive to both 6 MV and 18 MV fields. These appeared to be a good choice for a detector pair. Results of the study included both positive and negative findings. The CR-39NTD and TLD-100 were not a successful pairing. The CR-39NTD signals were too saturated to be of use under this experiment's exposure conditions. The TLD-100 had a combination of detector noise and detector sensitivity that made extracting the 6 MV signal from the total signal impractical, unless the total exposure was overwhelmingly 6 MV. Nevertheless, the TLD-100 proved to be excellent for determining workloads when it was exposed to a single energy with 1% accuracy and 3% precision. The theory and data analysis demonstrated the importance of understanding the noise contributions for the more general problem of pairing any two detector types. This experiment indicated the TLD-100 could be an excellent detector choice if paired with a suitable second detector. This research could lead to a much more efficient way for LINAC operators to calculate workload thereby making it easier to manage their associated radiation safety programs. (PI: Robert Corns [Eastern Carolina University, USA]; Charles Schroeder [CancerCare Manitoba]; Gurpreet Sandhu [BC Cancer]; Keith Henderson [RPB]; Ian McKay [RPB])

Nuclear Emergency Preparedness and Response Division

Estimating the geospatial requirements for protective actions in the vicinity of Canadian nuclear generating stations

Health Canada is the lead department responsible for administration of the Federal Nuclear Emergency Plan (FNEP). Under the FNEP, Health Canada has specific responsibilities related to assessing the radiological impacts of a nuclear emergency in Canada or abroad and recommending the use of protective actions to reduce radiation exposures. Current international guidance related to preparedness planning for protective actions is based on an understanding of the impact of nuclear emergencies at Light Water Reactor (LWR) technology nuclear generating stations rather than the CANada Deuterium Uranium (CANDU) technology used at nuclear generating stations in Canada. This research will examine the potential environmental contamination and radiation doses resulting from a hypothetical severe CANDU reactor accident and will take into consideration the unique meteorological conditions encountered at each of the four nuclear generating station locations in Canada. The study will analyse daily atmospheric dispersion modeling runs completed using the Accident Reporting and Guidance Operations System (ARGOS) in combination with Environment and Climate Change Canada's long-range atmospheric dispersion model, Modèle Lagrangien de Dispersion de Particules (MLDP). MLDP is the only atmospheric dispersion model available in Canada that utilises a full 3-D representation of the atmosphere based on the Global or Regional Deterministic Prediction System and is operationally used for modeling the transport, dispersion and deposition of various types of pollutants (e.g. radioactive materials, volcanic ash, chemicals, etc.). The results will be analysed in the framework of the dosimetric guidance values recommended in Health Canada's 2018 publication 'Generic Criteria and Operational Intervention Levels for Nuclear Emergency Preparedness and Response' and will provide insight on the geospatial extent of the need for protective actions to reduce radiation exposures due to a nuclear emergency in Canada. (PI: Lauren Bergman)

Safe Environments Directorate (SED)

Climate Change and Innovation Bureau (CCIB)

Health of Canadians in a changing climate: Advancing our knowledge for action 2021

The Government of Canada is preparing a series of resources about how Canada's climate is changing. To this end, the Climate Change and Innovation Bureau (CCIB) at Health Canada is leading, with a range of governmental and non-governmental partners, the development of the next climate change and health assessment that will be part of the Government of Canada Climate Change Impacts and Adaptation Knowledge Assessment to be released in 2021.This report will build on the two previous climate change and health assessments, delivered in 2008 and 2014. The objective of the assessment is to present new knowledge about climate change impacts on the health of Canadians, populations of highest concern and vulnerable regions to inform effective actions by health sector decision makers to protect health. Through consultation with partners and input from individual Canadians the resulting report, *Canada in a Changing Climate: Advancing our Knowledge for Action* will:

- Examine climate change impacts on the health of Canadians;
- Explore climate change impacts to the health system; and,
- Investigate measures to effectively adapt to a changing climate and reduce future climate change

The final assessment is expected to be released in 2021. (PI: Peter Berry)

Establishing evidence-based indoor temperature thresholds to protect health

Extreme heat is a major health risk in Canada resulting in a significant number of preventable illnesses and deaths annually, and is only expected to increase in severity, frequency and duration due to the changing climate. Most heat-related fatalities occur indoors where Canadians, especially vulnerable people like the elderly and the chronically ill, spend most of their time. The aim of this research is to establish evidence-based indoor temperature guidance in support of Health Canada's role in reducing negative health impacts of climate change. In 2018, the Climate Change and Innovation Bureau funded a review authored by Dr. Glen P. Kenny (University of Ottawa) that identified a need to improve understanding of how the human body responds to heat stress indoors, especially in people more at risk. Physiological experiments are now underway to assess how individuals respond to a range of temperatures in order to determine indoor temperature conditions that are potentially dangerous for human health. This laboratory-based research was launched in early 2019 for older adults (65 to 80 years old), who have a reduced ability to adapt to heat and are therefore a population of concern. In 2019, preliminary field observations were completed for children and adolescents (10-14 years old) another population of concern. Data gathering and further literature reviews were completed as a means of building the evidence-base for this project, including for children and other potential vulnerable populations. These reviews are currently being prepared for publication in 2020. This project is expected to be completed in 2022 and the results will be used in developing guidance needed to better protect Canadian health from heat risks indoors. (PI: Meagan Brettle; Graydon Paitich)

Building sustainable health systems: focus on climate resilience

Climate change affects health through a range of pathways, including increasing frequency and intensity of hazardous extreme weather events, altering transmission of water-borne and vector-borne disease, and undermining the environmental and social determinants of health such as the quality and quantity of freshwater supplies, and of food. It therefore places stress on the infrastructure, management systems and capacity of health systems. Health Canada and the World Health Organization (WHO) have collaborated on climate change and health for approximately 20 years, resulting in publications, webinars and activities that continue to assist health authorities globally and across Canada in their efforts to prepare for the health impacts of climate change. This multi-year project will investigate and develop:

1. Tools for assessing climate change vulnerability of healthcare facilities;
2. Targeted guidance for prioritization of available health adaptation options, and indicators for measuring overall health system resilience; and
3. A framework for monitoring and surveillance of climate-sensitive diseases.

Results of this research and guideline development will advance efforts to promote health system resilience to climate change around the world. (PI: Rebekka Schnitter)

CanTEMP: National temperature-related excess mortality and morbidity estimates

The Climate Change and Innovation Bureau has a long-term target of ensuring that Canadians are resilient to the health effects of climate change. This includes monitoring the heat-related health impacts in Canada (per 100 000 people) every 3 years, with a baseline established by the end of fiscal year 2020-2021. This project aims to establish baseline risk estimates for climate-related illness and death in Canada by cities and health regions, and project future temperature-related mortality and morbidity risk under different climate change scenarios. Mortality data will come from the Canadian Vital Statistics-Death Database for 1986 to 2015, and the morbidity data will be available from the Discharge Abstract Database for 1994 to 2015. This research takes into account demographic changes through projections made by Statistics Canada with weather data obtained from weather stations in the different cities and health regions. Investigators will obtain modeled daily temperature series for 1990-2099 for each city and health region, from five Global Circulation Models (GCM), under each Representative Concentration Pathway (RCP) and will compute health impacts by estimating exposure-response relationships between observed daily temperature and daily mortality and morbidity counts in each city and health region. The excess mortality and morbidity (with a sub-analysis investigating cause-specific mortality and morbidity, and analyses by sex and socioeconomic factors where available) for each GCM/RCP combination will subsequently be projected. This study will offer a comprehensive characterization of climate change impacts due to changes in exposure to non-optimal outdoor temperature, across various regions in Canada, and under alternative scenarios of global warming. (PI: Chris Hebbern; Éric Lavigne)

Economic analysis of climate change impacts on health and on the health system: An overview

Although climate change could affect some countries and regions more than others, all countries are expected to be affected. The objective of this project is to provide a targeted, evidence-based (where data are available) overview of the literature published between 2000 and 2019 linked to climate change and climate-related health impacts and their attributed costs in Canada and elsewhere. This project is a first step in addressing the need to better understand increased costs on the health system (the need for costing of these impacts was identified as a priority at a February 2018 Experts Meeting on Climate Change and Health Monitoring and Surveillance that was hosted by Health Canada, as well as by

HealthADAPT G&C recipients in March 2019). The report will serve as an informational tool to increase the awareness of public health officials, planners, decision makers, and other stakeholders of the costs that climate change could pose to human health and the health system. The analysis, impacts, methods and data identified in this project may be used to inform the conduct of an in-house economic cost-benefit analysis in the future. (PI:Victor Gallant; Modjgan Alishahi, RAP PhD Student)

Climate change and heat vulnerabilities of Canadian workers: Focus on central and western provinces of Canada

Increases in temperature and the number of extreme heat events have been identified as key issues related to climate change for workers in Canada. Studies conducted in Quebec have highlighted that the daily compensation of workers for health problems related to excessive exposure to heat and for traumatic work-related injuries increases with outdoor temperature in the summer. These associations have never been evaluated elsewhere in Canada and impacts of a warming climate on these claims have not been studied in Quebec or in other Canadian provinces. This project aims to establish associations between the summer outdoor temperatures of five provinces (Ontario, Quebec, Manitoba, Saskatchewan, and Alberta) and the compensated occupational health problems related to overexposure to heat and associated traumatic work-related injuries. In addition, it aims to estimate the health impacts of climate warming by calculating the change in such compensation by 2050. The project is expected to be completed by the Fall of 2020. (Collaborator: Peter Berry; Monique D'Amour)

Urban trees and human health outcomes: A scoping review

While the environmental benefits of urban trees are well understood, no review to date has comprehensively examined the research literature concerning how urban trees impact people's health. The objective of this review collates a diverse body of empirical evidence on the associations between exposure to urban trees and human health, notes inconsistencies in findings, and provides a comprehensive map of existing literature that can inform future research, policy, and nature-based public health interventions. Peer-reviewed articles were systematically searched based on pre-determined human health, environmental health, and urban forestry keywords. Titles and abstracts were subsequently screened, and articles that met the inclusion criteria were retained. Articles were critically appraised using a quality assessment tool and then classified and summarized based on an existing conceptual framework of the pathways linking green space to health. Based on the conceptual framework, 201 studies were sorted into three domains, each containing multiple research themes. 'Reducing Harm', which represents 41 percent of the studies, includes topics such as air pollution, ultraviolet radiation, heat exposure, and pollen. 'Restoring Capacities', representing 31 percent of the collection, includes attention restoration, mental health, stress reduction, and clinical outcomes. 'Building Capacities', at 28 percent, includes topics such as birth outcomes, active living, and weight status. While the reviewed studies had substantial heterogeneity in purpose and method, they nevertheless suggest important health outcomes associated with people's exposure to trees. This review could help inform future research and practice. Urban forest planning and management approaches should strategically incorporate trees as a social determinant of public health. (PI: Gregory Richardson)

Investigation of the conditions for thermally comfortable playgrounds in Canada

Play is important to a child's physical, intellectual, and social development. Playgrounds are a central hub for child play. Any concerns affecting levels of play at playgrounds, such as unsafe temperatures or

equipment, may thus hinder children's health and well-being. Playgrounds often present some of the highest surface temperatures within an urban area. Unsafe heat exposure and resulting heat-related illnesses and injuries is a rising concern in Canada. Existing playground standards focus on equipment and surfacing to reduce trip- and fall- related injuries, but have not addressed environmental factors affecting unsafe exposure and heat stress. In partnership with the Standards Council of Canada, the goal of this project was to develop proposed guidelines for designing thermally comfortable playgrounds in Canada, for inclusion within the CAN/CSA-Z614 Children's play spaces and equipment standard. To that end, the project team conducted a detailed literature review of relevant research, standards, and design practices, conducted a needs assessment survey with a broad range of Canadian and international experts and stakeholders, and produced recommendations for an informative thermal comfort annex. This project has resulted in several important outcomes. First, the project team produced a report with design advice for improving thermal comfort at playgrounds across Canada. Second, the Canadian Standards Association has approved a six page annex with similar guidance. Third, an NGO has integrated "thermal comfort" considerations into their national school ground greening design competition. Building awareness of environmental considerations in design will ensure that Canada's playgrounds are safe and comfortable for children's play. Ultimately, this helps improve future utilization and enhance the benefits of active outdoor play. (PI: Alexandra Rutledge; Victor Gallant)

A qualitative and quantitative evaluation report on the Alberta Real Time Surveillance System Network

The Climate Change and Innovation Bureau has a long-term target of ensuring that Canadians are resilient to the health effects of climate change. This study is the second in a series of proposed evaluations of existing real-time syndromic surveillance systems, the purpose of which is to compare the operability of each system to identify the key components for an effective, comprehensive real-time surveillance system to assess the health impacts of climate change. The outputs from this research, in combination with reports from previous studies, will directly address program activities HC is required to deliver on as written in the treasury board submission approved in 2016, Adapting to Climate Change Impacts. Specifically, these will inform HC in the development of Pan-Canadian national monitoring and surveillance activities and provide guidance as HC works with provincial and territorial partners to expand the availability of systems that collect real-time data about climate-related health issues and the public health information management systems that support them. (PI: Victor Gallant)

Flood risk analysis of Canadian health infrastructure

Flooding is one of Canada's most frequent and costly climate change risks. It is a severe threat to socially vulnerable communities and it poses damaging effects on interconnected critical public infrastructure sectors including health, food, finance, water, information and communication technology, safety, energy and utilities, manufacturing, government, and transportation. With the support of the Climate Change and Innovation Bureau, the Interdisciplinary Centre on Climate Change at the University of Waterloo led this research, which identified whether, and to what extent, health and emergency service facilities across the Canadian provinces and territories are exposed to fluvial, pluvial and coastal flood hazards. The healthcare system is one of the most critical emergency response resources across the country. As a result, managing the risks and vulnerabilities of healthcare facilities' exposure to flood hazards is critical to assist decision makers in building adaptation and/or mitigation techniques, disaster recovery mechanisms and critical infrastructure resiliency. The outputs from this work provide CCIB with information regarding potential at-risk facilities across Canada. This information will be used to assist

and inform decision makers in the building and implementation of adaptation and/or mitigation techniques and future planning, therefore strengthening resiliency. (PI: Kerri Warner; Victor Gallant)

Improving the identification of heat associated deaths in Canada: Estimating the effectiveness of medical attendance at the place of death and implications for Heat Alert and Response Systems (HARS) (Health Canada – British Columbia Centre for Disease Control MOA, 2019-21)

One of the mandates of the Climate Change and Innovation Bureau, in relation to heat hazard, is to improve the estimation of the health risks of heat. In many locations, heat associated mortality is greatly under-estimated and there are wide variances in heat-associated death estimates between jurisdictions for the same heat event. It is unclear if these differences reflect true differences or different approaches to estimation. By identifying all indirect and direct heat-associated deaths and when, where and why these deaths happen, effective and appropriate risk communication approaches and risk management actions can be informed. In 2016, the British Columbia Centre for Disease Control (BC CDC) published an unique methodology (https://doi.org/10.1186/s12940-016-0195-z) for identifying deaths associated with heat that may have otherwise been missed in traditional reports of coroners and other surveillance sources. In collaboration with local and provincial health authorities, BC CDC is examining the mortality data from past heat events and control periods in Ontario and Quebec to apply this framework. This research study will compare results from current and new methodologies to assess differenecs in deaths attributed to hot weather across jurisdictions. The results will be used to inform development of a more cohesive Canadian approach. (Collaborator: Rebecca Stranberg)

Extreme weather and climate change: population health and health system

Extreme weather and disasters are among the most severe threats of climate change facing Canadians in the future. Climate change is expected to increase the frequency and severity of a number of natural hazards including extreme heat events, floods, wildfires, droughts, ice storms, and tornadoes. To inform the development of effective adaptation measures from local to national levels in Canada, greater information on links between meteorological, hydrological and climate hazards and health, including key drivers of vulnerability are needed. This research project will provide information on the latest scientific research on extreme weather in a changing climate and implications for population health and health system implications. (PI: Peter Berry)

Psychosocial adaptation to climate change in High River, Alberta: Implications for policy and practice

There is a nascent, yet growing, research base identifying the psychosocial heath effects of climate change, however the topic of psychosocial adaptation to climate change-related events remain understudied. Noting this research gap, researchers in this study investigated the long-term mental-health effects of the 2013 Southern Alberta flood and explored how the psychosocial consequences of a major flood event were addressed via public health responses (e.g. programs, policies, and practices) that aimed to enhance, protect, and promote mental health in the town of High River. Psychosocial consequences and public health responses are considered within the broader context of psychosocial adaptation to climate change, with outcomes highlighting policy and practice opportunities for public health to enhance psychosocial adaptation within our changing climate. (PI: Katie Hayes)

Existing Substances Risk Assessment Bureau (ESRAB)

Exploring the application of the bioactivity exposure ratio for risk-based priority setting and assessment

The toxicology community have focused on a vision for human health assessments relying on high-throughput *in vitro* screening and predictive toxicokinetic models to serve as a surrogate to traditional animal studies to be used as a conservative point of departure (POD_{NAM}). Advancement toward this goal requires confidence that *in vitro* bioactivity data, in concert with high-throughput toxicokinetic information and reverse dosimetry, can be used to estimate a POD_{NAM} at or below the points of departure derived from traditional animal studies ($POD_{traditional}$). As part of the Accelerating the Pace of Chemical Risk Assessment Initiative, regulators and researchers from several authorities including Health Canada, the U.S. Environmental Protection Agency, the European Chemicals Agency and the European Food Safety Authority are collaborating on a study that compares PODs derived from ToxCast™ *in vitro* bioactivity (POD_{NAM}) with those used in traditional chemical assessments ($POD_{traditional}$). To examine 448 chemicals, the objectives were to: (1) determine whether POD_{NAM} provides a conservative estimate of $POD_{traditional}$; (2) calculate the bioactivity-exposure ratio (BER); (3) determine whether these BERs provide a robust means to prioritize chemicals and/or serve as a low tier risk assessment approach and; (4) characterize the uncertainties, strengths and possible areas for improvement of POD_{NAM} derivation for use in screening-level human health risk evaluations. The results of the study showed that the majority of the POD_{NAM} values were found to be protective compared to the $POD_{traditional}$ (400/448 chemicals). The median difference between the PODs was approximately 100-fold. POD_{NAM} was not considered conservative for carbamates or organophosphate chemicals; these should be excluded from the approach. Preliminary results were presented at the 2018 Society of Toxicology Annual Meeting and the project won the Risk Assessment Specialty Section Top Abstract Award for 2019. A manuscript with the final results was published in Toxicological Sciences in 2020. The foundational work of this international collaboration informs the Health Canada BER Science Approach Document under the Chemicals Management Plan. Methods aimed at accelerating assessment through modernization would support Health Canada priority setting and assessment as many environmental chemicals lack traditional toxicity data. (PI: Matthew Gagné)

Evaluation of select ADME models to determine suitability and performance for existing substances and for broader implementation in chemicals risk assessment

Absorption, Distribution, Metabolism, and Excretion (ADME) characteristics of a chemical are important for understanding (toxico) kinetics and the mode of action for predicting toxicity. These parameters provide important insight into how a chemical behaves inside the body following exposure. *In vitro* and/or *in vivo* toxicokinetic data are often not available for the large number of chemicals that require assessment. Since prediction and simulation of various ADME properties is considerably more resource efficient than generating *in vitro* or *in vivo* data there is an emphasis on the development of methods such as those based upon quantitative structure–activity relationship (QSAR) and molecular modeling to complement or replace the need for empirical data when sufficient confidence can be demonstrated. To ensure applicability of the ADME predictive tools to environmental chemicals in Canada, there is the need to carry out internal validation of these *in silico* models in a focused manner to support priority setting and assessment of chemicals of greatest interest for human health risk assessment under the ongoing and future Chemicals Management Program. In this project, we are collecting available published experimental ADME data on chemicals. Through statistical analysis on the predictions

obtained for known chemicals the performance of select *in silico* ADME prediction models will be evaluated. Further, using chemical similarity analysis (clustering analysis) we will determine how many of these chemicals (with ADME data) are structurally similar (or identical) to chemicals on the Canadian Domestic Substances List (DSL). This exercise will provide an approach to assess confidence in the ADME predictions both from the perspective of model reliability as well as model suitability for the DSL chemical space. (PI: Sunil Kulkarni)

Expanding high-throughput toxicokinetics chemical space to increase its applicability to existing substances

There is increased interest in the use of new approach methodologies (NAMs) in risk assessment, including bioactive concentrations (µM) measured in *in vitro* toxicology assays. In order to translate bioactivity concentrations to human relevant doses (mg/kg/bw) for hazard assessment, *in vitro* to *in vivo* extrapolation (IVIVE) methods are required. The US Environmental Protection Agency developed a high-throughput toxicokinetics (HTTK) model for IVIVE that is being explored at Health Canada. The model has been paired with ToxCast™ data to enhance chemical screening through determination of Bioactivity Exposure Ratios. However, the HTTK chemical space is primarily comprised of pesticides and pharmaceuticals, with limited data for industrial or environmental compounds. Furthermore, there are few comparisons between *in vitro* predictions with the model and *in vivo* toxicokinetics analyses. This study aims to identify and compile available toxicokinetics data to understand the chemical space covered by HTTK models and how this compares to the chemical space of interest (i.e., Canada's Domestic Substance List). This will allow for the establishment of the applicability domain for current HTTK models and the identification of environmental compounds to which the models can be appropriately applied. Also, this project seeks to establish and provide recommendations for addressing the uncertainty when applying HTTK methods to chemicals outside this defined applicability domain. The findings will guide future research into expanding on the coverage of HTTK chemical space through the targeting of chemical features or properties, currently inadequately covered by HTTK models, for future toxicokinetics analyses. (PI: Marc Beal; Sunil Kulkarni)

Development of a screening approach to assess endocrine disrupting activity of chemicals using (Quantitative) Structure Activity Relationship ([Q]SAR) approaches and *in vitro* high throughput data

In the follow up report to the review of the *Canadian Environmental Protection Act* (CEPA 1999), the Government of Canada committed to continuously improving its ability to address endocrine disrupting substances and to keep pace with scientific developments including new approach methodologies (NAM). In line with this commitment, the current study begins to advance the development of a tiered strategy that proposes to incorporate predictive models and a sequential testing strategy involving the consideration of NAMs. In this pilot analysis we are evaluating a group of bisphenols and related substances to determine the relevance and reliability of a suite of models to predict the endocrine disrupting potential of these select chemicals. It is well known that endocrine disrupting chemicals act through interaction with receptors to interfere with hormonal signalling leading to health effects. Accordingly, this study aims to assess a chemical's binding potential to a series of receptors using both *in silico* models and high throughput *in vitro* data generated by the US Environmental Protection Agency ToxCast™ Program in order to determine endocrine activity for our set of chemicals. Models under evaluation include Oasis TIMES, VEGA, CASE Ultratox, USEPA rtER Expert System, P&G's DART scheme, ChemProp models as well as Endocrine Disruptome. To begin to incorporate the next tier of information, data available from various endocrine related assays from the ToxCast™ and Tox21™

programs will be integrated. The information acquired from the analysis and integration of the *in silico* and *in vitro* data sources will support the early development of a proposed tiered approach to screen chemicals for potential endocrine disrupting activity. (PI: Sunil Kulkarni)

Toward risk assessment modernization - A new approach methodology based integrated approach for screening potential genotoxic chemicals

New Approach Methodologies (NAMs) are emerging approaches or tests, considered to be synonymous with alternative test strategies, that can inform chemical risk assessments in the absence of traditional toxicity data. Currently, there are substantial international efforts to develop NAM based approaches that provide information related to regulatory endpoints. The aims of this project are to provide support for applying *in vitro* genetic toxicity data, with a novel data analysis and interpretation framework, in future priority setting initiatives and quantitative risk assessments of organic chemicals. In this study, assessment will be based on the results of a high throughput *in vitro* test battery currently being developed by collaborators within Environmental Health Science and Research Bureau. The test battery consists of higher throughput versions of well-established genetic toxicity assays, some of which are functionally related to established OECD test guidelines (TG). Specifically, *in vitro* assays that detect DNA damage, including MicroFlow® (related to TG 487), CometChip® (related to TG 489), and MultiFlow™, as well as two assays that detect gene mutations, Ames II (related to TG 471) and MutaMouse FE1 (related to TG 488). Gene expression profiling of 64 markers will also be used to classify DNA damaging agents and provide more mechanistic information. The development of this NAM-based approach will begin with the assessment of 33 reference compounds and other chemicals with *in vitro* genetic toxicology data made available by international collaborators. An in-depth case-study is being conducted to scrutinize the utility of the NAM-based approach for risk assessment and regulatory decision-making. Specifically, *in vitro* to *in vivo* extrapolation will be coupled with assay results to establish administered dose equivalents, which will be compared to human exposure estimates. Once established, this integrated approach could be used for routine chemical screening and future risk assessments. (PI: Marc Beal [ESRAB]; Paul White [EHSRB])

Use of gene expression profiles to facilitate potency ranking and read-across for 15 bisphenols

BPA is an endocrine disrupting chemical (EDC) that is the topic of both regulatory and public concern. Its use has been banned from products available to consumers, including baby bottles (Canada) and thermal paper (European Union). These bans have led to increased use of BPA replacements many of which are chemically similar substances (i.e., analogues). Work is needed to understand the toxicological potential and potency of the BPA analogues relative to BPA. BPA's cellular effects occur primarily through its interaction with the estrogen receptor (ER). When active, the ER interacts with the DNA to modify gene expression. Therefore, changes in gene expression represent BPA's earliest toxicological effect on the cell that can be reliably measured. The objectives of this research project are: (1) to expose human mammary epithelial cells (MCF7 cells) to an extended dose range of 15 known BPA analogs; (2) to measure changes in gene expression; (3) to perform dose response modeling and potency ranking of these substances relative to BPA and estradiol; and (4) to gain mechanistic understanding of each substance. In so doing, this study aims to investigate the utility of an *in vitro* system that is suitable for the screening and dose-response assessment of potential EDCs. The study is being conducted collaboratively between ESRAB and EHSRB. Data generated through this research collaboration will be used to inform ongoing assessment activities related to the broader group of bisphenols.In addition, these data will contribute to the development of an Integrated Approach to

Testing and Assessment under the OECD Working Party for Hazard Assessment (WPHA), which has the overarching goal to advance the application of New Approach Methods (NAMs) in prioritization and risk assessment. (PI: Tara Barton-Maclaren [ESRAB]; Ella Atlas [EHSRB]).

Machine learning models for predicting endocrine disrupting chemicals

There continues to be ongoing efforts in the regulatory community to identify and assess chemicals with the potential for endocrine disrupting activity. Endocrine disrupting chemicals (EDCs) have been linked to effects on reproduction and development, learning disabilities, cognitive and brain development, thyroid effects as well as cancer. A majority of commercial chemicals have very limited data and conventional toxicity testing methods are time consuming and require significant resources, both in cost and animals. These methodologies are less feasible given the rapidly changing chemical landscape including a continual stream of new and complex chemistries. Further, the resource intensive approach may not always be needed when screening for a particular mode of action such as endocrine disruption when in fact a large number of chemicals on the market are not EDCs. To gain efficiencies in screening and identification of chemicals of greater potential concern, new approach methods are being developed and employed which can perform rapid screening to focus priority setting and assessment activities. In this project, multiple machine learning models were developed which to predict EDC properties of a chemical. This is accomplished by using simple structural information and training the model to predict the activity in a methodology known as (quantitative or qualitative) structural-activity relationship ([Q]SAR). The aim of this work is to develop and implement the machine learning models to screen the Domestic Substances List for substances of potential concern as a result of endocrine activity to allow for more focused prioritization and evaluation of potentially harmful chemicals. A manuscript highlighting the methodology and models developed for this work is currently in preparation. (PI: Sean Collins)

Automated workflows for chemical scoping and data mining: Advance approaches to prioritization and problem formulation

Modernization of approaches to prioritization and assessment is fundamental to advance the manner by which complex and emerging issues of concern such as endocrine disrupting chemicals, regrettable substitution and cumulative risk are considered. Emerging existing substances are currently identified through the 2014 Approach For the Identification of Risk Assessment Priorities (IRAP) process; problem formulation (PF) provides a mechanism through which computational tools and innovative approaches can be used to define substance groupings, describe the data landscape and triage substances. PF defines the gap between a problem and a solution, and makes a plan that delineates what is needed to close the gap, which may include activities such as data collection or generation, risk assessment or monitoring, as examples. Following IRAP, further scoping based on structural similarity is needed to identify chemicals that may also be of concern but not captured due to the paucity of data for a large number of chemicals. There is also a desire to rapidly mine data to inform PF outcomes. This project explores automated workflows to obviate resource intensive manual tasks and expedite early steps in PF. A computational algorithm was developed to scan chemical inventories to identify those with a specific substructure common to a chemical class, e.g. a phenol ring. Chemicals that lack a defined chemical structure such as UVCB's can be searched for using key phrases, e.g. "bisphenol". Another computational program was developed, which cross-references chemical lists with online databases (e.g. PubChem, CompTox, and ChemIDplus), to gather information such as physical-chemical properties and toxicity and exposure data as available. The aim of this work is to develop and implement

automated workflows to gain efficiencies and enhance the robustness of early scoping activities. This work should allow for the refinement of chemical groups based on evolving science and for information to be collected that will be useful for decision making in the context of PF and assessment. (PI: Sean Collins)

New Substances Assessment and Control Bureau (NSACB)

Ecotoxicity of pharmaceutical substances to aquatic organisms

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives, natural health products and medical devices. The goal of this research project is to assess the acute and chronic toxicity of ten pharmaceuticals that can be found in aquatic ecosystems, and to identify the most sensitive trophic level for each substance. A series of bioassays along the food chain will be used from bacteria, yeasts, algae, invertebrates and fish to determine the concentration that protects almost all (99%) of the species. Among the substances that have proven to be the most toxic, the mechanism of action will be examined more closely by biomarkers in order to elucidate the adverse outcome pathways. This data will be used directly in the environmental assessments of substances listed on the Revised In Commerce List and new substances in products regulated by the F&DA notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Alison McLaughlin)

Environmental concentration of veterinary and human drug substances in surface water and sediment

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives, natural health products and medical devices. The goals of this research project are to: (a) develop and validate additional methodologies required to analyze a panel of drug substances; and (b) characterize environmental concentrations of 16 drug substances used in high volume in Canada from sites impacted by agricultural activities and waste water treatment plant (WWTP) effluents across Ontario. This data will be used directly in the environmental assessments of substances listed on the Revised In Commerce List and new substances in products regulated by the F&DA notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Alison McLaughlin)

Assessing toxicity and bioaccumulation of atovaquone using freshwater invertebrates

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives,

natural health products and medical devices. Atovaquone is a medication used to treat or prevent diseases such as pneumocystis pneumonia, toxoplasmosis and malaria (when used with proguanil). Unlike most drugs which are highly water soluble, this substance is thought to partition to sediments and algal particulates. Research on this drug could help us to refine our understanding of substances which partition preferably to sediments and refine out models for potential bioaccumulation in aquatic organisms. The objective of this research study is to determine whether the pharmaceutical atovaquone is toxic and bioaccumulative to aquatic species in a laboratory setting. The goals are to: (a) develop and verify methods to quantify atovaquone in complex matrices (tissue and biota) (completed in 2018-2019); (b) determine the toxicity of atovaquone to chironomid larvae and freshwater mussels; and (c) determine the uptake and depuration rates of atovaquone in bivalves. This data will be used directly in the environmental assessments of substances listed on the Revised In Commerce List and new substances in products regulated by the F&DA notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Alison McLaughlin)

Validation of the zebrafish (Brachydanio rerio) model as an *in vivo* NAM for the assessment of chemicals for endocrine disruption and general toxicity

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products, and to integrate innovative science into the risk assessment and risk management of new substances. The goals of this research project are to: (a) conduct a high-throughput screening (HTS) transcriptomic analysis of the 20 chemical compounds assessed in 2018-2019 (using the two National Resources Council of Canada (NRC) in-house zebrafish toxicity (GBT) assay); and (b) assess the uptake, metabolism and excretion of 10 out of the 20 compounds. This data will be used to validate the zebrafish New Approach Methods (NAMs) as predictive tools in assessing the toxicity of substances notified under the *New Substances Notification Regulations* of the *Canadian Environmental Protection Act* (CEPA). It will also be used to facilitate the 3Rs (reduction, refinement, and/or replacement of animals in toxicity testing) in chemical risk assessment. (PI: Luisa Carter)

Metformin environmental fate and effects study

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives, natural health products and medical devices. Metformin is a common medication used for treating type 2 diabetes and is one of the most prevalent pharmaceuticals detected in waste water sampling. Published science has raised questions about the potential for this substance to act as an endocrine disruptor in sentinel species such as fish and mussels. The goals of this field-based multi-tier project are to: (a) assess the environmental fate of metformin and its metabolite guanylurea in the aquatic environment; (b) assess the impacts of metformin and guanylurea on aquatic biota (including plants, microbial communities, aquatic invertebrates, and fish); and c) assess the effects of metformin and its metabolite in controlled laboratory studies using *Lemna gibba* and *Daphnia magna*. This data will be used directly in the environmental assessments of substances listed on the Revised In Commerce List and new substances in products regulated by the F&DA notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Alison McLaughlin)

Development of an Integrated Analysis Tool for Genotoxicity Assessment (IATGA)

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products, and to integrate innovative science into the risk assessment and risk management of new substances. The objective of this research study is to improve the manner in which genotoxic compounds are detected and assessed. The goal is to develop a bioinformatic platform tool for effective and efficient interpretation, analysis, and visualization of genotoxicity data and multi-endpoint results from various sources (e.g. ToxCast, Tox21, toxys BV) and make the software tool available and easily accessible. This tool will inform new approaches in assessing the genotoxicity of substances notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Luisa Carter)

Effects of the veterinary antibiotic florfenicol in freshwater aquatic species

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products such as human drugs, biologics, veterinary drugs, cosmetics, novel foods, food additives, natural health products and medical devices. Florfenicol is a veterinary broad-spectrum antibiotic effective against Gram-positive and Gram-negative bacteria used to treat bovine respiratory diseases, swine bacteriosis and intestinal infection. Florfenicol has been detected in stream waters at very high concentrations and thus may pose a risk to aquatic organisms. There is currently little knowledge on the chronic effects of florfenicol and very little information on exposures of florfenicol to Canadian species. The goals of this research study are to: (a) develop methods for florfenicol measurement and analysis in aquatic matrices; and b) assess the chronic toxicity of florfenicol (21 days) in embryo-larval fathead minnow (*Pimephales promelas*) and Daphnia magna in a static-renewal exposure. This data will be used directly in the environmental assessments of substances listed on the Revised In Commerce List and new substances in products regulated by the F&DA notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA). (PI: Alison McLaughlin)

Testing the effects of Selective Serotonin Reuptake Inhibitors (SSRIs) on zebrafish (*Brachydanio rerio*)

The *Food and Drugs Act* (F&DA) Substances Assessment Division within the New Substances Assessment and Control Bureau has been established to conduct assessments of the potential environmental and health risk to the general population associated with environmental exposure to substances in F&DA products, and to integrate innovative science into the risk assessment and risk management of new substances. There are twelve Selective Serotonin Reuptake Inhibitors (SSRIs) on the Revised In Commerce List (R-ICL) which have been identified as priorities for risk assessment and grouped together as they are known to have the same mode of action. One substance in particular has been widely detected in surface water and reported in media as well as having potential to impact the health of environmental organisms. The goals of this research study are to: (a) test the individual concentration-response profile of 5 different SSRIs on zebrafish larval behaviour; and (b) test the response profile of SSRIs in combination on zebrafish larval behaviour. This data will be used directly in the environmental assessments of substances listed on the R-ICL and will be used to scope the feasibility of a cumulative

risk assessment process for substances notified under the New Substances Notification Regulations of the *Canadian Environmental Protection Act* (CEPA), in support of a Chemicals Management Plan Post-2020 initiative. (PI: Alison McLaughlin)

Characterization and toxicology of metal nanoparticles

Substances manufactured at the nanoscale are being used in industrial applications as well as consumer products owing to their unique physico-chemical properties. However, these uses are also likely to lead to increased human exposure to these nanomaterials (NMs). Health Canada (HC) is responsible for risk assessment of NMs which are regulated under the *Canadian Environmental Protection Act* (CEPA, 1999). As part of Canada's Chemicals Management Plan (CMP) 3, HC has developed strategies to address NMs that are listed on the Domestic Substances List (DSL). For this purpose, HC has identified a number of priority DSL NMs for which data on physico-chemical characterization and toxicity are required for regulatory human health risk assessment. To fill these data needs, HC collaborated with the National Research Council's (NRC) Measurement Science and Standards group of the Metrology Research Centre on a research study to characterise the physico-chemical properties and to investigate the toxicological potential of several DSL NM substances, including cerium oxide, iron oxide, and nickel oxide. Characteristics of the nanoforms of these NMs, such as size, shape, surface area, surface charge, type and quantity of surface coating or surface modification, were studied along with their toxic effects on cell viability, membrane integrity, and cellular stress. Data obtained from this project allow Health Canada to evaluate the relationships between NM properties and their biological outcomes and to fill the data needs to inform regulatory decisions on the priority DSL NMs. (PI: Djordje Vladisavljevic; Kathy Nguyen)

Water and Air Quality Bureau (WAQB)

Air Program

Acute and chronic health effects of ambient $PM_{2.5}$ oxidative potential

Airborne fine particulate matter ($PM_{2.5}$) is measured as the mass of particles present in the air. This measurement is used worldwide to regulate ambient air quality and is based on years of epidemiological and toxicological evidence suggesting adverse health effects. Nevertheless, it is widely recognized that particle mass concentration is merely a surrogate measure of the true underlying cause of PM-induced health effects, often termed the "biologically effective dose". In particular, oxidative stress is known to play an important role in PM-induced health effects including both respiratory and cardiovascular outcomes. As a result, PM oxidative potential measurements have been proposed as a promising integrated measure of overall particle toxicity. This study builds on a national survey of outdoor $PM_{2.5}$ oxidative potential conducted between 2016-2018 at 40 locations across Canada with laboratory analyses completed in 2020. These data will be linked to data on emergency room visits and population-based cohorts to support epidemiological analyses. Analyses of acute health outcomes is currently underway. (PI: Scott Weichenthal)

Adverse birth outcomes and childhood diseases of ambient $PM_{2.5}$ oxidative potential and $PM_{2.5}$ components

Oxidative stress is known to play an important role in PM-induced health effects including both respiratory and cardiovascular outcomes. As a result, PM oxidative potential measurements have been proposed as a promising integrated measure of overall particle toxicity. In addition, composition elements of $PM_{2.5}$ may have differential toxicity and consequently different health impacts. This study evaluates whether $PM_{2.5}$ oxidative potential and $PM_{2.5}$ composition is associated with adverse birth outcomes and childhood diseases. The study will contribute to updating risk assessment guidelines for particulate matter and other criteria pollutants (i.e., O_3 and NO_2 [ozone and nitrogen dioxide]) and will contribute to the Air Quality Management System in identifying the most health effective approaches to improving air quality and local air zone management strategies. A scientific article was published in 2018 on the association of $PM_{2.5}$ components and adverse birth outcomes. Scientific articles focusing on $PM_{2.5}$ oxidative potential and development of childhood asthma and paediatric cancers will be published in 2020 and 2021. (PI: Éric Lavigne)

Calgary Spatial and Temporal Exposure Modelling (CSTEM) study

Canadian air zones represent a complex mixture of urban and rural land-use impacted by diverse emissions sources. The critical challenge for local air quality management lies in determining which pollution sources have the greatest impact on human exposure and health. This study collected summer and winter air pollution measurements at 125 locations in Calgary and surrounding rural areas, as well as yearlong measurements in a subset of sampling locations. These measurements are being combined with land-use and emissions data to identify source contributions and map short term (daily and weekly) and long term (seasonal and annual) exposure to air pollutants (NO_2, VOCs, PM_{10}, $PM_{2.5}$, black carbon, and metals) across these communities. Air pollution data generated by this study will be applied in existing health cohorts to examine a variety of adverse health outcomes. Results will also be used in collaboration with local and provincial air zone managers to develop and evaluate strategies for improving local air quality and reducing health risks. Models for NO_2 will be completed by spring 2020. (PI: Markey Johnson)

Canadian Atlantic Marine Air Pollution Study (CAMAPS)

Large marine vessels have historically used bunker fuel oil (BFO), which can significantly contribute to air pollution in areas near commercial ports and seaways and may even adversely influence air quality at inland locations through the movement of polluted air masses. Over the period 2012 to 2015, lower-sulphur marine fuel regulations were introduced for large ships operating in Canadian coastal waters and ports with the intention of reducing vessel emissions of SO_2 and $PM_{2.5}$ and thus improving ambient air quality in Canadian port cities. The *Canadian Atlantic Marine Air Pollution Study* (CAMAPS) investigates the impact these regulations have had on ambient exposures for Canadians living in Halifax, Nova Scotia. Ambient exposure sampling was carried out for criteria air pollutants (SO_2, $PM_{2.5}$, NO_2, CO, O_3) and $PM_{2.5}$ elemental composition over a one-year period downwind and upwind of the Halifax harbour (by prevailing winds), at the Bedford Basin inlet, and at select community sites to support pre- and post-Regulation comparisons, intra-urban comparisons, and source apportionment models. To further assess the potential impacts of the regulations on human health, sampling included measurement of black carbon (BC) and $PM_{2.5}$-oxidative potential. Analysis will apply toxicity-equivalent exposure estimates for $PM_{2.5}$-associated PAHs. Findings to date indicate that the low-sulphur marine fuel regulations have substantially reduced ambient exposures to SO_2 and contributed to a moderate

improvement in Halifax particulate air quality. Source apportionment modeling will be applied to quantify pre- and post-regulatory marine sector emission contributions to ambient $PM_{2.5}$ and $PM_{2.5}$-associated air toxics (e.g., heavy metals) relative to other transport and non-transport source types. A scientific article outlining the efficacy of the lower-sulphur marine fuel regulations will be published in 2021. (PI: Angelos Anastasopolos)

Characterisation of personal exposure in urban transport microenvironments

Transportation microenvironments are important sources of personal exposure for several pollutants including carbon monoxide, volatile organic compounds (VOCs), fine ($PM_{2.5}$) and ultrafine particulate matter (UFP), metals, and elemental carbon. Commuters are often in close proximity to traffic related air pollution (TRAP) and can experience short-term, high level exposures unique both in variety and level of air pollutants. Therefore a substantial portion of daily exposure to TRAP can occur during the relatively short time period when an individual is commuting. This project characterizes the variability of personal exposures within different Canadian transit environments. The Urban Transportation Exposure Study assessed private vehicle and metro (subway) commuting in Toronto, Montreal, and Vancouver as well as bus transit systems in Toronto, Vancouver and Ottawa. This project has added to knowledge of the impact that transportation microenvironments have on personal exposures and serves as a baseline for future comparisons of the impact of changes in vehicle design and fuel type on air pollutant levels in transportation environments. Two papers have been published presenting results of in-vehicle and subway exposure. Papers on urban UFP models have been published for Toronto and Montreal. Research relating chronic UFP exposure to health outcomes has also been published. This research has suggested UFPs increase the risk of incident hypertension and diabetes, incident prostate cancer, and postmenopausal breast cancer for women with positive oestrogen and progesterone receptor status. As well, no increased risk of congestive heart failure and asthma was found in relation to chronic UFP exposure. The final research paper of this study, which presents the bus exposures, was published in the spring of 2020. (PI: Keith Van Ryswyk; Scott Weichenthal)

Characterizing woodsmoke impacts in British Columbia communities

Wood burning is used to heat 1.7 million homes in Canada and emissions from wood combustion are an important source of fine particulate ($PM_{2.5}$) emissions. In a number of British Columbia (BC) communities where wood burning is common, levels of $PM_{2.5}$ may exceed the Canadian Ambient Air Quality Standards. Woodsmoke is believed to be a major contributor, but this has not been confirmed due to challenges in differentiating the portion of $PM_{2.5}$ that originates from woodsmoke. In this study, investigators employed an innovative continuous mobile monitor to detect woodsmoke in six BC communities: Whistler, Pemberton, Courtenay, Cumberland, Vanderhoof, and Fraser Lake in the winter of 2017. The study builds on previous woodsmoke work completed in Courtenay under Health Canada's program to address air pollution. The collected data will be used to develop woodsmoke concentration maps, which have been presented to the participating communities and other stakeholders. Currently the method is being refined for use by community groups. A draft manuscript has been developed and will be submitted to a journal in 2020. (PI: Nina Dobbin)

Commuter air pollution intervention study

Traffic related air pollution (TRAP) is a well-recognised contributor to smog and is linked to adverse health outcomes. Although traffic pollutants can travel long distances, exposure to the highest levels of

emissions occur closest to the source; e.g. in a car in dense traffic conditions. Time spent in-vehicle may contribute up to half of commuters' daily exposure to certain air pollutants. Most new cars now have, or allow for, a cabin air filter, but it is not known how well cabin air filtration can reduce exposure to TRAP. In this intervention study, Health Canada measured commuters' exposure to air pollutants in rush hour traffic during fall, 2014. Short term cardiopulmonary health indicators such as blood pressure, heart rate variability and respiratory inflammation and measured pollutant levels inside and outside vehicles were tracked. Effects on cognition (mental processing and judgement) were also measured in this real world environment where any deficit could be important to safety. Preliminary results show that participants' heart and cognitive function were found to be impacted by in-vehicle air pollution exposures. Cabin air filtration reduced in-vehicle particulate exposures by approximately one third. In-vehicle pollutant concentrations were notably elevated in tunnels. This research will contribute to the understanding of how this environment contributes to Canadians' overall air pollution exposure and potential health impacts as well as test the effectiveness of cabin filters as a direct and economical exposure reduction intervention. A scientific publication will be submitted in 2020. (PI: Gary Mallach)

Health effects of exposure to ultrafine particles

Recent work undertaken at Health Canada has focused on using land use regression models to develop exposure surfaces for ambient ultrafine particles (UFPs), a recognized marker of traffic-related air pollution, in two major Canadian cities (i.e., Toronto and Montreal). Previous research has shown that traffic-related air pollution is known to contribute to adverse health effects. However, few studies have investigated the long term health effects of exposure to UFPs. This study investigates long term exposure to UFPs on the risk of developing lung, breast and prostate cancers using data from three case-control studies (i.e., lung cancer case-control study in Toronto; breast cancer case-control study in Montreal, and prostate cancer case-control study in Montreal). As well, it investigates pregnancy exposure to UFPs on the risk of term low birth weight (<2,500g), preterm birth and small for gestational age using a provincial birth registry in Ontario for births in the city of Toronto. Exposure to UFPs on the development of childhood asthma will also be investigated. This epidemiological research will provide a better understanding of the biological mechanisms which govern the health effects of airborne particles and will inform the development of emission reduction strategies that target sources of UFPs. Several papers were published based on findings of this study, including one in March 2019 on the relationship between UFPs and asthma in children. Another scientific paper is expected to be published during 2020 looking at impacts on childhood cancers. (PI: Éric Lavigne)

Hybrid exposure models to predict spatially and temporally resolved air pollution concentrations at local and national scales

Land-use regression (LUR) models provide long term estimates of air pollution at a fine spatial scale. Chemical transport models produce temporally resolved estimates of air pollution concentrations at a coarse spatial state. This study combines LUR and chemical transport models to provide spatially and temporally refined estimates of air pollution exposure at both local and national scales. Better estimates of air pollution exposure improves our ability to assess the health risks associated with both long term and short term exposure to air pollution. The results will strengthen retrospective and prospective epidemiological studies by providing more accurate exposure estimates. Hybrid models for NO_2 and $PM_{2.5}$ have been developed for a single test year. These models will be expanded to cover the period from 2000-2014, and estimate contributions of different source types (e.g., transportation, industrial, and biomass burning) to ambient NO_2, $PM_{2.5}$, and O_3. The data generated by this project will be applied

in existing health cohorts to estimate the impacts of short term air pollution in urban and non-urban areas across Canada and to identify sources with stronger long term health impacts. (PI: Markey Johnson)

Spatial modelling to support health studies

Several high-profile national and local scale air pollution health studies in Canada rely on Health Canada scientists to provide estimates of exposure to air pollution which are required to carry out epidemiologic analyses. Health Canada is working with academic partners to carry out intensive ambient air pollution monitoring, and develop land-use regression (LUR) models for Ottawa, London, Calgary, and Halifax. Such models allow for the prediction of concentrations of pollutants at a neighbourhood or household level, which reduces the error associated with obtaining data from central site monitors. LUR models are being developed by Health Canada based on data obtained to predict the concentrations of elements (such as metals) in airborne particulate matter in Calgary and Halifax. LUR models are being used to support local- and national-scale health studies investigating air pollution impacts on respiratory, cardiovascular (e.g. stroke), developmental (e.g. birth outcomes, gestational diabetes), autoimmune diseases and cancer outcomes. These LUR models support research investigating links between air pollution and a variety of adverse health outcomes including mortality, atherosclerosis, systemic autoimmune rheumatic disease, and birth outcomes. LUR models and other exposure data developed by Health Canada's Air Program are now available through several venues including The Canadian Urban Environmental Health Research Consortium (CANUE). Two papers are anticipated for publication in 2020. (PI: Markey Johnson)

Time-dependent vulnerability to air pollution in a pregnancy cohort (MIREC)

Identifying impacts of air pollution exposure during critical fetal developmental periods has been prioritized under Health Canada's program to address air pollution and by international air pollution regulatory programs. However, traditional approaches have had limited success in addressing this issue. This study will apply an emerging novel approach (multilevel Bayesian modeling) to identify periods of susceptibility to air pollution during fetal development in the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. Air pollution exposures will be estimated using coupled satellite remote sensing and National Air Pollution Surveillance Program (NAPS) data, an approach that Health Canada researchers have previously validated in Windsor, Ontario. The study results suggest that exposure to ambient air pollution during critical periods of pregnancy may be associated with lower birth weight among term infants. A manuscript is expected for submission to a journal 2020. (PI: Markey Johnson)

Integrated Urban Models (IUM) project

In support of the federal government's plans to take action to address air pollution in Canada, researchers from the University of Windsor, Health Canada, and Ryerson University are leading a joint effort to develop tools to support local and federal agencies in making decisions that will reduce urban air pollution and create healthier cities. Integrated Urban Models (IUM) are complex simulation platforms that act as a virtual laboratory to allow urban planners and decision makers to evaluate the impacts of development and transportation decisions and policies. This study will add air pollution exposure and health impacts, as well as other sustainability indicators to SMARTPLANS, an existing IUM. This study will provide support for evaluating alternate land use and transportation planning policies

and create healthier Canadian cities. Specifically, SMARTPLANS will utilize data on local transportation, land use, economic and travel activity, as well as air pollution, health, and economic indicators, to simulate land use and transportation system infrastructure and policy changes, with the goal of assessing which decisions will maximize social and economic benefits, while minimizing negative environmental and health impacts. SMARTPLANS will help to promote healthier cities by facilitating analysis of the impacts of alternate planning and policy decisions on a variety of social, economic, environmental, and health indicators, including exposure to air pollution and health impacts of air pollution in the Canadian population. The study will culminate in the development of a user-friendly planning support tool that will be freely available to policy makers, air zone managers, researchers, public health practitioners, and other stakeholders across Canada. The SMARTPLANS platform will be developed for 5 cities across Canada: London, Halifax, Vancouver, Ottawa, and Calgary. (PI: Markey Johnson)

Subway Air Quality Investigation (SAQI)

Airborne particulate matter (PM) is a global health concern, and its metallic components have been shown to have cardio pulmonary health effects. Particulate matter in subway systems has been characterized as being highly enriched in steel-based elements such as iron, chromium, manganese, zinc, and nickel as well as brake pad-related elements such as copper and tin. In Canada, the Urban Transportation Exposure Study (UTES) characterized the PM exposures in three Canadian subway systems and found that most of a typical commuter's daily exposure to particulate iron manganese and chromium would occur while in the subway and more than 20% of their daily exposure to $PM_{2.5}$ mass would result from a typical 70-minute subway ride in the Toronto subway. Similar values were found for the Montreal and Vancouver subway systems. This study returned to the Toronto Subway and has evaluated two interventions, night time tunnel vacuuming and changes in subway trains, for their potential to reduce fine particulate matter (PM2.5). Further, fine particles from the subway are being compared to that of two ambient sites in Toronto. Data from this study will be valuable towards designing air quality policy in this unique environment which is visited by millions of Canadians on a daily basis. Two papers are anticipated for publication in 2020. (PI: Keith Van Ryswyk)

Indoor air quality and the effects on children's respiratory health in First Nations reserves in the Sioux Lookout Zone

According to the Canadian Paediatric Society, housing directly affects the health of children and youth. First Nations and Inuit are disproportionately affected by crowded and inadequate housing, which has been associated with increased hospital admissions of children for respiratory tract illnesses. It has been shown that Aboriginal children in communities in the Sioux Lookout Zone (Sioux Lookout First Nations Health Authority; SLZ) in northern Ontario have elevated rates of asthma, bronchiolitis and pneumonia, but there is little information on their indoor environmental quality. Working with local officials, a preliminary assessment revealed houses with issues including dampness and contaminants associated with wood stoves, as well as other problems. This study aims to evaluate Indoor Environmental Quality (IEQ) in houses of 50-100 children living in four isolated communities in this area in relation to respiratory health and related utilisation of health care services. Community consultations with the relevant Nations Hamlet Councils and local medical officers of health are incorporated into the process. Consenting households receive a respiratory health questionnaire for their youngest child and a standardized housing inspection is being carried out in partnership with Band officials. Monitors record basic indoor environmental quality and the relationship between it and the child's respiratory health will

be examined. Working more effectively with the communities, this research will help us to identify simple home improvements and other building interventions that could improve the respiratory health of this vulnerable population. The findings will also be used to inform future, similar studies/interventions in remote First Nations (FN) reserves across Canada. Field work was completed in the spring of 2019, and analysis of the data is underway. Participant reports for all four (4) First Nations communities have been completed and support given to housing authorities to support training of local technicians on air quality issues. One paper is anticipated for publication in 2020. (PI: Gary Mallach)

Joint effects of exposure to aeroallergens and outdoor air pollution in the urban environment

Short term exposure to aeroallergens has been associated with the exacerbation of asthma and allergy symptoms. The joint effects of aeroallergens and outdoor air pollution on asthma exacerbation has also been investigated, however findings have been inconclusive. As well, growing evidence is showing that exposure to outdoor air pollution during gestation and early life is associated with the development of asthma and allergic symptoms among children. Little is known regarding the joint exposures of aeroallergens and air pollution among children. A major limitation of the available epidemiologic literature is that exposure has typically been assessed on the basis of pollen data from only one or few monitoring stations per city. Thus, current data do not capture intra-urban spatial heterogeneity of pollen concentrations providing less accurate data for exposure assessment when studying potential human health effects and potential interactive effects with outdoor air pollution. In this context, a land use regression (LUR) model approach based on environmental determinants will be developed for predicting the variability of pollen concentrations at fine spatial scales in the city of Toronto. Results are expected for the fall 2019 and will be published in 2020. Using the Canadian Healthy Infant Longitudinal Development (CHILD) study, a Canadian Institute of Health Research (CIHR) and Health Canada funded birth cohort, the combined effects of exposure to outdoor air pollution and aeroallergens on asthma incidence among Canadian children will be evaluated. A scientific paper based on the characterization of aeroallergens in Canada has been published in 2018. A scientific paper based on results of joint effects of aeroallergens and air pollution on atopic disease development using the CHILD Study was submitted for publication in 2019. (PI: Éric Lavigne)

Short and intermediate-term exposures to ambient air pollution from biomass burning and changes in retinal microvascular responses in children

Epidemiological studies of the cardiovascular health effects of fine particulate air pollution ($PM_{2.5}$) primarily reflect urban areas and few studies have examined non-traffic sources of particulate air pollution. Recent studies have demonstrated that biomass burning as a source of $PM_{2.5}$ may modify the acute cardiovascular health effects of this pollutant among elderly subjects; however, the components and biological mechanisms underlying this association are not entirely clear. Moreover, it is not clear how such exposures may impact cardiovascular health in children. This investigation will examine the impact of short (e.g. 24-hours) and intermediate term (e.g. 1 month) exposures to $PM_{2.5}$ from biomass burning on microvascular responses in school children over the course of a heating season in Courtenay and Cumberland, British Columbia. Few studies have evaluated the cardiovascular health effects of air pollution exposures among children; however, since microvascular dysfunction is a known contributor to the development of cardiovascular disease, it is important to understand how early life exposures may impact vascular health. In particular, retinal arteriole narrowing has been identified as a predictor of hypertension in both children and adults and may serve as a marker for similar changes in the coronary microvasculature. In this study, retinal microvascular diameter will be assessed prospectively using

repeated *within-subject* measurements collected using a non-invasive retinal imaging technique. Daily mean $PM_{2.5}$ mass concentration data will be collected from fixed-site monitors and monthly mean $PM_{2.5}$ oxidative potential will also be determined. Collectively, the proposed investigation will provide important information related to the impact of $PM_{2.5}$ (and $PM_{2.5}$ oxidative potential) on cardiovascular health and will support ongoing efforts to reduce the public health impacts of air pollution from biomass burning in Canada and abroad. Data collection was completed in May 2020. Publications are expected in 2021. (PI: Scott Weichenthal)

Ice arena air quality project

Fossil fuel powered ice resurfacers (Zambonis®) emit several pollutants, notably nitrogen dioxide (NO_2) and carbon monoxide (CO). Some segments of the population that regularly use ice arenas (including children, the elderly and those with asthma and other cardiovascular and respiratory conditions) are considered susceptible to adverse health effects after exposure to these pollutants. Provincial partners requested assistance in developing improved best practices, based upon scientific evidence, to reduce the health effects from exposure to air pollution in ice arenas. Currently, there is insufficient data on the levels of combustion-related pollutants (namely NO_2 and CO) in arenas, and insufficient evidence supporting the effectiveness of currently recommended pollutant reduction strategies. The Indoor Air Contaminants Assessment Section (IACAS) of Health Canada designed a research study to investigate and address these issues. In the winter of 2017/2018, levels of air pollutants were measured continuously for seven days in four arenas in Ottawa and four arenas in Saskatchewan. These results are being used to better understand pollutant levels and temporal variation in the arenas, and to assess the effectiveness of different types of portable monitoring equipment. The second phase of the study, conducted in winter of 2019-2020, assessed pollution reduction strategies in ice arenas, including the impact of different ice resurfacer fuel types and impact of changes in ventilation practices. The data is currently being used for development of implementable best practices for air quality in ice arenas, targeted for provincial/territorial and municipal partners. Publication of the research results and best practices is slated for FY 2020-2021. (PI: Aaron Wilson; Christie Cole; Corinne Stocco; Morgan MacNeill)

Trainyard Neighbourhood Air Quality Study (TyNAQ)

Canada has a large railway network, with nearly 50,000 km of railway and hundreds of train yards. Train yards are nodes in the railway network that intensify polluting activity, with locomotives operating 24hr/day year-round along with transport trucks and freight-handling equipment. Railway corridors and train yards frequently intersect residential areas, including large urban cities where the majority of Canadians live and work, raising health concerns about the rail sector's significant air pollution releases. Railway-generated air pollution is complex, combining fossil fuel (diesel) combustion emissions with friction/wear emissions (steel rails/wheels, brakes) and dust resuspension. These gaseous and particulate matter (PM) releases include a suite of pollutants with known acute and chronic health effects, including nitrogen dioxide (NO2), sulphur dioxide (SO2), and respirable particles in multiple size fractions (UFP, PM2.5, PM2.5-10) and containing toxic elements (e.g., heavy metals, PAHs) that may contribute to oxidative stress. Residents exposed to railway air pollution may also experience related noise pollution with potentially cumulative health effects. Canadian train yards constitute an air health knowledge gap, lacking relevant emissions and exposure data to characterize impacts on urban air quality and health. To address this air health knowledge gap, the Trainyard Neighbourhood Air Quality (TyNAQ) research project will conduct near-source and community air quality sampling campaigns for

multiple air pollutants and noise near a large Canadian urban train yard in Toronto, Canada. Field work is taking place 2020-2021. (PI: Angelos T. Anastasopolos)

Quebec Air Pollution Exposure and Epidemiology study (QAPEE)

Urban air pollutants such as nitrogen dioxide (NO_2), Black carbon (BC), fine particulate matter (PM2.5), and ultrafine particles (UFPs) are ubiquitous in Canadian urban environments and have been suggested as factors contributing to the risk of several cardiopulmonary diseases and cancers. Past research at Health Canada has contributed to air pollution exposure modelling for several pollutants in several Canadian cities. However, Quebec City remains a major urban center with few air pollution exposure Land Use Regression (LUR) surfaces. The creation of new LUR surfaces would be beneficial for a city rich in epidemiological data from the Quebec Integrated Chronic Disease Surveillance System. As well, there is local concern that air pollution related to the Quebec City seaport and the Jean Lesage international airport pose risks to human health. Analyses that test the association of these point sources to ambient air pollutants would be valuable to developing policy around these issues. Oxidative potential can serve as an indicator the potential biological activity of particulate matter and provide a metric independent of mass concentration. Analysis of the spatial and temporal variation of oxidative potential (OP) of PM2.5 in the city and the relationship between OP and point sources will improve understanding of PM associated health risks. The source and size characteristics of different size ranges of UFPs may have distinct health effects. This study is applying novel techniques to characterise UFPs by source and test for associations with Quebec City's sea and air ports. Similarly, relating PM2.5 OP to health effects may reveal health risks of PM2.5 independent of mass concentration. It aims to generate exposure models for several pollutants in the region that will substantially reduce exposure misclassification in the linkage of air pollution data to epidemiological cohorts in Quebec City and advance understanding of health impacts of these pollutants. (PI: Keith Van Ryswyk)

New homes air quality study

Building materials have been found to release pollutants into indoor air. Recent studies suggest that, as building envelopes become even tighter, levels of volatile organic compounds (VOCs) in newly built homes may exceed health-based exposure limits. There is also concern over the concentrations of semi-volatile organic compounds (SVOCs), including flame retardants, in this environment. However, existing studies typically involve a small number of homes, usually occur at one point in time, and are not evaluated within a Canadian context. To address these knowledge gaps, this multi-year study measures concentrations of VOCs and SVOCs immediately before occupancy, as well as at multiple time points during the first year of occupancy, in 40 newly constructed homes in Ottawa. Information about factors that affect the monitoring results, including air exchange rate, occupant behaviour and housing characteristics are also being collected. The objectives of the New Homes Air Quality Study are to measure concentrations of VOCs and SVOCs in new homes; to understand how these concentrations compare to existing health-based exposure limits and/or concentrations previously measured in Canadian homes; and to examine how these concentrations change during the first year of occupancy. The study also provides the opportunity to undertake preliminary work on microplastics, an emerging issue and a priority for the Government of Canada. Results from the study will inform risk assessment and risk mitigation activities such as providing health-based guidance to organizations and individuals relating to indoor air contaminants in new homes. They may also inform the development of product standards and modifications to the national building code. Field work is underway from 2019 to 2022. (PI: Corinne Stocco)

An online survey on kitchen ventilation in Canadian homes

Health Canada's Guidance for Particulate Matter in Residential Indoor Air identified cooking as one of the major indoor sources of fine particulate matter (PM2.5), and gas stoves have the potential to be a significant source of indoor nitrogen dioxide (NO_2). Sufficient kitchen ventilation is important to reduce cooking exposures. Published data on residential cooking and ventilation behaviors are limited. In particular, little is known in the prevalence of kitchen ventilation and use patterns in Canadian homes. Without knowing how natural and mechanical ventilation is normally used during cooking, exposure estimates could be erroneous. To fill this gap, this research conducted a nationwide online survey to collect information on the characteristics of cooking and kitchen ventilation use in Canadian homes. Sample collection was built through a probability-based method to balance each sample group across age, gender, region, and household income for representative results. The survey was conducted from January 13 to February 24, 2020 with completed responses collected for 4500 homes across Canada. The survey responses will be used to develop a profile of characteristics and usage of kitchen ventilation systems in Canadian homes and to understand people's knowledge of cooking exposures and kitchen ventilation. The results can be used to support more accurate modeling of the impact of cooking on indoor air quality and to inform risk management strategies. A scientific paper outlining the results is expected to be submitted in 2021. (PI: Liu Sun)

CanEPIC Study - Canadian Environment, Pregnancy, Infant and Child Study

Exposure to ambient air pollution during pregnancy has been associated with low birth weight, preterm birth, maternal health outcomes and several childhood atopic diseases and neurodevelopmental outcomes. However, evidence of the impact of air pollution on these outcomes is still limited due to other factors that may be involved in this complex relationship that may not have been accounted for in previous studies (e.g. smoking and alcohol consumption during pregnancy, maternal body mass index, maternal weight gain during pregnancy, maternal comorbidities, etc.). Further evidence is also required regarding forest fire exposure during pregnancy and impacts of other important urban environmental factors (e.g. greenness, walkability, noise, heat, etc.) on adverse birth, maternal and childhood outcomes. This study aims to evaluate the risk of air pollution on birth outcomes, maternal pregnancy complications and childhood diseases while taking into consideration the complex exposures to other environmental factors present in urban environments. The findings of this study will be used to support Health Canada's risk assessments, regulatory decision-makings and health messaging in addressing impacts of air pollution. (PI: Éric Lavigne)

Water Program

Testing for enterococci in the raw groundwater sources of municipal drinking water systems

Health Canada works with the provincial and territorial governments to develop guidelines for microbiological contaminants in drinking water. These set out the basic parameters that every water system should strive to achieve in order to provide the cleanest, safest and most reliable drinking water possible. Testing for the indicator bacteria enterococci may help identify fecal contamination in groundwater systems that might otherwise be missed using only the mandated *E. coli* and total coliform testing. Health Canada requires data from additional provincial jurisdictions to inform settings and locations where enterococci monitoring may be most useful. The aim of this research is to initiate

limited monitoring in collaboration with Manitoba Sustainable Development's Office of Drinking Water to test for the fecal indicator enterococci in the raw groundwater sources of five municipal or semi-public drinking water systems over the course of one year. Results of the research will provide Canadian data to inform the development of health-based guidance on the bacteriological monitoring of drinking water. (PI: Gordon Yasvinski)

Transformation of microplastics by drinking water oxidants and its effects on sorption and leaching of emerging chemicals of potential health concern

Microplastics have been found to sorb (adsorb or absorb) organic pollutants and metals, some of which may be of concern to human health. Under certain environmental conditions and during drinking water treatment, microplastics may also undergo changes in their physical characteristics and chemical composition that may affect their sorption and leaching behaviour to these chemicals. It is unclear whether exposure to chemicals from microplastics represent a significant source of exposure compared to total exposure from other sources and more research is needed before a human health risk assessment on microplastics is possible. The aim of this research is to develop protocols for assessing how microplastics are transformed when subjected to oxidation and weathering conditions representative of oxidant and UV exposures in drinking water treatment plants, and how their capacity for sorption/leaching of selected target hydrophobic organic chemicals and a metal ion are influenced. Microplastics of different polymer types and sizes will be monitored for physical (size, shape) and chemical changes when exposed to different water treatment plant exposure conditions (e.g., ozonation). The sorption/leaching behaviour of the different types and sizes of microplastics will be assessed in water, and simulated gastric fluids. The results of this study will provide critical information on the transformations of microplastics in water and simulated biological fluids, as well as their interactions with select environmental pollutants. The data will have the potential to feed into longer-term studies of hydrophobic organic chemical interactions, with a wider variety of weathered plastics (fibers, fragments, pigmented particles) from other possible sources of human exposure. (PI: Subhasis Ghoshal [McGill University]; HC contact: Tamara Desroches)

Detection of effects and localization of microplastics on developing amniote embryos: protocol development using chicken embryos

Evaluating the toxicity of microplastics is a research need identified by Health Canada and other international groups. In particular, developmental toxicity is an endpoint that requires further study; however, there is also a need to develop test systems that can assess the developmental toxicity of microplastics. The aim of this project is to develop a toxicology test model for assessing the developmental effects of microplastics using developing chicken embryos. Chicken embryos are a practical model system for examining potential human fetus responses to toxicants because chickens have similar genomes sizes to mammals and similar relative organ sizes, including brains, during early development. This research builds on previous experiments that have examined the effects of crumb rubber leachate on the developing brain, liver, and heart during the first week of development in the chicken embryo, which is roughly comparable to the first trimester of human development. This data will be used to adapt the protocol to examine developmental effects of different sizes of polystyrene microplastic beads on chicken embryos. The beads will be injected into the yolk to simulate particles crossing the placental barrier, and into the veins that drain blood from the yolk sac to simulate complete uptake into the embryo. The study will also examine the localization and uptake pathways of microplastics using labelled polystyrene microplastic beads and the beads will be imaged in whole and

sectioned tissues. The results will provide preliminary findings on the effects of microplastics on developing chicken embryos, to serve as a possible analogue for potential human effects. (PI: Hans Larsson [McGill University]; HC contact: Tamara Desroches)

Consumer and Hazardous Products Safety Directorate (CHPSD)

Risk Assessment Bureau (RAB)

Product Safety Laboratory

Development of a new test method to evaluate mechanical hazards of corded window coverings

Health Canada has released new *Corded Window Coverings Regulations* to help eliminate the strangulation hazard and to help reduce the rate of fatal strangulations associated with corded window coverings. Cords that are in reach to a child and are long enough to become wrapped around the child's neck may lead to injury or even death due to strangulation. This project was initiated to develop and validate a new test method to evaluate the cords and loops of corded window coverings in a repeatable and reproducible manner to support the department's capacity to verify compliance of the new *Corded Window Covering Regulations* once in force. The test method assesses if there are any reachable cords using probes designed based on anthropometric data and built in house with a 3D printer. If a cord is determined to be reachable, it is then assessed to see if it is long enough to pose a hazard to a child when pulled in any direction with a force attaining 35 N. This is done using a test frame developed in house that utilises a set of pulleys and test mass to control and communicate the direction of pull, as well as maintain the applied force during further assessment. The test method assesses for both a length of cord greater than 22 cm and a loop perimeter greater than 44 cm, as well as sets of two cords that can be connected end to end for a combined cord length of 22 cm. Other testing elements such as an assessment of warnings, labeling and assessment of potential small parts using a 90 N Push / Pull included in the test method have been adapted from other Product Safety Laboratory test methods. This test method will be used to verify the compliance of corded window coverings sold in the Canadian market. (PI: Gregory Katchmar; Oliver Treen)

Validation of nicotine test method for high concentration levels

One of the potential risks associated with vaping products is poisoning through ingestion of the vaping liquid. A child may experience serious and potentially life-threatening health effects following accidental ingestion of even a small amount of vaping liquid that contains nicotine. In 2018-2019, the Product Safety Laboratory developed a method for the determination of nicotine at high concentration in vaping products using a gas chromatograph equipped with both a mass spectrometer and a flame ionisation detector (GC-MS-FID). Since the initial phases of that work, nicotine salts have become more widely used to allow for a less harsh vape with higher nicotine concentration. This project validates the high

concentration method using GC-MS-FID for the analysis of vaping products containing nicotine salts. This method can be used to verify the compliance of vaping liquids containing nicotine salts on the market. (PI: Jane Situ)

Determination of flame retardants in a survey of consumer products

The Chemicals Management Plan (CMP) is a Government of Canada initiative aimed at reducing the risks posed by chemicals to Canadians and their environment. Organic flame retardants were among the chemicals identified as priorities for action in the second and third phases of CMP. Risk management options, including additional regulatory measures, for organic flame retardants are now being considered. To support the decision making process, the Product Safety Laboratory (PSL) developed methods for triethyl phosphate (TEP), isopropylphenyl phosphate (IPPP), and updated and revalidated a test method for higher concentrations of 1,3,5-Triazine-2,4,6-triamine (melamine). The PSL tested a series of polymeric foam consumer products for five flame retardants: tris(1-chloro-2-propyl)phosphate (TCPP), tris(1,3-dichloro-2-propyl) phosphate (TDCPP), melamine, TEP, and IPPP. Fifty products, with 150 components, were tested. Thirty-one products contained one or more of the identified flame retardants exceeding the limit of quantification. Melamine was the most prevalent flame retardant identified. (PI: Katrina Griffiths; Nathalie Ritchot)

Exploration of the thermal degradation products of vaping liquids containing nicotine salts by pyrolysis

In 2018-2019, two projects were completed by the Product Safety Laboratory with the objective of examining chemical compounds related to vaping liquids. One was a qualitative examination of the chemical composition of commercially available flavoured vaping liquids using gas chromatography-mass spectrometry (GC-MS) and the other investigated the preliminary parameters for pyrolysis of vaping liquids. This project builds on the work of the two previous projects by examining the compounds observed prior to and following the pyrolysis of commercially available vaping liquids containing nicotine salts. Between 30 and 50 compounds were identified in each of the three vaping liquids tested in this project. Four organic acids, acetic acid, benzoic acid, maleic anhydride (acid anhydride of maleic acid), and lactic acid, were identified. Pyrolysis of the vaping liquids confirmed the presence of aldehydes as thermal degradation products (TDPs) of carrier liquids, the increase in abundance of TDPs at high temperature and the increase in TDPs as the result of flavouring. (PI: Katrina Griffiths)

Triage and Surveillance Division

Strengthening surveillance of consumer products in Canada: The vaping example

Surveillance information collected by the Consumer Product Safety Program (the Program) is used to identify emerging hazards. In this study the above is demonstrated through characterization and quantification of trends associated with vaping reports received by the Program over the past 5 years. Data collated by the Program were extracted for the period from January 1, 2015 to September 30, 2019. The data was summarized using descriptive statistics and trends were quantified for average annual percent change. In order to compare characteristics of vaping reports, ratios were used to compare vaping-related injuries to all other reports received by the Program. A total of 71 vaping-related reports were received between January 1, 2015 and September 30, 2019. During this period, the

average percent change increase in the number of reports received was quite high (approximately 73 percent annually). Among those who reported an injury, nearly half (48.5%) were due to burn injuries. In addition, there were proportionally, more vaping reports involving males and individuals between the ages of 15-19 years as compared to all other reports submitted to the Program. While the number of reports relating to vaping products is small, the results of this analysis suggest that certain groups, including males and youth, are more likely to be the subject of a vaping-related incident. (PI: Minh Do)