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Human Health Risk Assessment for Gasoline Exhaust

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ACP	acid phosphatase
AHR	airway hyperresponsiveness
ALP	alkaline phosphatase
ALL	acute lymphoblastic leukemia
AM	alveolar macrophages
AML	acute myeloid leukemia
ANP	atrial natriuretic peptide
APEI	Air Pollutant Emission Inventory
AQBAT	Air Quality Benefits Assessment Tool
AURAMS	A Unified Regional Air Quality Modelling System
BALF	bronchoalveolar lavage fluid
BC	black carbon
BTEX	benzene, toluene, ethylbenzene and xylenes
bw	body weight
CAC	criteria air contaminant
CD	census division
CEPA 1999	*Canadian Environmental Protection Act, 1999*
CGSB	Canadian General Standards Board
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COX-2	cyclooxygenase
CRF	concentration–response function
DE	diesel exhaust
DNA	deoxyribonucleic acid
ECCC	Environment and Climate Change Canada
ECG	electrocardiogram
FE_{NO}	fractional exhaled nitric oxide
GDI	gasoline direct injection
GE	gasoline exhaust
GEE	organic solvent extract of GE
GEP	gasoline exhaust particle
GPx	glutathione peroxidase
GSH	glutathione
GST	glutathione *S*-transferase
HC	hydrocarbon
HDV	heavy-duty vehicle
HI	hazard index
HO-1	hemeoxygenase-1
HQ	hazard quotient
HR	hazard ratio
IARC	International Agency for Research on Cancer
Ig	immunoglobulin (e.g. IgE, IgG_1, IgG_{2a})
IHD	ischemic heart disease
IL	interleukin (e.g. IL-2, IL-4, IL-5, IL-6, IL-10, IL-12, IL-13, IL-1β, IL-1α)
IQR	interquartile range
IT	intratracheal

JEM	job exposure matrix
LDH	lactate dehydrogenase
LDV	light-duty vehicle
MCh	methylcholine
MIP-2	macrophage inflammatory protein-2
MMP	matrix metalloproteinase
mRNA	messenger ribonucleic acid
NAPS	National Air Pollution Surveillance
NHL	non-Hodgkin's lymphoma
NMHC	non-methane hydrocarbon
NOx	nitrogen oxides
OR	odds ratio
PAH	polycyclic aromatic hydrocarbon
PM	particulate matter
$PM_{2.5}$	fine particulate matter
PND	postnatal day
ppb	parts per billion
ppm	parts per million
RBC	red blood cell
RfC	reference concentration
ROS	reactive oxygen species
RR	risk ratio
SI	spark-ignition (engine)
SMR	standardized mortality ratio
SOD	superoxide dismutase
TBARS	thiobarbituric acid reactive substances
TNF-α	tumour necrosis factor alpha
TWBL	tire wear and brake lining
UFP	ultrafine particle
US EPA	United States Environmental Protection Agency
UTES	Urban Transportation Exposure Study
VOC	volatile organic compound

Human Health Risk Assessment for Gasoline Exhaust

Executive Summary

Gasoline, or spark ignition, engines are used throughout Canada, representing 92% of on-road vehicles and 87% of off-road engines or equipment. It is reasonable to assume that exposure to gasoline engine exhaust (GE) is nearly ubiquitous, particularly for Canadians living in urban areas or in close proximity to a major roadway: it is estimated that approximately 2 million people live within 50 m of a major road in Canada. GE is a highly variable and complex mixture of particulate and gaseous pollutants, the composition of which depends on numerous factors, including fuel quality, engine and pollution control technologies, vehicle operating conditions and ambient temperature. GE is an important source of criteria air contaminants (CACs) associated with adverse effects on human health, including fine particulate matter ($PM_{2.5}$), ground-level ozone (O_3), nitrogen dioxide (NO_2), volatile organic compounds (VOCs) and carbon monoxide (CO). In addition, GE constituents include air toxics that are recognized internationally as carcinogens, such as benzene and polycyclic aromatic hydrocarbons (PAHs).

Gasoline fuel, vehicles and engines are subject to multiple federal regulations that have successfully reduced air pollutant emissions from gasoline mobile sources, representing a major success in the management of air quality in Canada and the protection of human health. However, given the number of vehicles and engines in use, the age structure of the in-use fleets, and the vehicle kilometres travelled by Canadians, gasoline engines remain a key source of air pollution. The adverse health effects of individual pollutants in GE or produced secondarily in the atmosphere from primary GE emissions (e.g. $PM_{2.5}$, O_3, NO_2, benzene and PAHs), are well characterized in the scientific literature and include increased risk of cardiorespiratory mortality and morbidity and of cancer, among other outcomes.

This report is a comprehensive review and analysis of the potential adverse health effects associated with gasoline fuel use in Canada. Two distinct approaches are used. Part A provides an evaluation of scientific studies that have examined the health effects associated with exposure to GE as a mixture. Studies on the health effects of individual GE constituents, such as $PM_{2.5}$ and benzene, were not considered, as these substances have been extensively reviewed by Health Canada elsewhere. Part B provides a quantitative assessment of the contribution of on-road and off-road gasoline mobile source emissions to individual air pollutant concentrations in Canada and the population health impacts associated with that incremental contribution. The health impact analysis in Part B, which is based on well-established quantitative estimates of risk of adverse health impacts associated with incremental changes in air concentrations of individual pollutants, is complementary to the traditional risk assessment approach presented in Part A.

Following a weight of evidence analysis in Part A of this document, it is concluded that the available literature database of studies that have examined the health effects of GE as a mixture is limited in both study quality and quantity. It is inherently difficult to examine the health effects of GE as a mixture in epidemiological studies, given that most populations are co-exposed to GE and diesel exhaust (DE), and that a unique surrogate for GE exposure has not been identified. Overall, the database of studies examining the role of the GE mixture in adverse health effects (including cancers and cardiovascular, immunological, reproductive, developmental and neurological outcomes) is inadequate, i.e. too limited to infer a causal role for GE. The weight of evidence suggests that GE affects the respiratory system, which is consistent with the known health effects of air pollution to which GE contributes, but the available data examining the GE mixture itself are limited and further study is required. These causality determinations do not preclude the known and well-documented carcinogenicity of individual

compounds found in GE, such as benzene and PAHs, nor the well-established non-cancer health effects of GE constituents.

In Part B, analyses were conducted in a stepwise manner: (1) estimation of emissions from gasoline on-road vehicles and off-road applications in Canada; (2) estimation of the impact of those emissions on ambient concentrations of $PM_{2.5}$, NO_2, O_3, CO, sulphur dioxide (SO_2), benzene, formaldehyde and acetaldehyde across the country using air quality models; and (3) estimation of population health impacts or risks resulting from the incremental contribution of gasoline emissions to ambient concentrations of these pollutants. Modelling was conducted for calendar year 2015.

On-road and off-road gasoline applications represent an important source of air pollutant emissions (e.g. 11% of nitrogen oxides (NOx) emissions, 67% of CO emissions and 20% of VOC emissions), especially in populated urban areas, where a large fraction of the Canadian population resides and where personal vehicle use is ubiquitous. Furthermore, on-road gasoline vehicles contribute 98% of CO, 46% of NOx, 28% of $PM_{2.5}$, 83% of SO_2 and 91% of VOC emissions from all on-road vehicles (all fuel types). Off-road gasoline vehicles and engines contribute 94% of CO, 14% of NOx, 27% of $PM_{2.5}$, 32% of SO_2 and 89% of VOC emissions from all off-road vehicles and engines (all fuel types).

Air quality modelling results indicate that gasoline emissions influence ambient concentrations of $PM_{2.5}$, NO_2, O_3 and CO. On-road gasoline emissions contribute to air pollutant concentrations in urban areas (e.g. Greater Vancouver, Calgary, Winnipeg, Toronto and Montréal) and along major transportation routes. Specifically, on-road gasoline emissions are estimated to contribute 0.5–2 micrograms per cubic metre ($\mu g/m^3$) to $PM_{2.5}$ concentrations, 0.5–5.5 parts per billion (ppb) to NO_2 concentrations, and 100 to over 500 ppb to CO concentrations in and around urban areas. On-road gasoline emissions decrease summer O_3 concentrations by 0.01–4 ppb within large urban centres, and increase summer O_3 concentrations by 0.5–4 ppb in areas surrounding urban centres. These seemingly opposite effects are due to the complex photochemical reactions between O_3 and NOx, and the associated impact of high levels of NOx emissions in urban centres. The impact on ambient air pollutant concentrations of off-road gasoline emissions appears more widely distributed geographically, affecting air quality in both rural and urban areas, but the impact is lower in magnitude than that of on-road gasoline emissions.

The health effects of individual air pollutants are well recognized by Health Canada and internationally. The current health impact analysis estimates that on-road and off-road gasoline emissions, via their contributions to ambient concentrations of CACs, lead to population health impacts and societal costs in Canada. For calendar year 2015, on-road gasoline emissions are associated with 700 premature mortalities (valued at $5.0 billion), where 69%, 20%, 6%, and 5% of the estimated mortalities are attributable to ambient $PM_{2.5}$, NO_2, CO, and O_3, respectively. On-road and off-road gasoline emissions are associated with 940 premature mortalities (valued at $6.8 billion), where 66%, 17%, 11% and 6% of the estimated mortalities are attributable to ambient $PM_{2.5}$, NO_2, and O_3 and CO, respectively. The mortality endpoints considered result from both acute and chronic exposure to air pollutants, and include cardiovascular, respiratory and lung cancer mortalities. Gasoline emissions are also associated with acute respiratory symptom days, restricted activity days, asthma symptom days, hospital admissions, emergency room visits, child acute bronchitis episodes and adult chronic bronchitis cases across Canada. The total societal cost for calendar year 2015 associated with on-road and off-road gasoline emissions is estimated to be $7.3 billion.

A similar health impact analysis was previously undertaken by Health Canada for on-road and off-road diesel emissions in Canada, also for calendar year 2015. For that assessment, it was estimated that on-

road diesel emissions were associated with 320 premature mortalities and combined on-road and off-road diesel emissions were associated with 710 premature mortalities. Hence, the population health impacts from gasoline emissions are estimated to be greater than those from diesel emissions, based on these model-based analyses. This finding highlights the important contribution of gasoline emissions to ambient air pollution, including the contribution of NOx and VOCs to the secondary production of $PM_{2.5}$. It also highlights that the geographic distribution of gasoline emission sources and human populations are closely aligned, increasing population exposures.

Recent amendments to the Canadian *On-Road Vehicle and Engine Emission Regulations*,[1] *Sulphur in Gasoline Regulations,*[2] and *Off-Road Small Spark-Ignition Engine Emission Regulations*[3] will result in reductions in air pollutant emissions from gasoline engines over the next decade, and associated population health benefits. These amendments were not reflected in the current analysis, which targeted calendar year 2015.

This assessment report was undertaken to provide Canadian jurisdictions, regulators and policy makers with a comprehensive evaluation of the potential health effects of gasoline emissions.[4] It is intended that the report be used to inform further efforts to mitigate emissions and population health impacts associated with this key source of air pollution in Canada. Overall, it is concluded that air pollutants from gasoline sources continue to pose a risk to human health in Canada.

[1] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=65
[2] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/DetailReg.cfm?intReg=18
[3] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=81
[4] The content of this document is based on information presented in a comprehensive supporting document prepared by Health Canada.

Human Health Risk Assessment for Gasoline Exhaust

Gasoline engines are an integral component of the North American way of life, present on every roadway in every neighbourhood. Primarily fuelled by petroleum-based gasoline, these internal combustion engines are also known as spark ignition (SI) engines because a spark is required to initiate the combustion process. SI engines were first developed in the late 1800s in Europe and have many current applications. In Canada, and more broadly throughout North America, these engines are predominantly used in on-road passenger vehicles, light trucks and motorcycles. Other uses include various off-road applications such as all-terrain vehicles, snowmobiles, outboard motors for boats, and lawn and garden equipment. In Canada, gasoline vehicles represent 92% (22.2 million vehicles) of on-road vehicles and 87% (13.6 million) of off-road engines or equipment.

Gasoline engine exhaust (GE) is a complex mixture of both particulate and gaseous pollutants. Although the emissions from an individual gasoline engine may be relatively low and have been drastically reduced over time by successive regulations, GE contributes to air pollution in Canada, due to the high prevalence of these engines in both on-road vehicles and off-road equipment. Because of the extensive use of gasoline engines in Canada, their emissions are ubiquitous and human exposure to gasoline emissions is widespread. GE as a mixture and constituent components of GE have been studied to elucidate their impacts on human health.

Air pollutants, including those emitted from gasoline engines or produced secondarily in the atmosphere from primary gasoline emissions, are associated with population health impacts. GE is an important source of key criteria air contaminants (CACs), including primary and secondary fine particulate matter ($PM_{2.5}$), ozone (O_3) and nitrogen dioxide (NO_2), the health effects of which have been extensively studied in the scientific literature and which have been reviewed in depth elsewhere by Health Canada (Health Canada 2013, 2016a) and other international regulatory agencies. It is recognized that these air pollutants cause adverse health outcomes, such as cardiorespiratory mortality, asthma exacerbation and hospitalization, and adverse cardiac outcomes. Importantly, the evidence indicates that there is no exposure threshold for many of these health effects: that is, any incremental increase in air pollutant concentration is associated with an increase in risk of the adverse health outcome. For example, it has been estimated for 2011 that ambient concentrations of $PM_{2.5}$ above natural background levels were associated with approximately 5600–9500 premature mortalities, 1400 hospital admissions and 3900 emergency department visits in Canada (Stieb et al. 2015). Gasoline-powered engines and vehicles are a key source of air pollution in Canada and are expected to be responsible for air-pollution-related health impacts in terms of both mortality and morbidity, resulting in considerable societal costs. Previously, Health Canada estimated that diesel emissions from mobile sources are associated with 710 premature mortalities annually, and over $5 billion in health and welfare costs (Health Canada 2016b).

GE constituents also include individual air toxics, such as benzene, 1,3-butadiene, formaldehyde, acetaldehyde and polycyclic aromatic hydrocarbons (PAHs). These substances have been recognized as human carcinogens or likely human carcinogens by Health Canada and other international regulatory agencies (Environment Canada and Health Canada 1993, 1994, 2000a, 2000b, 2001; Health Canada 2006; IARC 2010, 2012, 2013).

This report, Human Health Risk Assessment for Gasoline Exhaust, is a comprehensive review and analysis of the potential adverse health effects associated with gasoline fuel use in Canada. The report focuses on emissions from gasoline vehicles and engines used in on-road and off-road mobile applications (excluding rail, marine and aviation applications). Two distinct approaches are used to

assess the health risks associated with GE in Canada and are presented in this document as Parts A and B. Part A provides a review of scientific studies that have examined the health effects associated with exposure to GE as a mixture. Part B provides an analysis of the population health impacts associated with the contribution of GE to ambient air pollution. This report does not address the effect of gasoline fuel use on greenhouse gas emissions in Canada. In addition, this report does not address the health risks of gasoline fuel itself, which is under review as part of the Chemicals Management Plan of the Government of Canada and will be reported elsewhere.

Part A includes a review of gasoline fuels, engines and emissions, a review of exposure to GE, and a weight of evidence analysis of health effects associated with exposure to GE as a mixture. For the latter, only studies that evaluated GE as a mixture were reviewed; studies on the health effects of individual GE constituents (e.g. benzene, NO_2 or $PM_{2.5}$) were not considered in this assessment, as these compounds have previously been reviewed by Health Canada and their health effects are well documented, as discussed above. In addition, studies examining the health effects of exposure to traffic emissions in general were not reviewed, as those studies did not distinguish between exposure to GE and diesel emissions. Overall, the database of studies that have examined the health effects of exposure to GE as a mixture is relatively limited in study quantity and quality, with many older studies and significant limitations in the design of many studies. The weight of evidence analysis presented in Part A provides an evaluation of this literature database, the findings of which are in addition to the extensive evidence base regarding the health effects of individual constituents of GE and of compounds produced secondarily in the atmosphere from GE, such as $PM_{2.5}$, O_3, NO_2, and air toxics.

Part B provides a quantitative assessment of the contribution of on-road and off-road gasoline mobile source emissions to air pollutant levels in Canada and the population health impacts associated with that incremental contribution to specific individual air pollutants, including CACs and some air toxics. The gasoline mobile source emissions that were considered in this analysis include exhaust, evaporative and tire-wear/brake lining (TWBL) emissions from gasoline vehicles and engines. The analysis of population health impacts presented in Part B is conducted in a stepwise manner with the use of computer modelling to (1) estimate air pollutant emissions from gasoline vehicles and equipment in Canada, (2) estimate the impact of those emissions on ambient concentrations of CACs and air toxics across the country, and (3) estimate population health impacts resulting from the contribution of gasoline emissions to air pollution levels and the societal costs of those impacts. This type of analysis is possible because the relationship between emissions and ambient concentrations of individual pollutants is well understood, many of the health effects of CACs are well characterized in the scientific literature and studies have quantified the health risks associated with incremental changes in air concentrations of individual pollutants. Part B is complementary to the traditional risk assessment approach presented in Part A of this document.

This assessment report was undertaken to provide Canadian jurisdictions, regulators and policy makers with a comprehensive evaluation of the potential health effects of gasoline emissions. It is intended that the report be used to inform further efforts to mitigate emissions and population health impacts associated with this key source of air pollution in Canada.[1]

[1] The content of this document is based on information presented in a comprehensive supporting document prepared by Health Canada.

Part A – Human health risk assessment for gasoline exhaust

1 Gasoline fuels, engines and emissions

Gasoline fuel is designed for use in SI engines. SI engines are internal combustion engines that use a spark to ignite the air and fuel mixture in the combustion chamber. SI engines are also commonly called gasoline engines, although they can operate on a variety of non-gasoline fuels, such as ethanol or natural gas. Gasoline engines are the main source of power for passenger cars, motorcycles, and many other on-road (small commercial fleets) and off-road applications (e.g. lawn and garden equipment) (IARC 2013). Gasoline fuels intended for on-road vehicles and off-road engines (excluding aviation gasoline) are generally composed of hydrocarbons (HCs) containing 4 to 12 carbon molecules (C4–C12), which include saturated HCs (i.e. paraffins or alkanes), unsaturated HCs (i.e. olefins or alkenes) and aromatics (HC rings) (Speight 2015). The exact composition of HC compounds is variable, owing to different sources of crude oil with specific characteristics that are refined and blended to meet regulatory requirements. Additives, which generally make up less than 2% by volume of the final fuel, are blended downstream of refineries and can also influence the fuel composition. Additives have several purposes, such as extended storage stability and improved performance. They include detergents, biocides, octane improvers, antifreeze and oxygenates. Additive packages can vary between blenders and retailers. Ethanol, a renewable fuel and also an oxygenate, is a fuel component. In Canada, ethanol comprises up to 10% by volume of gasoline fuel and tends to vary according to fuel specification (e.g. regular and premium) and season (e.g. higher in summer than winter).

Key characteristics of a gasoline fuel are its volatility and octane number. Fuel volatility is associated with the composition of gasoline vapours in the fuel tank and the fuel delivery system (NRC 1999), and it is tailored according to meteorological (e.g. winter and summer temperatures), operational (e.g. efficient cold starts) and environmental or health (e.g. reduced evaporative emissions in summer) considerations. The octane number reflects a fuel's resistance to self-ignition (Stone 2012). High octane fuels enable the use of high compression ratios, which increase power output and fuel efficiency.

Fuel quality in Canada is ensured via provincial and federal regulations and also through commercial processes and specifications under the guidance of the Canadian General Standards Board (CGSB). The CGSB is a federal government organization that develops standards in support of the economic, regulatory, health, safety and environmental interests of government, industry and consumers.[1] The standards define properties that will be required of any acceptable gasoline blend regardless of its chemical composition. For example, the CGSB standard for *Automotive Gasoline* (CAN/CGSB-3.5-2011) and the one for *Oxygenated Automotive Gasoline Containing Ethanol (E1-E10)* (CAN/CGSB-3.511) apply to grades of gasoline and oxygenated gasoline, respectively, intended for use in SI engines under a range of environmental conditions. Fuel standards are generally developed based on functional engine and emission control technology performance requirements. They are not chemical-specific requirements, but gasoline blend standards may include limits for benzene, sulphur, lead and phosphorus.

SI engines are available as two-stroke and four-stroke models. The number of strokes refers to the time a piston travels up and down the cylinder, which happens twice per crankshaft revolution, before the fuel is combusted. Most gasoline vehicles are equipped with four-stroke SI engines. Two-stroke SI

[1] www.tpsgc-pwgsc.gc.ca/ongc-cgsb/index-eng.html

engines are commonly used in non-road applications, such as chainsaws and lawnmowers, where weight, simplicity and output are more important than fuel economy and emission control considerations. Two-stroke engines are less efficient in terms of fuel efficiency and pose additional challenges for exhaust emission control (Stone 2012).

Gasoline engines in the current automotive fleet use mainly two types of fuel injection strategies, port fuel injection (PFI) and direct injection (gasoline direct injection, or GDI). PFI engines are the predominant type currently in use, but the GDI technology is expected to gain a higher share of the market in the near future due to its higher fuel efficiency (US EPA 2016). PFI and GDI systems differ in terms of air and fuel mixing times and fuel vaporization. In PFI engines, fuel is injected upstream of the cylinder, whereas fuel is injected directly into the cylinder in GDI engines (MECA 2013a). Three-way catalytic (TWC) systems are used for simultaneously reducing the pollutants carbon monoxide (CO), nitrogen oxides (NOx) and HCs (the latter are volatile organic compounds [VOCs]). TWCs are the principal emission control technology that is used in gasoline engines and vehicles; 95% of the gasoline vehicles sold in the world today are equipped with a TWC system (including all new gasoline vehicles sold in Canada and the US; MECA 2013b). Gasoline particulate filters were recently developed to control PM emissions from GDI engines, but commercial applications are currently limited to a few vehicle models.

Emissions from gasoline engines or vehicles originate from exhaust (i.e. combustion) and non-exhaust (e.g. mechanical wear, volatilization) sources. Exhaust emissions are generally the dominant source of emissions. Gasoline exhaust is characterized by a variable composition of gaseous and particulate pollutants, which will influence its impact on ambient air quality (e.g. aerosols and oxidants) and health (i.e. toxicity). Individual constituents are emitted at different rates depending on several factors, such as engine type, engine maintenance, model year or usage (i.e. kilometres driven), fuel and lubricating oil quality, emission control technologies, vehicle operating conditions (e.g. cold start, load and speed) and environmental conditions (e.g. temperature, road grade) (Fujita et al. 2007). Their composition depends on several factors, such as fuel characteristics and engine or vehicle technologies. Evaporative emissions are released into the atmosphere owing to leaks throughout the fuel system (i.e. fuel tanks, hoses and other engine components) or uncontrolled venting (Gentner et al. 2009, 2013). Gasoline vehicles are more prone to evaporative emissions than diesel vehicles, as the vapour pressure of gasoline is relatively high. TWBL emissions, mineral dust resuspension and road surface wear are generally the most important components of non-exhaust vehicle emissions (Dall'Osto et al. 2014; Grigoratos and Martini 2015; Pant and Harrison 2013). Although considerable data and extensive scientific literature exist for exhaust emissions, non-exhaust emissions are more difficult to assess, owing to insufficient data.

Key pollutants emitted from gasoline-fuelled mobile sources are CO, NOx and VOC emissions because of the magnitude of their releases, the contribution of NOx and VOCs to the production of secondary PM in the atmosphere, and their association with health impacts. Primary particulate emissions from gasoline emissions, albeit of low mass on a per vehicle or engine basis, are also a key health concern.

It is challenging to identify and quantify the variety of chemical species found in GE. PM generally consists of $PM_{2.5}$ and ultrafine particles (UFPs), which are released directly or formed secondarily via

gaseous precursors in exhaust and evaporative emissions.[1] The small size of exhaust-related particles implies a very large surface area on a per mass basis with a potential to adsorb large amounts of compounds, including organic and sulphur compounds. NOx includes nitric oxide (NO) and NO_2. Following combustion, NOx is generally dominated by NO, which is gradually converted to NO_2 following its release. VOCs refer to organic compounds that may be found in the gaseous or aerosol phase under ambient conditions. This group of compounds includes hundreds of different chemical species, some of which are recognized for their toxicity to humans, such as benzene, formaldehyde and acetaldehyde.

Air pollutant emissions from transportation sources are controlled through fuel quality standards and vehicle and engine emission standards. Federal provisions to control both fuels and vehicle and engine emissions are included in the *Canadian Environmental Protection Act, 1999* (CEPA 1999).[2] Part 7 Division 4 of CEPA 1999 is dedicated to *Fuels*, whereas Part 7 Division 5 focuses on *Vehicle, Engine and Equipment Emissions*. In addition, the *Regulations Amending the Benzene in Gasoline Regulations*, which target control of a toxic substance, were published under Part 5 of CEPA 1999. The Act provides Environment and Climate Change Canada (ECCC) the legislative authority to control emissions from on-road vehicles and from engines used in off-road applications. Engines used in aircraft, trains and large marine vessels are administered by Transport Canada under separate federal legislation.

Gasoline fuel regulations, such as the *Benzene in Gasoline Regulations*,[3] apply to those who produce, import, blend or sell gasoline fuels. These regulations often include a requirement for some type of reporting to ECCC regarding specific constituents or additives, either with or without volume thresholds. More information on fuel regulations is available on the CEPA website.[4]

Several regulations have been adopted since 2000 to limit emissions from the operation of SI engines and vehicles. These regulations require that new vehicles, engines or equipment conform to the prescribed standard. On-road vehicle regulations include requirements specifying standards to be met for a specified minimum service period (useful life) and stipulating the use of on-board diagnostic systems. Useful life requirements also exist for off-road SI engines. The adoption of increasingly stringent regulations over time has resulted in considerable reductions in engine and vehicle emissions, especially for regulated pollutants such as $PM_{2.5}$, NOx and CO (e.g. Liu and Frey 2015). Vehicle emission regulations targeting light-duty vehicles (LDVs) have also become fuel neutral; i.e. they apply to all LDVs regardless of fuel type. The Canadian on-road regulations align with the federal emission standards of the United States Environmental Protection Agency (US EPA) in light of the integrated North American motor vehicle market.

An example of a vehicle or engine regulation under CEPA 1999 is the *On-Road Vehicle and Engine Emission Regulations (on-road regulations)*.[5] The *on-road regulations* introduced more stringent national emission standards for on-road vehicles and engines beginning with the 2004 model year. On July 29, 2015, the *Regulations Amending the On-Road Vehicle and Engine Emission Regulations and Other Regulations Made Under the Canadian Environmental Protection Act, 1999* (SOR/2015-186) were

[1] For regulatory purposes, exhaust particulates are currently defined as all solid or liquid matter collected at temperatures of 47°C ± 5°C on a filter surface.
[2] www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=26A03BFA-1
[3] SOR/97-493; https://ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=1
[4] www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=26A03BFA-1
[5] SOR/2003-2; http://www.ec.gc.ca/lcpe-cepa/eng/regulations/DetailReg.cfm?intReg=65

adopted.[1] The amendments introduce stricter limits on air pollutant emissions from new passenger cars, light-duty trucks and certain heavy-duty vehicles (HDVs), beginning with the 2017 model year, in alignment with the US EPA Tier 3 vehicle standards.[2] Once fully phased-in in 2025, the standards for air pollutant emissions from new vehicles and engines will be up to 80% more stringent than the current light-duty on-road standards that were adopted in 2004.[3]

Emissions from off-road engines were not federally regulated prior to CEPA 1999. ECCC signed an agreement with engine manufacturers for the supply in Canada of engines meeting the US EPA Tier 1 standards starting with the 2000 model year. The *Off-Road Small Spark-Ignition Engine Emission Regulations*, under the CEPA framework, established emission standards for 2005 and later model year small spark-ignition (SSI) engines rated up to 19 kW (25 hp).[4] SSI engines are typically gasoline-fuelled engines found in lawn and garden machines, in light-duty industrial machines (e.g. generators, welders and pressure washers) and in light-duty logging equipment (e.g. chainsaws and log splitters).

In 2017, ECCC adopted the *Regulations Amending the Off-Road Small Spark-Ignition Engine Emission Regulations* in order to maintain alignment with more stringent Phase 3 US federal exhaust emission standards.[5] Compared with the Phase 2 standards, the Phase 3 standards reduce HC + NOx emissions by 33–38% for non-handheld engines, whereas they remain the same for handheld engines.[6] The amendments will apply to the 2018 and later model year SSI engines.

Greenhouse gas (GHG) emission regulations are also relevant to air quality considerations, as they can have an impact on both fuel efficiency and non-GHG emissions, such as CACs and air toxics. The *Passenger Automobile and Light Truck Greenhouse Gas Emission Regulations*[7] aim to align with US federal standards (US EPA 2016). The regulations apply to a company or person that manufactures or imports new 2011 and later model year passenger automobiles and light trucks. A company's fleet average standard is determined based on the size (i.e. footprint) and the number of vehicles it sells in a given model year. The fleet average GHG emission standards become progressively more stringent with each new model year from 2012 to 2025. As a result of the regulations, company fleet average 2025 model year vehicles are expected to emit 50% less GHG than 2008 models (US EPA 2016).

2 Exposure to gasoline exhaust

Most Canadians experience exposure to traffic-related air pollution, including GE, on a daily basis. Given the ubiquity of gasoline-powered engines throughout Canada, exposure to GE is widespread and, in

[1] www.gazette.gc.ca/rp-pr/p2/2015/2015-07-29/html/sor-dors186-eng.php
[2] www.epa.gov/regulations-emissions-vehicles-and-engines/regulations-smog-soot-and-other-air-pollution-passenger
[3] Cleaner vehicles and fuels for Canadians - Final Tier 3 vehicle and fuel standards; www.canada.ca/en/news/archive/2015/07/cleaner-vehicles-fuels-canadians-final-tier-3-vehicle-fuel-standards.html
[4] Upon adoption, the *Off-Road Small Spark-Ignition Engine Emission Regulations* aligned with the US EPA regulations, as defined in Title 40, Part 90, of the US CFR (www.law.cornell.edu/cfr/text/40/part-90).
[5] http://ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=FB004F2D-1
[6] These standards are outlined in Part 1054, Title 40 of the CFR, sections 103, 105 and 107 of the US CFR (www.law.cornell.edu/cfr/text/40/1054.103).
[7] http://laws-lois.justice.gc.ca/eng/regulations/SOR-2010-201/

most areas, unavoidable. This is particularly true for the many Canadians living in urban areas or in close proximity to a major roadway: it is estimated that approximately 2, 4 and 10 million Canadians live within 50, 100 and 250 m, respectively, of a major road (Evans et al. 2011). The complex and variable nature of GE makes assessing general population exposure to GE a difficult task, and it has been poorly studied. For this document, several approaches were taken to provide insight into Canadian exposures to GE. Firstly, constituents of GE were considered for their value as GE surrogates. Ambient concentrations of those compounds were examined for different site types, including traffic-influenced locations. The relative contributions of gasoline sources to transportation emissions and ambient concentrations of key air pollutants were also examined, in the latter case using source apportionment methodologies. More specifically relating to exposure, the concentrations of key air pollutants in microenvironments impacted by GE were reviewed from the scientific literature. No studies were identified that estimated personal exposures to GE.

The following pollutants, which are associated with traffic environments, were considered as potential GE surrogates: CO, NOx, $PM_{2.5}$, VOCs and PAHs. Each of these surrogates has the limitation that none is a unique marker of GE and all are confounded by other sources, including diesel exhaust (DE). However, CO is considered the best available candidate, for the following reasons: CO concentrations are much higher in commuter traffic settings and when following high-emitting gasoline vehicles, compared with settings away from highways (Fujita et al. 2011); CO is easily measured and has been known to vary with other constituents of GE (such as benzene, toluene, ethylene, and xylenes (BTEX)) over space and time; and in urban centres, ambient CO is predominantly attributable to mobile sources.

Ambient concentrations of potential GE surrogates are available from the National Air Pollutants Surveillance Program (NAPS). The program is not generally designed to quantify emissions from specific sources or to determine high-resolution pollutant gradients in complex environments, such as urban cores; however, there are air pollutant monitoring stations in locations that are more influenced by traffic or point sources, and other stations that have non-specific sources. In most cases, stations influenced by point sources had the highest air pollutant concentrations, but traffic-influenced stations also demonstrated elevated levels of CO, NO_2 and $PM_{2.5}$. For $PM_{2.5}$, a 25% concentration increase was observed during rush hour peaks, and concentrations were 17% lower on the weekend (Environment Canada 2011). In general, surrogate species measured at stations near large urban populations had higher 1-h daily maximum concentrations than those stations situated near areas with smaller populations. Estimates allocating pollutant concentrations to GE or DE were not available.

Estimates of Canadian air pollutant emissions from transportation sources are provided by ECCC's Air Pollutant Emission Inventory (APEI). GE emissions are an important source of transportation-related air pollutant emissions, particularly for CO and VOCs (80–90% of total transportation emissions). In contrast, diesel-powered vehicles are the dominant transportation source of NOx and $PM_{2.5}$ emissions (40–50% of total transportation emissions). On average between 2010 and 2014, the available data from the APEI show that nationally, on-road and off-road GE emissions contribute approximately half of total anthropogenic CO emissions, 18% of total anthropogenic VOC emissions, and 10% of total anthropogenic NOx emissions. GE emissions are responsible for less than 1% of $PM_{2.5}$ and PAH emissions.

Receptor modelling tools are available to estimate contributions of GE to pollutant levels measured at central site monitoring stations. However, since traffic characteristics (e.g. gasoline/diesel fleet mix, fleet age, road network) and other contributing sources vary from one location to another, model-estimated source contributions of GE to ambient air levels will also necessarily vary from one region to

another. Thus, source apportionment model results are best applied to regional-scale data on a study-by-study basis, with results generally not applicable to other regions significantly different from the modelled study area.

Several studies conducted in Canada reported GE contributions specifically, splitting mobile sources into various components (e.g. GE, DE, gasoline vapour). Brook et al. (2007) determined that 13.1% of $PM_{2.5}$ in Southern Ontario was contributed by GE using the US EPA UNMIX model. By comparison, Lee et al. (2003) did not distinguish between DE and GE: rather, the Positive Matrix Factorization model split motor vehicle exhaust into two categories: motor vehicle exhaust plus road dust and motor vehicle exhaust plus road salt. Overall, both models determined that motor-vehicle-related emissions were responsible for about 20% of the $PM_{2.5}$ (Brook et al. 2007). In Windsor, Li (2013) used chemical mass balance to determine VOC contributions to VOCs measured at regional monitoring stations. Vehicular contributions were broken down into three sources: GE, DE, and gasoline vapour, which were responsible for 20%, 7%, and 15% of the total VOCs.

Concentrations of GE pollutants are highly variable from one location to another, due to their non-uniform distribution through space and time, as well as the fact that pollutants are transported and transformed in the atmosphere. These locations are referred to as microenvironments. An exposure microenvironment can be defined as a well-characterized and relatively homogeneous location with respect to pollutant concentrations, in which human contact with a pollutant occurs for a specified period of time. Overall, research data indicate that proximity to roadways with heavy traffic can significantly affect air quality and exposure to traffic-related pollutants in both indoor and outdoor microenvironments. Three key microenvironment impacts by GE are considered here: in-vehicle, near-road, and indoor.

Of the studies available, the Urban Transportation Exposure Study (UTES) conducted by Weichenthal et al. (2015) is the most relevant for Canadian in-vehicle exposure to GE, as it was conducted recently (2010 to 2013) in Canada's three largest cities: Toronto, Montréal, and Vancouver. In-vehicle air pollutant concentrations varied substantially between commutes but were similar for most pollutants between cities, except for $PM_{2.5}$ (median 8.65 $\mu g/m^3$, 4.07–56.2 $\mu g/m^3$) and NO_2 (median 49.5 ppb, 6.7–153 ppb), which were higher in Toronto than in Vancouver during summer months. Weichenthal et al. (2015) presented ratios of in-vehicle concentrations to outdoor vehicle rooftop concentrations measured concurrently. In general, in-vehicle concentrations were similar to out-vehicle concentrations and ratios were mostly below 1. For NO_2 and $PM_{2.5}$, there was no systematic difference between in-vehicle and out-vehicle concentrations. For UFPs, black carbon (BC), and CO, concentrations in-vehicle were lower than out-vehicle concentrations and for BTEX, in-vehicle concentrations were higher than out-vehicle concentrations. It was noted that in-vehicle BTEX could be influenced by in-vehicle sources of VOCs such as adhesives. Results showed that regional outdoor concentrations of $PM_{2.5}$ (median 4.02 $\mu g/m^3$, 0.663–31.3 $\mu g/m^3$) and NO_2 (median 15.0 ppb, 5.63–28.2 ppb) were generally low during commuting periods and were consistently below in-vehicle concentrations. In general, air pollutant concentrations were comparable to those reported in similar microenvironments in North America (Fujita et al. 2014; Weichenthal et al. 2008; Zielinska et al. 2012) and Australia (Hinwood et al. 2006). Notably different were CO concentration levels, which were higher in all three Canadian cities than those measured elsewhere and were more comparable to levels of CO measured in-vehicle in underground parking garages in Houston, Atlanta, and Chicago (Zielinska et al. 2012). In-vehicle concentrations measured in the UTES provide a reasonable range of values typically encountered by Canadian commuters.

Karner et al. (2010) conducted a meta-analysis of 41 monitoring studies investigating the decline of traffic-related air pollutant concentrations in relation to the distance from roadways. After normalizing the pollutant measurements to edge-of-road concentrations,[1] they found that most air pollutant concentrations decayed to background levels at a distance of between 115 and 570 m from the roadway (Karner et al. 2010). Although personal exposure levels are influenced by the mode of transport, traffic density, and type of vehicle, pollutant concentrations to which commuters are exposed are generally lower for pedestrians and cyclists in near-road microenvironments compared with in-vehicle exposures (Adams et al. 2001; Boogaard et al. 2009; Kaur et al. 2007; Weichenthal et al. 2012, Zielinska et al. 2012). However, personal exposure of pedestrians and cyclists is often higher when minute ventilation is considered, due to the increase in breathing rate from increased activity. In addition, the location of the cycling lane or sidewalk can influence the exposure of an active commuter to GE pollutants.

Canadians of every age group spend the majority of their time indoors, whether at home, in school or at work (Matz et al. 2014). Indoor GE pollutant levels vary based on traffic density and composition, along with meteorological conditions and land use patterns. As previously mentioned, the concentrations of GE-related pollutants also decrease with distance from their source (e.g. roadways). Therefore, residing, working or attending school located close to busy roads or highways may result in increased exposure to GE pollutants.

Notwithstanding the limitations of identifying specific GE markers of air pollution and associated human exposures to GE, studies are generally consistent in showing that pollutant concentrations in microenvironments influenced by traffic are higher than concentrations reported at background locations not affected by mobile source emissions.

Given the complex makeup, fate and transport of GE emissions, measuring or estimating ambient concentrations of GE components is difficult. For example, temporal (e.g. continuous measurements and discrete samples) and spatial (e.g. density of monitoring stations) resolutions may influence pollutant level measurements and make the use of central monitoring sites challenging for GE exposure assessment. The multiple sources of pollutants associated with GE also limit the use of central monitoring sites, such as those in the NAPS network, as non-gasoline sources may dilute or blur the GE signal. Furthermore, variations in individual or population time–activity patterns and the variability in air quality data for different microenvironments limit the use of central monitoring stations to accurately characterize and quantify GE exposures. In order to improve upon the use of central monitoring station data in air pollution exposure studies, several types of exposure models of varying complexity have been developed to assess personal exposures to traffic-related air pollutants. Jerrett et al. (2005a) classified these models into six groups: proximity-based assessments, statistical interpolation, land use regression (LUR) models, line dispersion models, integrated emission-meteorological models, and hybrid models. Proximity assessments use distance of a subject to an air pollution source (such as distance between residence and roads) as a substitute for population exposure and have been used to assess variations in intraurban exposure. While these models are commonly used to derive estimates for population exposure to traffic-related air pollutants, population exposure to GE specifically has not been assessed using these tools.

[1] Edge-of-road concentrations: the relative concentration of pollutants in the near-road zone compared with concentrations measured at the roadway edge, which is the point of expected maximum roadway influence.

Currently, the most widely cited exposure model with which to assess inhalation exposures to air toxics from outdoor sources in North America is the Hazardous Air Pollutant Exposure Model (HAPEM), developed by the US EPA. However, HAPEM estimates of population exposures to GE were not reported as part of the US National Air Toxics Assessment (US EPA 2007), and the Canadian data necessary to undertake such an analysis are unavailable. In Part B of this document, the impact of Canadian on-road and off-road gasoline emissions on ambient levels of CO, NO_2, O_3, $PM_{2.5}$ and sulphur dioxide (SO_2) is estimated using photochemical modelling techniques, and the population health impacts of the incremental contributions of GE to air pollution are quantified.

Although GE sources and exposure are pervasive in modern society, data are currently insufficient to estimate the personal exposure of the Canadian population to GE. There is a notable lack of GE exposure data associated with the use of off-road applications despite a large market in consumer lawn and garden equipment, agricultural and industrial vehicles, and recreational vehicles. However, it is clear that populations residing in urban centres are exposed to higher pollutant concentrations than populations residing in rural areas, and that proximity to GE traffic sources is associated with elevated exposure to multiple pollutants. Data suggest that GE emissions contribute considerably to transportation emissions of some air pollutants, notably CO and VOCs. Evidence also indicates that transportation sources are associated with increased air pollutant concentrations in microenvironments influenced by traffic, including in-vehicle, near-road, and indoor microenvironments. More importantly, many factors have been shown to influence GE air pollutant concentrations (e.g. vehicle type, meteorology) and population exposure parameters (e.g. time–activity patterns), which underlines the need for temporally and spatially resolved data for representative exposure estimates.

3 Health effects of gasoline exhaust

A detailed review of the scientific literature pertaining to GE as a mixture was conducted with the objective of identifying and characterizing the human health effects associated with ambient exposure to emissions from gasoline engines. The literature review for health effects was limited to studies published by December 15, 2014. A comprehensive review of the carcinogenicity of GE was recently conducted by the International Agency for Research on Cancer (IARC) (IARC 2013) and was considered in the preparation of this report. Only studies that evaluated GE as a mixture were reviewed; studies on the health effects of individual GE constituents (e.g. benzene, NO_2 or $PM_{2.5}$) were not considered, as these compounds have previously been extensively reviewed by Health Canada and their health effects are well documented (Environment Canada and Health Canada 1993, 1994, 2000a, 2000b, 2001; Health Canada 2006, 2013, 2016a). Studies on the health effects of traffic pollution in general (mixed GE and DE emissions) or of general air pollution were also not considered within the scope of this review. Epidemiological studies were limited to those examining groups predominantly exposed to GE (e.g. taxi drivers) or general population studies with an exposure metric directly linked to GE. Toxicological studies that examined exposure to GE, GE particles or GE extracts were considered within the scope of this review.

3.1 Weight of evidence for determination of causality

Evidence from epidemiological (cancer and non-cancer), controlled human exposure and toxicological (animal and *in vitro*) studies is assessed using a weight of evidence approach in order to determine the causal role of GE exposure in the identified adverse health effects. Epidemiological studies have focused primarily on the development of cancers (specifically bladder/urothelial, lung and lymphohematopoietic cancers) in association with GE exposure. In addition, a small number of epidemiological studies

investigated various non-cancer endpoints. Controlled human exposure to GE was examined in one study assessing cardiovascular endpoints. The majority of the toxicological evidence was composed of animal toxicity studies that examined a variety of different health effects, with greater emphasis on respiratory and carcinogenicity health outcomes. *In vitro* toxicity assays have focussed primarily on genotoxicity, but other endpoints such as cytotoxicity and altered gene expression were also assessed. For this assessment, studies addressing exposures to all types of GE were considered for evaluation, including emissions from on-road vehicles (e.g. cars and motorcycles) and non-road engines and equipment (e.g. lawn mowers, chainsaws and forklifts). The composition of GE from these multiple sources can vary, which may influence the relative health effects of the emissions; however, all studies of GE (regardless of engine type or source) were considered to contribute to the overall understanding of the health effects of GE exposure.

In order to evaluate the overall weight of evidence presented by published findings and to determine the causal role of GE in the development of specific health effects, consideration is given to the criteria of causal inference proposed by Bradford Hill (1965) and widely used in reviews of epidemiological literature. The criteria used here, which are considered collectively in the evaluation of the evidence of GE-related health effects, are:

- *Biological plausibility*: there is a plausible mechanism between GE exposure and the effect;
- *Temporal sequence*: the exposure precedes the health outcome;
- *Consistency of the association*: the association is reported by different researchers, for different study designs, in different populations, etc.;
- *Coherence*: evidence from toxicological, controlled human exposure and epidemiological studies of various types provides support for the effects observed and potential modes of action;
- *Biological gradient*: there is evidence of an exposure–response relationship;
- *Strength of the association*: the greater the magnitude of the risk estimate, the less likely that the relationship is due to uncontrolled residual confounding.

The above considerations are used to inform a conclusion as to whether the association between GE exposure and a given health effect or related set of health effects is a causal relationship, likely to be a causal relationship, suggestive of a causal relationship, inadequate to infer a causal relationship or not likely to be a causal relationship. The definition of each of these causal determinations is derived from the US EPA (2015a) determinations, which are described in Table 3-1. It is important to note that these conclusions reflect the available evidence from studies that examined the health effects of GE as a mixture. These conclusions do not preclude in any way the previously recognized carcinogenic, respiratory, cardiovascular, immunological, reproductive/developmental and neurological effects of individual constituents of GE or of compounds produced secondarily in the atmosphere from GE constituents.

Table 3-1. Weight of evidence for determination of causality

Relationship	Description
Causal relationship	Evidence is sufficient to conclude that there is a causal relationship with relevant pollutant exposures (e.g. doses or exposures generally within one to two orders of magnitude of recent concentrations). That is, the pollutant has been shown to result in health effects in studies in which chance, confounding, and other biases could be ruled out with reasonable confidence. For example: (1) controlled human exposure studies that demonstrate consistent effects, or (2) observational studies that cannot be explained by plausible alternatives or that are supported by other lines of evidence (e.g. animal studies or mode of action information). Generally, the determination is based on multiple high-quality studies conducted by multiple research groups.
Likely to be a causal relationship	Evidence is sufficient to conclude that a causal relationship is likely to exist with relevant pollutant exposures. That is, the pollutant has been shown to result in health effects in studies where results are not explained by chance, confounding, and other biases, but uncertainties remain in the evidence overall. For example: (1) observational studies show association, but copollutant exposures are difficult to address and/or other lines of evidence (controlled human exposure, animal, or mode of action information) are limited or inconsistent, or (2) animal toxicological evidence from multiple studies from different laboratories demonstrates effects, but limited or no human data are available. Generally, the determination is based on multiple high-quality studies.
Suggestive of, but not sufficient to infer, a causal relationship	Evidence is suggestive of a causal relationship with relevant pollutant exposures but is limited because chance, confounding, and other biases cannot be ruled out. For example: (1) when the body of evidence is relatively small, at least one high-quality epidemiologic study shows an association with a given health outcome and/or at least one high-quality toxicological study shows effects relevant to humans in animal species, or (2) when the body of evidence is relatively large, evidence from studies of varying quality is generally supportive but not entirely consistent, and there may be coherence across lines of evidence (e.g. animal studies or mode of action information) to support the determination.
Inadequate to infer a causal relationship	Evidence is inadequate to determine that a causal relationship exists with relevant pollutant exposures. The available studies are of insufficient quantity, quality, consistency or statistical power to permit a conclusion regarding the presence or absence of an effect.
Not likely to be a causal relationship	Evidence indicates there is no causal relationship with relevant pollutant exposures. Several adequate studies, covering the full range of levels of exposure that human beings are known to encounter and considering at-risk populations and life stages, are mutually consistent in not showing an effect at any level of exposure.

US EPA (2015a)

3.1.1 Carcinogenicity

3.1.1.1 Evidence from epidemiological studies

The potential carcinogenicity of GE has been examined in many epidemiological studies. The majority of the studies have evaluated lung cancer (11 studies), bladder cancer (12 studies), and lymphohematopoietic cancers (10 studies). Overall, most of the studies reviewed were based on occupations with exposure to gasoline engine emissions, such as taxi drivers, chauffeurs, policemen, and forestry and logging workers. Compared with the general public, people employed in these occupations are anticipated to have greater exposures to GE. Most studies relied on job title to classify exposure,

while a small number of studies employed a job exposure matrix (JEM) to semi-quantitatively estimate exposures. A limited number of studies examined childhood cancers in relation to elevated GE exposure.

3.1.1.1.1 Lung cancer

For lung cancer, three cohort studies (Borgia et al. 1994; Forastiere et al. 1994; Guo et al. 2004a), one nested case–control study (Forastiere et al. 1994), and seven case–control studies (Hansen et al. 1998; Hayes et al. 1989; Parent et al. 2007; Schoenberg et al. 1987; Siemiatycki et al. 1988; Tse et al. 2011; Villeneuve et al. 2011) were evaluated. The cohort studies reported risk estimates ranging from 0.91 to 1.31 for men and from 2.73 to 5.18 for women in GE-influenced occupations. In these studies, a consistent association between lung cancer and GE exposure was not observed for each of the occupational groups evaluated. Of these estimates, only the increase in lung cancer risk for women in the bus/tram service worker occupational group reached a level of significance (Guo et al. 2004a), and notably this group was not co-exposed to DE. An increase in risk was not observed with longer employment durations in the cohort studies. None of the cohort studies included adjustments for smoking or exposure to other confounders (e.g. in particular DE, a known carcinogen, which also contributes to traffic-related emissions), limiting the weight of evidence from these studies.

The case–control studies evaluated provide limited evidence of an association between GE exposure and lung cancer. For the five studies that classified exposure based on employment in certain occupational groups (e.g. taxicab driver), odds ratios (ORs) ranged from 0.65 to 2.88 (Forastiere et al. 1994; Hansen et al. 1998; Hayes et al. 1989; Schoenberg et al. 1987; Villeneuve et al. 2011). Of these studies, non-significant increases were reported in three studies (Forastiere et al. 1994; Hayes et al. 1989; Schoenberg et al. 1987), and significant increases in risk were noted in the studies by Hansen et al. (1998) and Villeneuve et al. (2011). A significant effect for employment duration as taxi driver was noted in Hansen et al. (1998); however, the employment duration ranges are questionable to evaluate cancer risk, as the ranges were relatively short and all participants with >5 years of employment were in the same category. It is important to note that individuals in job categories with exposures to traffic-related emissions, such as taxi drivers, may have been exposed to both GE and DE, making it difficult to identify the effects of GE alone. The significant effect reported by Villeneuve et al. (2011) for taxi drivers/chauffeurs was not maintained when exposure analysis for all participants was conducted using a JEM (discussed further below).

By comparison, four studies semi-quantitatively estimated exposure to GE based on occupational history and reported a narrower range of ORs: 0.8–1.3 (Parent et al. 2007; Siemiatycki et al. 1988; Tse et al. 2011; Villeneuve et al. 2011). A consistent effect was not observed between the studies. A significant increase in risk and an exposure–response trend were only reported in the study by Siemiatycki et al. (1988). However, the authors reported a 90% confidence interval (CI) and the significance of the results would not be expected at a 95% CI. Additionally, a later study using the same cases and refinements in exposure assessment (Parent et al. 2007) reported ORs of less than 1, and did not observe an exposure–response trend.

In a well-designed case–control study, Villeneuve et al. (2011) evaluated cumulative exposure using a JEM and did not observe a clear association between GE and lung cancer or an exposure–response relationship. Of the studies reviewed, this investigation provided the clearest evaluation of GE and lung cancer, as adjustments for smoking and DE exposure (two key confounders) and a cumulative exposure–response assessment were included in the analysis; however, this study had relatively modest response rates, which could lead to a selection bias. Analysis by exposure duration and highest attained exposure concentration did not indicate an increase in lung cancer risk. Based on cumulative lifetime exposure,

the risk estimates indicate a trend of increased risk with increasing cumulative exposure, though not statistically significant (low: OR = 0.92; medium: OR = 1.08; high: OR = 1.11). Similar results were reported when individuals exposed to DE were excluded (low: OR = 0.84; medium: OR = 1.10; high: OR = 1.17). As a complement to JEM-based exposure analysis, the authors also included analysis by occupational classification. Classification of exposure as ever employment[1] as a taxi driver/chauffeur was associated with a significant risk of lung cancer (OR = 2.88 [95% CI: 1.68–4.94]). By comparison, the highest tertile of cumulative GE exposure, calculated using a JEM, was associated with a lower and non-significant risk of lung cancer (OR = 1.11 [95% CI: 0.88–1.39]). By allowing for a direct comparison, this study exemplifies the potential bias that can arise from relying solely on occupational title and ever employment in certain occupations or industries to evaluate risk (in this case the occupations include exposure to DE), providing a basis to give a greater weight of evidence to studies that employed a JEM for exposure assessment.

Overall, the literature provides only limited evidence of a potential link between GE exposure and an increased risk of lung cancer in adults occupationally exposed, and the magnitude of the elevated risks is generally low. The studies did not report any significant negative risk estimates, the majority of the risk estimates are positive, and the majority of the range of risk estimate values represented by the CIs are also greater than a value of 1. However, a number of factors limit the interpretation of the findings of the studies reviewed. A consistent effect was not observed across the literature, as some of the studies reported risk estimates less than 1.0 (Forastiere et al. 1994; Guo et al. 2004a; Hansen et al. 1998; Parent et al. 2007; Villeneuve et al. 2011), and few of the risk estimates were significantly elevated. Additionally, an exposure–response relationship was noted in some studies (Hansen et al. 1998; Siemiatycki et al. 1988), though other studies reported no significant increase in risk or a decreased risk (Borgia et al. 1994; Forastiere et al. 1994; Hayes et al. 1989; Parent et al. 2007; Villeneuve et al. 2011). Only a few studies included adjustments for key confounders including smoking and DE exposure: these studies reported small non-significant increases in lung cancer risk (Siemiatycki et al. 1988; Tse et al. 2011; Villeneuve et al. 2011). Results from a single cohort study (Guo et al. 2004a) suggest that women may be more susceptible to lung cancer risk from GE exposure; however, further study is required to examine that issue. Overall, interpretation of the evidence of an association between GE exposure and lung cancer is largely limited by the level of confidence in the exposure evaluation within the individual studies; the lack of adjustments for known confounders including DE exposure and smoking; and the fact that some of the studies had modest response rates, which can lead to selection bias. Furthermore, each exposure assessment is limited by the inherent difficulties in isolating and characterizing occupational and non-occupational exposure to GE. The lack of more quantitative exposure characterization reduces the likelihood or ability of a study to detect a significant effect. Most studies classified exposure based on occupational title and a few studies employed a JEM to semi-quantitatively assess exposure. None of the studies directly quantified or measured GE exposure. Additional, well-designed studies, including quantitative exposure assessment and adjustment for confounders, are required to better evaluate and understand the relationship between GE exposure and lung cancer risk. Presently, the most well designed studies do not provide clear evidence of an association. In addition, the potential for chance, bias, and confounding to impact the observed results cannot be ruled out.

[1] Ever employment: this term is used in exposure classification of workers and refers to those who have ever been employed in a given job category for any length of time.

3.1.1.1.2 Bladder cancer

For bladder cancer, three cohort studies (Borgia et al. 1994; Forastiere et al. 1994; Guo et al. 2004b), one nested case–control study (Forastiere et al. 1994), and eight case–control studies (Band et al. 2005; Colt et al. 2004, 2011; Dryson et al. 2008; Samanic et al. 2008; Siemiatycki et al. 1988; Silverman et al. 1986; Steineck et al. 1990; Villeneuve et al. 2011) were evaluated. The cohort studies reported non-significant risk estimates that ranged from 0.82 to 1.88 for men in GE-influenced occupations. There was some evidence of an exposure–duration trend in the cohort of policemen in Rome, Italy; however, the small number of cases in the groups by employment duration resulted in very large CIs, reducing the strength of the trend. Additionally, none of the cohort studies included adjustments for smoking or exposure to other confounders, limiting the weight of evidence from these studies.

The case–control studies provide limited evidence of an association between GE exposure and bladder cancer risk. From the seven studies that classified exposure from employment in certain occupational groups (e.g. taxicab driver), ORs ranged from 0.43 to 6.3 (Band et al. 2005; Colt et al. 2004, 2011; Dryson et al. 2008; Forastiere et al. 1994; Samanic et al. 2008; Silverman et al. 1986). Non-significantly reduced risk of bladder cancer (i.e. OR <1) was reported in four of the studies (Colt et al. 2004; Dryson et al. 2008; Forastiere et al. 1994; Samanic et al. 2008), with the studies by Colt et al. (2004), Dryson et al. (2008) and Samanic et al. (2008) including adjustments for smoking. Non-significant increases in risk were reported in three of the studies (Band et al. 2005; Colt et al. 2011; Samanic et al. 2008), and significant increases were noted in the study by Forastiere et al. (1994) and Silverman et al. (1986). In the nested case–control study by Forastiere et al. (1994), a significant increase in risk was noted for car drivers, but not traffic wardens or motorcyclists; however, this study did not include any adjustments for smoking or other confounders. Silverman et al. (1986) noted a significant increase in risk of bladder cancer for both ever employment and usual employment as a taxicab driver/chauffeur, with adjustment for smoking; however, a consistent exposure–duration effect was not observed from the analysis based on employment duration.

Only two case–control studies used a JEM to semi-quantitatively assess exposure to GE based on occupational history. Both Siemiatycki et al. (1998) and Steineck et al. (1990) reported no association between ever exposure to GE and bladder cancer (OR and relative risk (RR) = 1.0), including adjustments for smoking and no history of DE exposure in Steineck et al. (1990). Analysis by exposure level (i.e. low, medium and high) was suggestive of an exposure–response trend in the study by Steineck et al. (1990). However, none of the exposure-level-based estimates reached significance, no trend analysis was performed, and there were a small number of cases in each of the groups, limiting the strength of this evidence.

Overall, the literature provides only limited evidence of a potential link between GE exposure and an increased risk of bladder cancer in adults occupationally exposed, including some indications of an exposure–response effect. However, a number of factors limit the interpretation of the findings. A consistent effect was not observed across the literature, as some of the studies reported risk estimates less than 1.0. Furthermore, an inconsistent response was observed for studies evaluating the same occupational group of taxicab drivers and chauffeurs, reducing the likelihood of GE as a causative factor in the observed risk. Results from a few studies suggest an exposure–response relationship, though this was not reported in all studies. A key limitation of the literature is confidence in the exposure evaluation. Nearly all studies relied on occupational title to evaluate exposure, with only a small number of studies estimating exposure using a JEM, and none of the studies included direct measurement or quantification of exposure. The potential influence of confounders such as smoking and exposure to DE is a major limitation in most of the studies. Additional well-designed studies, including quantitative

exposure assessment and adjustment for confounders, are required to better evaluate and understand the relationship between GE exposure and bladder cancer risk. Presently, the potential for chance, bias, and confounding to impact the observed results cannot be ruled out.

3.1.1.1.3 Lymphohematopoietic cancer

For lymphohematopoietic cancers, three cohort studies (Borgia et al. 1994; Forastiere et al. 1994; Guo et al. 2004b), one nested case–control study (Forastiere et al. 1994), six case–control studies (Boffetta et al. 1989; Demers et al. 1993; Heck et al. 2013; Heineman et al. 1992; Reid et al. 2011; Siemiatycki et al. 1988), and one ecological study (Nordlinder et al. 1997) were evaluated. This body of literature encompasses several different types of cancer, including leukemia, non-Hodgkin's lymphoma (NHL), multiple myeloma and childhood leukemia. As a result there were small numbers of investigations for each type of cancer, limiting the weight of evidence for a particular lymphohematopoietic cancer.

The cohort studies reported non-significant risk estimates that ranged from 0.67 to 14.8, with most estimates being less than 1.2 (Borgia et al. 1994; Forastiere et al. 1994; Guo et al. 2004b). For the cohort studies of policemen and taxi drivers in Rome, non-significant increases in risk were reported for NHL and a non-significant decrease in risk for leukemia (Borgia et al. 1994; Forastiere et al. 1994). There was evidence of a trend of decreasing risk with employment duration for lymphatic and hematopoietic cancers and a trend of increasing risk for NHL among policemen. However, there were small numbers of cases in the groups by employment duration, limiting the strength of the associations. Additionally, none of the cohort studies included adjustments for smoking or exposure to other confounders including DE, a likely co-exposure in all traffic-related exposures, limiting the weight of evidence from these studies.

There is very limited evidence of increased risk of NHL with GE exposure; however, a clear association is not evident from the literature. Most of the analysis on NHL is from the cohort and nested case–control study of policemen in Rome, which did not include adjustments for any possible confounders (Forastiere et al. 1994). In the nested case–control study, a non-significant increase in risk was noted for motorcyclists and a trend of increased risk with employment duration. By comparison, there was a non-significant decrease in risk and a trend of decreased risk with employment duration for traffic wardens in the same study. Additionally, a study that semi-quantitatively assessed GE exposure based on occupational history did not find an association between GE and risk of NHL, with adjustment for smoking and other confounders (Siemiatycki et al. 1988). Based on study design, this study provides stronger evidence of the two evaluated.

Three case–control studies evaluated multiple myeloma risk associated with GE exposure and mainly reported non-significant associations (Boffetta et al. 1989; Demers et al. 1993; Heineman et al. 1992). The two studies that utilized occupational title for exposure assessment reported non-significant increases in risk for multiple myeloma among motor vehicle operators and chauffeurs; a significant increase in risk and no association were noted, respectively, for forestry and logging-based occupations (Demers et al. 1993; Heineman et al. 1992). The ORs for forestry and logging occupations had large CIs, reflective of the smaller sample sizes of this occupational group. By comparison, occupational exposure to GE was not associated with an increased risk in a nested case–control study of the American Cancer Society Cancer Prevention Study II cohort (Boffetta et al. 1989). Of these three studies, Boffetta et al. (1989) included a greater number of adjustments for possible confounders.

Childhood leukemia risks associated with GE exposure were evaluated in one case–control study (Reid et al. 2011) and one ecological study (Nordlinder et al. 1997). Paternal and maternal occupational

exposures to GE were not associated with a significant increase in risk of acute lymphoblastic leukemia (ALL), although an exposure–response trend was noted for low vs. moderate/substantial GE exposure any time prior to birth and an elevated risk was noted for the latter (OR = 1.59 for mother's exposure and OR = 1.20 for father's exposure) (Reid et al. 2011); however, the study did not account for occupational exposure to multiple chemicals. An ecological study (Nordlinder et al. 1997) reported a greater incidence of acute myeloid leukemia (AML) in communities in Sweden with higher car densities, though no linear trend was observed and no association was found for NHL, ALL, or chronic myeloid leukemia (CML). In addition, the study design did not consider any other factors or causes that could be related to the AML incidence.

Additionally, three case-control studies evaluated childhood leukemia risks associated with exposure to traffic surrogates of GE (Heck et al. 2013; Huot et al. 2015; Raaschou-Nielsen et al. 2001). Raaschou-Neilsen et al. (2001) modelled ambient concentrations of benzene from traffic at residence. No increase in risk of leukemias was observed when considering exposure during pregnancy or childhood. For lymphomas, a significant increase was reported for the pregnancy period with cumulative benzene exposure of 1.3 to <3.5 1000 ppb-days (RR = 2.2 [95% CI: 1.2–3.9]); however, the risk in the higher cumulative exposure group (≥3.5 1000 ppb-days) was lower and non-significant. When analysis was restricted to Hodgkin's lymphoma and benzene exposure during pregnancy, a significant increase in risk was observed at the highest exposure level of ≥ 1.3 1000 ppb-days (RR = 4.3 [95% CI: 1.5–12.4]). Also, a significant exposure–response trend was noted when cumulative exposure was evaluated as a continuous variable (RR = 1.84 [95% CI: 1.21–2.80]). However, similar results were noted for cumulative exposure to NO_2 (for which both DE and GE are major sources) during the pregnancy period, limiting the ability to ascribe the observed effects to GE. Huot et al. (2015) estimated benzene concentrations at residence using a combination of monitoring data and modelling methods. For ALL, a non-significant decrease in risk was observed at ≥1.3 μg/m^3 benzene (OR = 0.9 [95% CI: 0.7–1.0]), and for AML, a non-significant increase in risk was observed (OR = 1.6 [95% CI: 1.0–2.4]); however, this study did not account for DE exposure. Heck et al. (2013) reported small but significant increases in ALL risk based on an increase in modelled traffic-related CO, a surrogate for GE exposure, during the first trimester of pregnancy (OR = 1.05 [95% CI: 1.01–1.10]), a borderline significant association was observed for NHL (OR = 1.10 [95% CI: 0.95–1.28]), and a significant decrease in risk was observed for AML (OR = 0.85 [95% CI: 0.73–0.98]); a similar response was observed when exposure was evaluated during the first year of the child's life. An exposure–response trend was observed for ALL, when exposure was evaluated by quartile. When the analysis was based on $PM_{2.5}$, a surrogate for DE exposure, similar estimates were reported, limiting the ability to attribute the effects to GE. Had these traffic surrogate studies utilized a multi-pollutant model for analysis, it would have provided more specific information regarding the role of GE in the observed effects.

Overall, these studies provide only very limited evidence of increased risk of lymphohematopoietic cancers in association with exposure to GE, including in children and in adults exposed occupationally, with most of the studies reporting no significant effects or equivocal results. The studies reviewed and the conclusions that can be drawn are limited by a number of factors, including the small number of studies evaluating each of the different types of lymphohematopoietic cancer; the conflicting results across studies; the methodological limitations (including study design, lack of adjustment for confounders and small sample sizes); and the lack of quantitative assessment of GE exposure. Presently, the potential for chance, bias, and confounding to impact the observed results cannot be ruled out. Hence, the literature does not provide clear evidence of a link between GE exposure and lymphohematopoietic cancers, but well-designed studies including quantitative exposure assessment and adjustment for confounders are warranted to better elucidate this relationship.

3.1.1.1.4 Other cancers

For other types of cancers, including colonic, gastric, pancreatic, liver, kidney, endocrine gland, esophageal, reproductive, developmental or childhood, and head and neck cancers and melanoma, a limited number of studies have been conducted (Borgia et al. 1994; De Stefani et al. 1998; Elci et al. 2003; Fang et al. 2011; Forastiere et al. 1994; Guo et al. 2004b; Heck et al. 2013; Santibañez et al. 2010; Siemiatycki et al. 1988; Vasama-Neuvonen et al. 1999). Some studies reported positive associations, including significant associations for colonic, esophageal, ovarian, developmental or childhood, and head and neck cancers. However, conclusions cannot be drawn given the limited number of studies, inconsistent associations, and study limitations.

Further studies and evaluations are necessary to elucidate the role of GE in carcinogenicity. For these studies, efforts should be taken to address the limitations in the existing database, including confounding by smoking and co-exposure to DE and other carcinogens. Furthermore, improved quantification of GE exposure would address a major limitation in the existing literature.

3.1.1.1.5 Evidence from molecular epidemiological studies

Three cross-sectional studies evaluated biomarkers of genotoxicity in traffic policemen occupationally exposed to GE compared with office workers. Two of the studies reported an increase in micronuclei frequency in peripheral blood lymphocytes, but did not observe a dose– or duration–response effect (Angelini et al. 2011; Maffei et al. 2005). The third study did not observe any genotoxic effects in the occupationally exposed group, including measures of sister chromatid exchanges, proliferation index, or deoxyribonucleic acid (DNA) strand breaks (Carere et al. 2002). These studies are limited by lack of adjustment for confounders, including exposure to DE. Additionally, the cross-sectional design precludes the ability to evaluate the temporal association between exposure and effect.

3.1.1.2 Evidence from controlled human studies

No controlled human exposure studies addressing the genotoxicity, mutagenicity or carcinogenicity of GE were identified for this review.

3.1.1.3 Evidence from toxicological studies

GE is a variable mixture of gaseous and particulate compounds. The gaseous component includes a mixture of compounds such as benzene, formaldehyde, and 1,3-butadiene, which have been determined to be carcinogenic or likely carcinogenic by various agencies (Environment Canada and Health Canada 1993, 2000, 2001; IARC 2012). Additionally, the particulate component includes compounds that have similarly been identified as known or likely carcinogens, including PAHs (e.g. benzo[a]pyrene and chrysene) (Environment Canada and Health Canada 1994; IARC 2010, 2012, 2013). This supports the biological plausibility that GE as a mixture is carcinogenic in humans.

The majority of evidence of mutagenicity and genotoxicity is from *in vitro* studies using organic extracts of gasoline exhaust particles (GEPs), which contain PAHs. Several studies demonstrated that organic extracts of GEPs caused mutations in Ames tests, both with and without metabolic activation, indicating the presence of both direct- and indirect-acting mutagens (Carroll et al. 2000; Cheng et al. 2004; Cooper and Shore 1989; Crebelli et al. 1991; Kokko et al. 2000; Liu et al. 2005; Magnusson et al. 2000; Pohjola et al. 2003b; Seagrave et al. 2002; Westerholm et al. 1988; Westphal et al. 2010; Ye et al. 1999; Yuan et al. 1999; Zhang et al. 2007; Zhou and Ye 1997, 1998). Studies in mammalian cells also demonstrated that organic extracts of GEPs can induce DNA strand breaks, oxidative DNA damage, micronuclei formation, chromosomal aberrations, sister chromatid exchanges, and aberrations in mitotic division (e.g.

aneuploidy) (Cheng et al. 2004; Hadnagy and Seemayer 1988, 1989, 1991; Kuo et al. 1998; Liu et al. 2005; Pohjola 2003a; Yuan et al. 1999; Zhang et al. 2007). A smaller number of *in vitro* studies have evaluated the mutagenicity and genotoxicity of condensates, semivolatiles, and/or the gaseous phase of GE. Organic extracts of the semivolatiles were demonstrated to cause mutations in Ames test, in the presence and absence of metabolic activation (Liu et al. 2005; Magnusson et al. 2000; Zhang et al. 2007). In mammalian cells the extract from semivolatiles induced DNA strand breaks and formation of micronuclei, though the magnitude of the effect was typically less than observed for organic extracts of GE condensates, as well as the gaseous phase (Zhang et al. 2007). The *in vivo* studies evaluated in this assessment provide additional evidence of genotoxicity, as micronuclei formation and DNA strand breaks were observed following whole-body inhalation to whole GE, intraperitoneal injection of organic extracts of GEPs, intratracheal (IT) instillation of GEPs, and IT instillation of organic extracts of GE (GEE) (Che et al. 2009; Cheng et al. 2004; Massad et al. 1986; Ye et al. 1999; Zhou and Ye 1997, 1998). The observed mutagenic and genotoxic effects of GE and its constituents may be mediated, at least in part, by an oxidative mechanism. A limited number of studies reported an attenuation of genotoxic or mutagenic effects with co-administration of antioxidants (Cheng et al. 2004; Kuo et al. 1998), and an increase in DNA adducts was reported in one study (Pohjola et al. 2003a). Alterations in the expression of oncogenes and tumour-suppressor genes were demonstrated in a human cancer cell line exposed to organic extracts of GEPs (Ueng et al. 2005).

In animal studies, the potential for carcinogenic risk with GE was demonstrated, and the presence of increased tumour incidences with GE condensate, GE condensate fractions and organically extracted GEPs were observed in some studies. Subchronic whole-body inhalation exposure to GE in rats and mice resulted in hypermethylation of rat lung DNA, and hypomethylation of mouse lung DNA (Reed et al. 2008). However, studies of chronic inhalation of GE conducted with various species, including mice, rats, dogs, and hamsters, did not demonstrate a significant increase in tumour incidences due to GE exposure (Brightwell et al. 1989; Campbell et al. 1936; Heinrich et al. 1986 in IARC 2013; Stara et al. 1980; Yoshimura 1983).

In a carcinogenicity study, exposure to GE condensate and to one fraction of GE condensate containing polycyclic aromatic compounds with greater than 3 rings resulted in a dose-dependent increase in lung tumour development in rats. The GE condensate fraction of polycyclic aromatic compounds with greater than 3 rings was determined to account for approximately 81% of the total carcinogenicity of the condensate, while representing 2.8% of the GE condensate on a weight basis. However, it should be noted that the route of exposure for the GE condensate and polycyclic aromatic fraction was implantation into the lung lobe via a thoracotomy, and the GE condensate was derived from GE generated by a passenger vehicle using leaded gasoline (Grimmer et al. 1984).

Three IT instillation studies examined the carcinogenicity of GE condensate exposure in Syrian golden hamsters. An increased incidence of pulmonary adenomas was observed in treatment group animals of two studies (Green et al. 1983; Mohr et al. 1976). In addition, an increased number of hyperplastic nodules was noted in the two highest treatment groups of the Green et al. (1983) study. However, no dose–response effect was observed for either the pulmonary adenomas or hyperplastic nodules. By contrast, one IT study did not observe a difference in the incidences of metaplasia in the respiratory tract of animals exposed to GE condensate or to different fractions of GE condensate (Künstler 1983).

Several dermal studies were conducted to investigate the potential carcinogenicity of GE condensate, fractions of GE condensate and organically extracted GEPs. Brune et al. (1978) demonstrated a dose-related increase in squamous cell carcinomas and papillomas in mice dermally applied with GE

condensate and fractions of GE condensates containing PAHs. Similarly, dermal exposure of GE condensate and one fraction of GE condensate containing polycyclic aromatic compounds with greater than 3 rings to mice also resulted in a dose-dependent increased incidence of carcinomas and papillomas (Grimmer et al. 1983a, b). It should be noted that the GE condensate and fractions of GE condensate used by Brune et al. (1978) were provided by Grimmer. A weak tumorigenic-initiating response was observed in mice dermally exposed to organically extracted GEP and then administered 12-O-tetradecanoylphorbol-13-acetate topically to induce tumour development (Nesnow et al. 1982, 1983). Other reviewed dermal studies were deemed inadequate due to poor study design, lack of detail in reported information, or the use of benzene to extract GE or GEPs.

Lastly, increased skin tumour incidences were demonstrated in mice injected subcutaneously with GE condensate fractions containing PAHs, but there was no significant increase in tumour incidence in mice administered GE condensate (Pott et al. 1977). However, there was a lack of detail in the reported information, which limits the interpretation of the study results.

The literature evidence for GE exposure inducing carcinogenicity in animal toxicity studies is poor due to the small number of studies, the age of the studies, the use of leaded gasoline (which may have confounded study findings) and the limited number of mechanistic studies on tumorigenesis. Biological plausibility of GE exposure and potential carcinogenic activity are demonstrated based on evidence from *in vitro* and *in vivo* assays that GE and the constituent components of GE (i.e. GEPs, the gaseous phase, GE condensates, and organically extracted GEPs) induced genotoxicity and mutagenicity. However, there was no statistically significant increase in tumour incidences in multiple species (mice, rats, hamsters and dogs) exposed to GE via whole-body inhalation. Dose-related increased tumour incidences are observed in rodents exposed to GE condensate and PAH fractions of GE condensate via lung implantation and dermal application, which are less relevant routes of exposure. Furthermore, there are inconsistent findings on the potential carcinogenicity of GE condensate and PAH fractions of GE condensate in IT instillation studies conducted in hamsters. Although there are indications of carcinogenic potential for GE condensates and PAH fractions of GE condensate, there is weak evidence for carcinogenicity associated with relevant GE exposures.

3.1.1.4 Determination of causality

Overall, **it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and carcinogenicity**, based on insufficient study quantity, quality and relevance in the epidemiological and toxicological literature for evaluating carcinogenicity effects associated with exposure to GE as a mixture. In epidemiological studies, key limitations were in exposure assessment methodologies and lack of control for confounders. Although GE and the constituent components of GE demonstrated genotoxicity and mutagenicity, there was no significant increase in observed tumour incidences in multiple animal species exposed to GE by whole-body inhalation. Increased, dose-related incidences of tumours were observed in rats and mice exposed to GE condensate and PAH fractions of GE condensate; however, the routes of exposure (i.e. lung implantation and dermal) and high exposure concentrations employed in those studies are considered to be of lesser relevance for the determination of a causal relationship (see Table 3-1). To address the inconsistencies and limitations, there is a need for high-quality epidemiological studies that provide more accurate exposure estimates to address bias, confounding and exposure misclassification. In addition, mechanistic studies on tumorigenesis may provide more clarity on the significance of the genotoxic and mutagenic effects of GE and the potential for carcinogenicity.

This causality determination does not preclude the well-established carcinogenicity of individual air pollutants that are constituents of GE, such as benzene and PAHs.

3.1.1.5 Gasoline exhaust—evaluations of carcinogenicity by other organizations

The IARC has evaluated the carcinogenicity of GE (IARC 2013). The IARC Working Group consisted of 24 international experts, who reviewed all the published literature on GE pertaining to human carcinogenicity, animal carcinogenicity, genotoxicity and other relevant mechanistic data in order to support the classification of GE carcinogenicity.

In its most recent evaluation of GE in IARC Monograph 105, the IARC Working Group determined that there is inadequate evidence in humans for the carcinogenicity of GE, due in part to the limited number of epidemiological studies and the difficulty in separating exposure between diesel and gasoline exhausts. Inhalation studies in experimental animals exposed to whole GE demonstrate no significantly increased incidences of lung tumours in rodents (References from IARC 105: Brightwell et al. 1989; Campbell 1936; Heinrich et al. 1986; Yoshimura 1983) and a lack of lung tumour development in dogs (Stara et al. 1980). A significant increase in skin papillomas and lung carcinomas was observed in mice exposed to GEE condensate via the dermal route of exposure (Brune et al. 1978). Furthermore, significantly increased lung carcinomas were also noted in rats exposed to condensate from GE via intrapulmonary implantation (Grimmer et al. 1984).

With respect to mechanistic data, the IARC Working Group found strong evidence that a genotoxic mechanism is associated with the carcinogenicity of organic extracts of GEPs; the extracts were found to induce DNA and chromosomal damage, mutagenicity in bacterial and mammalian cells, morphological cell transformation in mammalian cells and tumours in mouse skin. *In vivo* studies assessing mechanistic actions of GE demonstrated perturbations of lung DNA; methylation was noted with whole-body inhalation exposure to whole GE, which resulted in hypermethylation in rats and hypomethylation in mice (Reed et al. 2008). A significant dose-related increase in micronuclei frequency was demonstrated in mice following intraperitoneal administration of particulate matter (PM) extracted from GE (Cheng et al. 2004; Zhou and Ye 1997 1998). *In vitro* studies assessing the genotoxic effect of GE particles and organic extracts in cultured mammalian cells demonstrated significant dose-dependent increase in DNA strand breaks (Liu et al. 2005; Zhang et al. 2007), micronuclei (Yuan et al. 1999), aberrant cells (Cheng et al. 2004), sister chromatid exchange (Hadnagy and Seemayer 1988, 1991; Kuo et al. 1998), C-metaphases (Hadnagy and Seemayer 1988, 1991), transformed foci (Hadnagy and Seemayer 1989), and bulky DNA adducts (Pohjola et al. 2003a). Numerous *in vitro* Salmonella reverse mutation assays demonstrated increased mutagenic activity in the presence and absence of metabolic activation (Carroll et al. 2000; Cheng et al. 2004; Cooper and Shore 1989; Crebelli et al. 1991; Kokko et al. 2000; Liu et al. 2005; Seagrave et al. 2002; Westphal et al. 2010; Zhang et al. 2007). In addition, one study showed that particulates from motorcycle exhaust may alter cell cycle, leading to tumour progression based on increased gene expression and messenger ribonucleic acid (mRNA) levels of oncogene fra-1 and tumour suppressor p21, as well as decreased gene expression and mRNA levels of tumour suppressor Rb in human lung adenocarcinoma CL5 cells (Ueng et al. 2005).

Overall, the IARC Working Group classified GE as possibly carcinogenic to humans (Group 2B) (Benbrahim-Tallaa et al. 2012; IARC 2013), which was the same classification determination as from IARC Monograph 46 (1989). The IARC classification for GE is based on inadequate evidence of cancer in humans and experimental animals exposed to whole GE, strong mechanistic evidence of the ability of GE to induce cancer, and sufficient evidence that GE condensates can cause cancer in animals.

3.1.2 Respiratory effects

3.1.2.1 Evidence from epidemiological studies

The current review consists of five epidemiological studies that examined respiratory effects associated with GE exposure in humans. This included three cross-sectional studies (Hoppin et al. 2004; Sancini et al. 2010; Volpino et al. 2004) and two cohort studies (Borgia et al. 1994; Forestiere et al. 1994). All the aforementioned studies examined occupational GE exposures, with four out of the five targeting exposures in a traffic-impacted environment, thus implicating possible confounding by DE exposure.

The first cross-sectional study involved an analysis of common farming activities as risk factors for wheeze among farmers in the United States Agricultural Health Study, in which one of the farming activities was driving a gasoline tractor (Hoppin et al. 2004). Driving a gasoline tractor was found to be associated with an elevated risk of wheeze. Also, asthmatics were found to have greater sensitivity to developing wheeze due to driving gasoline tractors when compared with non-asthmatics. Although an increased risk of wheeze was observed with driving gasoline tractors, this activity was not determined to be a consistent predictor of wheeze among farmers due to the lack of a duration–response relationship as well as attenuation in the risk for wheeze when driving a diesel tractor was included as a variable in the model.

Two cross-sectional studies investigated the effects of GE on traffic policemen compared with a control group of indoor office workers. In the Volpino et al. (2004) study, traffic policemen were found to have lower exercise capacity and efficiency on a cycling ergometer than office workers, based on respiratory testing parameters. Furthermore, ventilator anaerobic threshold measurements after the exercise test demonstrated a reduced ability to recover from exercise in traffic policemen in comparison to the control group. However, there was a lack of accounting for other exposures (e.g. diesel) or factors (e.g. smoking, exercise or lifestyle) that may have contributed to reduced exercise fitness in traffic policemen, limiting the interpretation of the study results. The association between GE exposure and lung lesions in traffic policemen was examined in a study by Sancini et al. (2010), which reported a significant increased RR of lung nodules with a diameter of 5–10 mm in traffic policemen compared with a control group of indoor office workers. The RR was also elevated among non-smoking traffic policemen compared with non-smoking controls, although it was not statistically significant. No difference was noted between the smoking and non-smoking groups for other observable lung lesions. The results suggest that cigarette smoking may have predisposed the traffic policemen or had synergistic effects on GE-related health outcomes.

In the two cohort studies, mortality due to respiratory disease was determined for taxi drivers and urban policemen in Rome, Italy, who were predominantly exposed to GE because of their occupations (Borgia et al. 1994; Forestiere et al. 1994). In addition, mortality resulting from bronchitis was evaluated, specifically in the taxi driver cohort. Decreased standardized mortality ratios (SMRs) for respiratory diseases were observed in taxi drivers and urban policemen, as well as a decreased SMR for bronchitis in taxi drivers; however, only the SMR for respiratory disease in policemen was found to be significantly reduced. Contrary to the reduced exercise capacity in the cross-sectional study (Volpino et al. 2004), this particular group of urban policemen appears to have been biased by the healthy worker effect, since there likely would have been an assessment on the physical fitness of an individual prior to joining the police force and the daily activities of policemen may have been more physically demanding than those of other occupational groups. Therefore, the low SMR for respiratory disease in urban policemen might reflect this selection bias.

Association of GE with adverse respiratory health outcomes was assessed solely in occupational studies. In the studies reviewed, occupational GE exposure resulted in increased risks of wheeze, reduced exercise capacity and efficiency, reduced ability to recover after exercise, as well as increased risk of lung nodules (in traffic policemen who smoked). However, interpretations of these study results are limited due to a lack of robustness in the findings, as well as a lack of adjustment for confounders. In contrast, two cohort studies found decreased SMRs for respiratory disease in taxi drivers and urban policemen, and for bronchitis in taxi drivers, to be associated with predominately occupational GE exposure.

In addition, there were five studies (one panel, three cross-sectional and one longitudinal cohort) that examined the association of exposure to traffic-related surrogates of GE (benzene and CO) with respiratory health outcomes in the general population. Healthy, non-smoking adults participated in a panel study involving the assessment of respiratory parameters following cycling on a low-traffic route and a high-traffic route (Weichenthal et al. 2012). An interquartile range (IQR) increase of benzene exposure was positively associated with a change in baseline exhaled FE_{NO} (fractional exhaled nitric oxide) levels, but the magnitude of the change was small. Lung function FEV_1 (forced expiratory volume in 1 sec) was non-significantly elevated with an IQR increase in benzene in a multi-pollutant model. Although direct sampling was conducted along the cycling routes and a multiple-pollutant model was used in the analyses, the high correlation ($r > 0.8$) between individual VOCs makes interpretation of the findings more difficult.

Three studies investigated the association between estimated levels of local traffic-related surrogates of GE and adverse respiratory outcomes in children. In a cross-sectional study, high residential exposure to soot, benzene and NO_2 was found to significantly increase the risk of current asthma, cough, and current wheeze in children (Nicolai et al. 2003). All these adverse respiratory outcomes in children were found to be significantly associated with the estimated levels of benzene in air. In addition, increased risks of cough and current wheeze were associated with traffic-related levels of NO_2; however, NO_2 is present in the exhaust from both gasoline- and diesel-powered engines. Furthermore, soot was also significantly associated with risk of cough and risk of current asthma, indicating that the potentially differential roles of GE and DE cannot be determined. In another study (Delfino et al. 2009), increased risk of repeated hospital admissions for asthma in children was associated with exposure to IQR increases in traffic-related CO (OR = 1.073 [95% CI: 1.013–1.137]) and NOx (OR = 1.097 [95% CI: 1.034–1.164]) levels at residences. A borderline effect was also noted for NO_2. Stratification of the sample population by sex and age demonstrated that girls and infants (age group 0) appeared to be at greater risk for asthma-related hospital admissions, but statistical significance was not achieved for either analysis. In a longitudinal cohort study (Pénard-Morand et al. 2010), elevated risk of exercise-induced asthma in children was associated with increased concentrations (estimated at school addresses) of benzene, CO, PM_{10}, SO_2, and NOx. Also, the risk of asthma in the last year was increased with exposure to benzene, CO, SO_2 and NOx, and the risk of lifetime asthma was increased with exposure to benzene, CO, PM_{10}, and SO_2. It should be noted that elevated risk of all types of asthma was noted for benzene and CO, as well as SO_2. Exposure to VOCs in children was not associated with increased risk of asthma. The strengths of these studies are the large, sensitive subpopulation sample size and detailed exposure assessment. However, traffic-related air pollutant exposure values at residences and school addresses were modelled rather than measured, which introduces uncertainty. Furthermore, multi-pollutant models were not evaluated, and there was a high correlation coefficient between benzene and CO with other traffic-related air pollutants, which contributed to the difficulty in differentiating GE exposure from other sources, such as DE.

A cross-sectional study (Bentayeb et al. 2010) investigating the association between traffic-related air pollutants (PM_{10}, NO_2, SO_2, benzene, CO and VOCs) and adverse respiratory health outcomes in the elderly found an elevated risk for usual cough with exposure to PM_{10} and SO_2, and phlegm with SO_2 only. No associations were observed for exposure to benzene or CO in relation to the prevalence of adverse respiratory effects. This study was conducted in a large subpopulation with estimated exposure assessments; however, exposure was modelled, there was potential for exposure misclassification and the traffic-related air pollutants were highly correlated.

Overall, the effect of GE exposure on respiratory health outcomes was assessed using benzene and CO from traffic sources as a GE surrogate. The predominant finding was increased risk of asthma-related findings (current asthma, repeated hospital admissions due to asthma, exercise-induced asthma, asthma in the last year, and lifetime asthma), in relation to modelled benzene or CO exposure at residential or school addresses. Other noted respiratory symptoms in children included cough and current wheeze. In healthy, non-smoking adults, increased exposure to benzene resulted in changes to baseline exhaled FE_{NO} levels, with no significant effect on lung function. In contrast, GE surrogate (benzene and CO) exposures in the elderly were not associated with examined adverse respiratory effects.

A key limitation among the respiratory studies was the lack of quantitative assessment of exposure to GE or GE surrogates, with the exception of one study (Weichenthal et al. 2012). In occupational studies, exposure characterization was based solely on occupational classification; hence, the exposure–response relationship was not evaluated. In addition, most of the occupations were exposed to GE in a traffic-related environment, making confounding by DE a major limitation. Sources of bias, including selection bias and gender bias, were present in a few of the studies that were reviewed. For example, the SMR of urban policemen was likely influenced by the healthy worker effect. Additionally, several of the studies were poorly designed in that they failed to adequately match the test subjects with an appropriate control and did not control for the effects of confounders, such as socioeconomic status (SES) and smoking. In addition, several of the studies were cross-sectional in design, limiting the ability to ensure that exposure preceded the outcome. Five studies that were reviewed estimated exposure to traffic-related surrogates of GE (benzene and CO); however, these surrogates are highly correlated with other traffic air pollutants. Furthermore, there were likely co-exposures to other pollutants and sources, including DE. As a whole, the epidemiological evidence for respiratory effects due to exposure to GE or traffic-related surrogates of GE is limited because of the lack of high-quality studies.

3.1.2.2 Evidence from controlled human studies

No controlled human exposure studies related to respiratory effects of GE were found in the literature.

3.1.2.3 Evidence from toxicological studies

Toxicological studies investigating adverse respiratory effects focussed primarily on pulmonary inflammation, lung damage, lung function and lung microsomal activity.

Results from 7 of 10 acute and subacute animal studies demonstrated that exposure to whole GE, filtered GE and GEPs from different engines (i.e. automobiles, motorcycles) had the potential to elicit significant changes in various markers of oxidative stress and/or inflammation in the pulmonary system. Measures of pulmonary oxidative stress included significantly increased *in situ* lung chemiluminescence for oxidative reactions in rats exposed to whole GE (Seagrave et al. 2008). By contrast, no significant alterations in GE-induced pulmonary oxidative stress were observed based on thiobarbituric acid reactive substances (TBARS) levels in rats (Seagrave et al. 2008), and $ApoE^{-/-}$ mice (Lund et al. 2009). In

addition, decreased superoxide and peroxidase responses and no significant effects for potency estimates for glutathione (GSH) and oxidized protein in the bronchoalveolar lavage fluid (BALF) were noted in rats exposed to GE (Seagrave et al. 2002).

GE-induced pulmonary inflammatory responses included inflammatory cell infiltration in the lungs of rats and mice (Tzamkiozis et al. 2010; Ye et al. 1999); increased macrophages (filtered GE only) in rats (Seagrave et al. 2008); elevated inflammatory cytokines (tumour necrosis factor alpha) (TNF-α), interleukin-6 (IL-6), and interferon gamma-γ (IFN-γ) in the BALF of mice (Sureshkumar et al. 2005); and increased mRNA expression levels in rat lung for pro-inflammatory cytokine IL-1α (Ueng et al. 2005). A weak pulmonary inflammatory potency estimate for inflammatory cells and a slight response for macrophage inflammatory protein-2 (MIP-2) (an inflammatory cytokine) were also observed in the BALF of rats exposed to emissions from gasoline vehicles (Seagrave et al. 2002). Similarly, two studies (Lee et al. 2004, 2008) conducted in mice IT instilled with 12 mg/kg bw of GEPs from a two-stroke motorcycle engine resulted in elevated BALF inflammatory cells (e.g. neutrophils, eosinophils, lymphocytes and macrophages) and cytokines (i.e. TNF-α, IL-4, IL-5, IFN-γ). In addition, dose-related increases in inflammatory cells and polymorphonuclear neutrophil cells were noted in rats and mice for three of the studies that tested multiple dose levels. An exposure durational effect was observed in Sureshkumar et al. (2005), which demonstrated an increasing level of TNF-α and IL-6 in the BALF of mice with longer duration exposure to GE (0.635 mg/m^3 PM, 0.11 mg/m^3 SO_2, 0.49 mg/m^3 NOx, 18.67 ppm CO). Furthermore, the noted effects were observed shortly after cessation of exposure to GE or GEPs (ranging from 1 to 24 h post-treatment); in addition, some inflammatory cell infiltration was detectable up to 7 d post-treatment. However, no significant changes were observed to pro-inflammatory cytokine IL-β and anti-inflammatory cytokine IL-10 in GE-exposed mice (Sureshkumar et al. 2005). Pulmonary inflammation was also not evident in three acute studies, based on the lack of change in BALF macrophage (due to whole GE) or neutrophil counts in rats (Seagrave et al. 2008) and a decrease in BALF neutrophils and eosinophils of $ApoE^{-/-}$ mice (Day et al. 2008), as well as no inflammatory cell infiltration in the BALF of mice (Campen et al. 2006). Additionally, exposure to GE was found to suppress TNF-α levels in rat BALF (Seagrave et al. 2002).

Short-term effects on respiratory inflammation from GE exposure were investigated in one study with both rats and mice (Reed et al. 2008), and in another study with atherosclerosis-prone mice (Lund et al. 2007). In the subchronic Reed et al. (2008) study, MIP-2 was significantly increased in the BALF of rats exposed to high levels of whole GE (59.1 μg/m^3 PM, 18.8 ppm NOx, 107.3 ppm CO, 0.62 ppm SO_2, 15.9 mg/m^3 non-methane hydrocarbon (NMHC)) and filtered GE (2.3 μg/m^3 PM, 17.8 ppm NOx, 103.9 ppm CO, 0.47 ppm SO_2, 25.9 mg/m^3 NMHC). However, it was noted that oxidative stress was significantly decreased in rats. No treatment-related adverse pulmonary effects were observed in mice. The Reed et al. (2008) study also determined that the observed increased inflammatory response and decreased oxidative stress in the BALF of rats may have been impacted more by the gaseous fraction of GE than the particulate component, given that results were not significantly different following exposure to filtered GE (removal of PM) compared with whole GE. In the Lund et al. (2007) study, no treatment-related effects were noted for inflammatory modulating cytokine levels (i.e. IL-4, IL-6, IL-12, IFN-γ, or TNF-α) from whole lung homogenate in atherosclerosis-prone mice exposed to up to a high GE exposure concentration of 61 μg/m^3 PM, 19 ppm NOx, 80 ppm CO, and 12 ppm HC, or a filtered GE exposure concentration of 2 μg/m^3 PM, 19 ppm NOx, 80 ppm CO, and 12 ppm HC.

In a chronic study (Heinrich and Wilhelm 1984; Muhle et al. 1984) that exposed rats and hamsters to GE by whole-body inhalation, G6PD (the antioxidant enzyme that maintains cytosolic nicotinamide adenine dinucleotide phosphate (NADPH) levels to produce GSH) was found to be significantly elevated in the

BALF of both rats and hamsters following one year of high exposure to GE (73 µg/m^3 PM, 22.8 ppm NO, 1.0 ppm NO_2, 306 ppm CO, 0.38 ppm SO_2, 37 µg /m^3 lead), which is suggestive of an adaptive response due to the presence of oxidative stress. No treatment-related effects were noted for inflammatory cell infiltration to the BALF of rats or hamsters. Furthermore, *in vitro* studies (Lee et al. 2005; Ueng et al. 2000, 2005) conducted with GEP or GEE from a two-stroke motorcycle engine demonstrated the potential to increase oxidative stress in different human cell lines. In addition, two of the three *in vitro* studies also examined inflammatory cytokine levels. A dose-related increase in inflammatory cytokines IL-1α and IL-8 was observed. The addition of antioxidants to the *in vitro* system was found to attenuate the production of these inflammatory cytokines, which indicates that oxidative stress likely plays a role in the inflammatory response.

Evidence of lung damage following GE exposure was observed in subacute and subchronic studies in rats and mice exposed to GE or GE fractions via nose-only, IT instillation, or ET (endotracheal) injection. Various biomarkers of lung damage, including alkaline phosphatase (ALP), lactate dehydrogenase (LDH), γ-glutamyltransferase (γ-GT), acid phosphate (ACP), *N*-acetylneuraminic acid, albumin and protein in the BALF, were significantly increased in animals acutely exposed to GE (Sureshkumar et al. 2005; Ye et al. 1999). Of these biomarkers, a dose-dependent increase in LDH, ALP, ACP, *N*-acetylneuraminic acid, albumin and protein in the BALF, as well as an exposure durational effect for ALP, LDH, and γ-GT were noted in mice exposed to GE in the Ye et al. (1999) and Sureshkumar et al. (2005) studies. Weak cytotoxicity potency estimates for LDH and total protein in BALF of rats exposed to GE were also noted (Seagrave et al. 2002). By contrast, one study showed that LDH and ALP levels were comparable to controls in rats exposed to GE by whole-body inhalation for 5 wk; however, the findings from this study may be confounded by a previous pneumonia infection in the experimental animals (Massad et al. 1986). Histopathology examination of the lungs in animals exposed to GE was limited to two acute studies. Parenchymal changes in the lungs, primarily fibrosis, were noted in rats (Seagrave et al. 2002). In the Sureshkumar et al. (2005) study, histopathology revealed perivascular and peribronchiolar cuffing of mononuclear cells, sloughing of epithelial cells lining the bronchiolar region, and accumulation of inflammation cells in alveolar regions in mice exposed for short intervals (15 min/d, up to 21 d) to GE (0.635 mg/m^3 PM, 0.11 mg/m^3 SO_2, 0.49 mg/m^3 NOx, 18.67 ppm CO). Subchronic exposure to high GE (59.1 µg/m^3 PM, 18.8 ppm NOx, 107.3 ppm CO, 0.62 ppm SO_2, 15.9 mg/m^3 NMHC) also resulted in increased LDH levels in the BALF and PM loading in alveolar macrophages (AMs) of rats (Reed et al. 2008). The elevation of LDH appears to be more affected by the particulate component than the gaseous fraction of GE, since filtered GE exposure did not elicit the same magnitude of effect for LDH. An increased number of AMs with granular black pigment were also observed in another subchronic study conducted in rats (Pepelko et al. 1979); however, this finding was confounded by the possibility of a suspected infectious agent in the test animals. Chronic exposure to GE (112 ppm CO, 1.8 ppm NO, 0.1 ppm NO_2, 0 ppm O_3, 18 ppm HC as methane) or irradiated GE (109 ppm CO, 0.2 ppm NO, 1.8 ppm NO_2, 0.4 ppm O_3, 16 ppm HC as methane) was examined in dogs from a study conducted in the 1970s. Histopathology examination revealed hyperplasia of the non-ciliated bronchiolar epithelium, and this finding was found to be more severe in animals exposed to GE compared with irradiated GE exposure (Hyde et al. 1978). In addition, chronic exposure to irradiated GE resulted in significantly increased levels of prolyl hydroxylase, a key enzyme involved in the synthesis and stability of collagen. However, no significant difference between exposed and control animals was observed in the collagen content of their lungs (Orthoefer et al. 1976).

Significantly increased P450-dependent monooxygenase was observed in male rats exposed acutely and short-term to motorcycle GE by whole-body inhalation, or motorcycle GEPs via IT instillation. Elevated levels of benzo(a)pyrene hydroxylation, 7-ethoxyresorufin *O*-deethylation, NADPH cytochrome *c*

reductase and methoxyresorufin *O*-demethylation activity were observed in lung microsomes. In addition, significantly increased glutathione-*S*-transferase (GST) activity was noted in lung microsomes (Ueng et al. 1998). *In vitro* studies also showed increased CYP1A1 and CYP1B1 mRNA expression and protein levels in lung cell lines (NCI-H322 and CL5) exposed to GEP from a two-stroke motorcycle engine (Wang et al. 2002).

Lung function changes related to GE exposure were investigated in seven animal studies, while two animal studies examined the effect of GEPs from a two-stroke motorcycle engine on lung function. In an acute study (Stupfel et al. 1975), tracheal pressure was measured in the lungs of anaesthetized guinea pigs exposed to different dilutions of GE. Polyphasic tracheal pressure changes (increases and decreases) were observed; in addition, the time for induction of tracheal pressure change was shortened with increasing concentrations of GE. Although tracheal pressure changes were noted, the interpretation of these results was unclear, due to the small number of animals and a lack of statistical analysis. Significantly decreased mean expiratory flow and peak flow were observed in (non-pathogen-free) rats exposed to GE (509 ppm CO, 0.50 ppm NOx, 1.0 ppm SO_2, 50 ppm HC) in a subchronic study (Massad et al. 1986). Long-term exposure to GE resulted in increased pulmonary resistance in rats, but this finding was found to be comparable with control at the end of the 6-month recovery period following cessation of GE exposure (Heinrich and Wilhelm 1984). There were no significant treatment-related effects on lung function due to GE exposure in acute studies with rats and guinea pigs (McDonald et al. 2007; Murphy 1964; Seagrave et al. 2008), a subchronic rat study (Pepelko et al. 1979) and chronic dog studies (Hyde et al. 1978; Lewis et al. 1974; McDonald et al. 2007; Vaughan et al. 1969). IT instillation of 1.2 mg/kg bw and 12 mg/kg bw of GEPs from a two-stroke motorcycle engine and the benzene-extracted fraction of GEP exacerbated airway hyperresponsiveness (AHR) in mice following a methylcholine (MCh) challenge (Lee et al. 2004), which may be related to the concurrently observed inflammatory responses. Exacerbation of AHR following motorcycle GEP exposure (12 mg/kg bw) in mice was also noted in a subsequent, similar study (Lee et al. 2008).

Overall, the animal toxicity studies provide evidence that GE has the potential to elicit oxidative stress and inflammatory responses in the lung following acute or short-term exposure. Multiple biomarkers for lung inflammation and damage are identified, and they are supported by limited histopathology findings in the lungs. One study also provided evidence that certain oxidative stress and inflammatory response markers may have been impacted more by the gaseous fraction of GE than the particulate component. Lung function change is evident by exacerbation of AHR due to GEP exposure from a two-stroke motorcycle engine; however, GE-induced lung function changes are less definitive because of equivocal evidence in the current database. Exposure to GE or GEPs from a two-stroke motorcycle engine was found to activate metabolic and detoxification processes in the lungs, as evidenced by increases to various CYP450 enzymes, P450-dependent monooxygenases and GST. Based on *in vivo* and *in vitro* findings, the pulmonary inflammatory response and damage are likely induced by the presence of increased reactive oxygen species (ROS) and oxidative stress in relation to GE exposure. Further research on the long-term health effects of GE is warranted due to the limited number and quality of the studies.

3.1.2.4 Determination of causality

Overall, **it is concluded that the evidence is suggestive of, but not sufficient to infer, a causal relationship between GE exposure and adverse respiratory health outcomes**, based on very limited evidence of increased risk of adverse respiratory outcomes (primarily asthma-related findings) in children that is associated with traffic-related GE surrogate exposure, and changes to baseline exhaled FE_{NO} levels in adults, as well as evidence of respiratory inflammation, respiratory oxidative stress, and

lung damage in animals following acute GE exposure. However, the evidence is of varying quality and not entirely consistent for all endpoints. There is also limited evidence of alterations in lung function in animal studies. Furthermore, there is insufficient evidence from a limited number of toxicological studies with respect to respiratory health effects following chronic GE exposure.

This causality determination does not preclude the well-established adverse respiratory effects of individual air pollutants to which GE contributes, such as $PM_{2.5,}$ O_3 and NO_2.

3.1.3 Cardiovascular effects

3.1.3.1 Evidence from epidemiological studies

The association between GE exposure and adverse cardiovascular effects was investigated in two occupational cohort studies in taxi drivers and traffic policemen (Borgia et al. 1994; Forestiere et al. 1994) and one occupational cross-sectional study in traffic policemen (Volpino et al. 2004). No significantly increased SMRs for diseases of the circulatory system, hypertension and ischemic heart disease (IHD) were observed in taxi drivers or policemen from Rome in either of the cohort studies. In an exercise study (Volpino et al. 2004), traffic policemen exhibited elevated blood pressure, arrhythmias and ST deviation, in comparison with the control group, who were asymptomatic during the exercise test. In addition, traffic policemen showed a reduced capacity to recover from exercise, based on the cardiopulmonary parameters measured. However, confounders, including smoking behaviours, were not assessed in this study, limiting the interpretation. In general, the number of studies assessing cardiovascular health outcomes is very limited; therefore, it was not possible to rule out chance, bias or confounding. Other study limitations regarding these studies were previously discussed in Section 3.1.2.1. There were no studies with traffic-related GE surrogates that investigated cardiovascular endpoints.

3.1.3.2 Evidence from controlled human exposure studies

A controlled human exposure study (Coppola et al. 1989) was conducted on male volunteers (*n* = 12) who were exposed to GE for 30 min. Following exposure, significantly increased carboxyhemoglobin and significantly decreased Hb-oxygen affinity were observed. These findings were perhaps attributable to high CO levels in the GE emissions. In addition, GE exposure significantly decreased platelet aggregation and viscosity, possibly due to NO, which has potent vasodilation and inhibitory effects on platelet activation properties. However, this study did not include a control exposure (i.e. filtered air), therefore limiting the ability to differentiate the effects attributable to GE or the exposure protocol (i.e. being in a test chamber). Overall, the current evidence on cardiac health outcomes in controlled human exposure is limited to one study. There are indications that the gaseous components of GE may affect the oxygen transport system and the platelet clotting properties in humans. However, no significant changes to cardiac function were noted in this study, including heart rate, blood pressure or electrocardiogram (ECG) parameters.

3.1.3.3 Evidence from toxicological studies

Eight animal toxicity studies and four *in vitro* studies investigated adverse cardiovascular outcomes, including oxidative stress, oxidative damage, pro-inflammatory factors, vascular remodelling and cardiac function, in association with GE, filtered GE, or GEP exposure from different engines.

Cardiovascular oxidative stress was evidenced by significantly increased TBARS levels in aortic tissue (Campen et al. 2010; Lund et al. 2007, 2009) and significantly increased aortic HO-1 mRNA expression (Lund et al. 2007) in $ApoE^{-/-}$ mice exposed to high levels of whole GE (60 µg/m^3 PM, 18 ppm NOx, 80 ppm CO, 12 ppm HC), or filtered GE (2 µg/m^3 PM, 19 ppm NOx, 80 ppm CO, 12 ppm HC). In addition, significantly increased heart chemiluminescence was observed in rats exposed to GE (59 µg/m^3 PM, 104 ppm CO, 16.7 ppm NO, 1.1 ppm NO_2, 1.0 ppm SO_2, 12 ppm HC), but this finding was not seen when rats were exposed to filtered GE (Seagrave et al. 2008). Moreover, a dose-related response was observed in TBARS and hemeoxygenase-1 (HO-1) levels (Lund et al. 2007). Aortic endothelin-1 (ET-1) mRNA expression, a marker of vascular change, was also found to be elevated (Lund et al. 2007). Furthermore, immunohistochemistry of the aorta revealed significantly increased nitrotyrosine levels, which were indicative of oxidative damage (Lund et al. 2007). Although there was evidence of oxidative stress, oxidative damage and pro-inflammatory responses, there were several negative findings in the studies reviewed. No treatment-related effects were noted in plasma TBARS levels (Lund et al. 2007), and significantly decreased aortic HO-1 mRNA expression was observed in $ApoE^{-/-}$ mice (Campen et al. 2010). In addition, there was no detectable change in ET-1 levels in blood taken from the vena cava of spontaneously hypertensive rats (SHRs) exposed to high levels of whole or filtered GE (Reed et al. 2008). In a subacute study (Campen et al. 2006), there was also a lack of systemic inflammatory responses, as revealed by no significant differences in serum SAA and IL-6 levels from $ApoE^{-/-}$ mice exposed to whole or filtered GE compared with control.

Inhalation exposure of rats to 1:10 diluted GE from a two-stroke motorcycle engine also demonstrated oxidative stress, as evidenced by increased lipid peroxidation, as well as decreased GSH, superoxide dismutase (SOD), GST and glutathione peroxidase (GPx) activities (Chen et al. 2013). Histopathology examination of the heart revealed increased heart weight, myocardial necrosis and degeneration, focal hyaline transformation (Zenkers degeneration), fibrosis, and mononuclear cell infiltration. Correspondingly, analysis of cardiac tissue demonstrated increased mRNA levels of pro-inflammatory cytokine (i.e. IL-1β) and markers of hypertrophy and fibrosis (i.e. atrial natriuretic peptide, fibrosis molecule types I and III, collagen, connective tissue growth factor and transforming growth factor), as well as decreased mRNA levels of antioxidant enzymes (i.e. GST-M1 and GST-P1). In addition, heart microsomal (7-ethoxycoumarin O-deethylase) activity was decreased.

Evidence of vascular remodelling was demonstrated by the perturbation of extracellular matrix homeostasis. Significant increases in aortic mRNA expression of several vascular matrix metalloproteinases (MMPs), which included MMP-2, MMP-3, MMP-7, and MMP-9, were observed in $ApoE^{-/-}$ mice after inhalation exposure to GE. Furthermore, dose-related increases in the aortic mRNA expression were noted for MMP-7 and MMP-9. However, no significant changes were noted for tissue inhibitor of MMP-1 (TIMP-1) or MMP-12. Interestingly, GE exposure also resulted in a significant dose-dependent increase in aortic mRNA expression of tissue inhibitor of MMP-2 (TIMP-2) (Lund et al. 2007). The increase in TIMP-2 may be indicative of the dysfunction of the extracellular matrix (ECM) homeostasis. In addition, an exposure durational effect was observed in a subacute study (Lund et al. 2009), where ROS, lipid peroxidation, MMP-2, MMP-9, ET-1 and TIMP-2 levels were found to be greater with longer exposure duration (comparison between d 1 and d 7 of exposure) in $ApoE^{-/-}$ mice exposed to whole GE. Similarly, $ApoE^{-/-}$ mice exposed to comparable whole GE concentrations for 7 d (subacute) or 7 wk (subchronic) revealed greater aortic mRNA expression levels for MMP-9 and ET-1 as well as lipid peroxidation with longer exposure duration (Campen et al. 2010; Lund et al. 2007). Exposure of $ApoE^{-/-}$ mice to whole GE and filtered GE produced similar findings in several biomarkers related to oxidative stress (i.e. ET-1, HO-1, TBARs) and vascular remodelling (i.e. MMP-3, MMP-7, MMP-9, TIMP-2), indicating a key role for the gaseous components of GE (Lund et al. 2007). Therefore, the gaseous

components of GE (including CO and NO) may play a critical role in eliciting certain oxidative stress and vascular remodelling responses, in comparison with the particulates of GE.

Echocardiography assessment, from rats exposed to 1:10 diluted motorcycle GE for 8 wk, revealed increased interventricular septum thickness and left ventricle posterior wall thickness but decreased left ventricle cavity and internal dimension (Chen et al. 2013). The echocardiographic data provided evidence that there was hypertrophy of the left ventricle (also supported by histopathology results noted above). However, the GE-induced left ventricle structural changes did not have an effect on cardiac function (i.e. fractional shortening or heart rate).

Similarly, results from four animal (subacute and chronic) studies provided limited evidence that GE affects cardiac function (Bloch et al. 1972; Campen et al. 2006; McDonald et al. 2007; Reed et al. 2008; Stupfel et al. 1973). In a subacute study (Campen et al. 2006), there was an increase in the absolute deviation of the T-wave area from baseline values in $ApoE^{-/-}$ mice exposed to whole GE (61 µg/m^3 PM, 19 ppm NOx, 80 ppm CO, 12 ppm HC) during the first 2 h of a 6-h daily exposure over a 3-d study duration. This occurred only when animals were exposed to the high GE treatment and not from high filtered GE treatment, indicating that the outcome was linked to the PM in GE. However, no treatment-related effects for other ECG parameters (such as P-wave area, PQ-interval, QRS-interval, or QT-interval) and no significant difference in heart rate measurements were observed in $ApoE^{-/-}$ mice (Campen et al. 2006) or SHRs (Reed et al. 2008). In addition, no significant difference in markers of vascular injury in the blood taken from vena cava (i.e. angiotensin II, haptoglobin, ET-1) was observed in SHRs (Reed et al. 2008). Long-term exposure of rats to whole GE (Stupfel et al. 1973) and dogs to raw or irradiated GE (Bloch et al. 1972; McDonald et al. 2007) resulted in slight alterations in measured ECG parameters compared with control; however, these findings were not considered to be adverse due to the lack of consistency.

Hematological findings revealed significantly increased red blood cell (RBC) counts, hemoglobin and hematocrit in male and female rats exposed to whole GE at 1 wk and 6 months. Furthermore, a dose–response relationship was evident for RBC counts in males and females at 1 wk and 6 months. These findings were likely an adaptive response to the CO within the GE test mixtures. In addition, incidental changes to clotting factors were observed, including increased fibrinogen in mid-dose group males and decreased thrombin-antithrombin complex in high-dose group females at 1 wk only; however, no significant changes in clotting factors were observed in either male or female rats at 6 months (Reed et al. 2008).

In vitro mechanistic studies provided some additional evidence that GEPs from a two-stroke motorcycle engine may affect the vascular contractility, oxidative stress and inflammatory processes. Exposure of aorta rings to GEPs resulted in altered vasoreactivity, including vasorelaxation in phenylephrine (PE) precontracted aorta rings (Cheng et al. 1999); however, pretreatment of aorta rings with GEPs showed an enhancement in vasocontraction following the administration of PE (Tzeng et al. 2003). In addition, the GEP-induced vasoreactivity effects were determined to be independent of the endothelium and may be dependent on Ca^{2+} regulation, suggesting that GEPs are likely acting on the vascular smooth muscle cells (VSMCs). In a subsequent study (Tzeng et al. 2007), GEPs were shown to increase VSMC proliferation and generate ROS, which upregulates cyclooxygenase (COX-2) expression via ERK (extracellular signal-regulated kinase) 1/2 phosphorylation and NF-κB (nuclear factor kappa-B) -p65 signalling pathway. Furthermore, GEPs and their generated ROS were shown to upregulate the expression of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1) through a pathway involving NF-κB activation, which may play a role in cardiovascular inflammation and development of atherosclerosis (Lee et al. 2012).

Overall, GE, filtered GE, or GEP exposure demonstrated the potential to induce oxidative stress and inflammatory responses and to alter the vasculature of the cardiovascular system; however, there were inconsistencies in some study findings. The observed cardiovascular oxidative stress, vascular modelling and cardiac function findings in $ApoE^{-/-}$ mice provide some evidence that GE exposure can potentially exacerbate the development and progression of atherosclerosis. Two studies provided some evidence that the gaseous or particulate components of GE may be the contributing factor in eliciting certain cardiovascular outcomes. Exposure to GE from a two-stroke motorcycle engine in rats resulted in cardiovascular gene expression changes for inflammation, an antioxidant and markers of hypertrophy and fibrosis. Furthermore, the gene expression changes corroborated the observed GE-induced histopathology and echocardiography findings. However, it should be noted that these findings were seen in animals exposed to high levels of GE from a two-stroke motorcycle engine. Although adverse effects due to GE exposure on the cardiovascular system were seen, cardiac function effects due to GE exposure were more subtle, and they manifested as transient alterations on heart rate and ECG parameters, whereas no cardiac function effects were noted with motorcycle GE exposure. The cardiovascular oxygen transport also demonstrated an adaptive response of increasing RBCs, hemoglobin and hematocrit, likely due to the formation of COHb from GE exposure. GE-induced cardiovascular effects may be partially attributable to CO in the GE mixture, and further investigations will be necessary to fully describe the mechanism of effects from GE exposure. Additionally, *in vitro* studies provided some insight into the potential pathways of GEP-induced vasoreactivity, inflammatory processes and cell adhesion signalling. It is noteworthy that toxicological studies for cardiovascular effects associated with GE were conducted primarily by one research group from The National Environmental Respiratory Center (NERC), and studies investigating cardiovascular effects with motorcycle GE were primarily carried out by one research group from Taiwan. However, this does not diminish the significance of the study findings, since there was repeatability of some results and consistency in generating similar test mixtures, which permitted the comparison of findings between studies. Further investigations are warranted to elucidate the mechanisms of cardiovascular oxidative stress, inflammation, and vascular remodelling.

3.1.3.4 Determination of causality

Overall, **it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and adverse cardiovascular health outcomes**, based on insufficient evidence in the epidemiological and toxicological literature for cardiovascular effects following GE exposure. Only limited conclusions can be drawn from the single controlled human exposure study, due to major study limitations. There was also limited animal study evidence demonstrating inflammation, oxidative stress, and minor alterations in cardiac function from a small number of studies. From studies in an animal model of disease, there is some evidence of altered gene expression associated with vascular remodelling, lipid peroxidation, oxidative stress, and limited cardiac function effects, indicating a potential for GE exposure to impact the development and progression of atherosclerosis. *In vitro* studies provided limited evidence that GE exposure may potentially result in altered vasomotor responses.

This causality determination does not preclude the well-established adverse cardiovascular effects of individual air pollutants to which GE contributes, such as $PM_{2.5}$ and O_3.

3.1.4 Immunological effects

3.1.4.1 Evidence from epidemiological studies

Atopic health outcomes were investigated in two cross-sectional studies in children exposed to traffic-related GE surrogates. Hay fever, skin sensitivity to indoor allergens, skin sensitivity to pollen and skin sensitivity to specific immunoglobulin-E (IgE) aeroallergens in relation to estimated air pollutant levels (soot, benzene and NO_2) were assessed in German children (Nicolai et al. 2003). Risk of atopic outcomes was non-significantly increased for children living in areas of high traffic count, with some evidence of an exposure–response relationship. However, risk was only elevated in relation to soot and NO_2 exposure, not to benzene exposure, which suggests a role for DE and not GE. In a second study (Pénard-Morand et al. 2010), exposure to elevated levels of traffic-related air pollutants in children resulted in a greater risk of developing lifetime allergic rhinitis, eczema in the last year and lifetime eczema. Although positive associations were observed with benzene and/or CO and atopic health outcomes, other air pollutants (PM_{10}, NOx and NO_2) also demonstrated significant findings, suggesting that there may be confounding by DE exposure. Owing to the high correlation between the air pollutants, it is difficult to separate the results for individual air pollutants. Other study limitations regarding these studies were previously discussed in Section 3.1.2.1.

The possibility of the results being influenced by chance, bias or confounding cannot be excluded, due to the limited number and quality of the studies. Overall, there was no clear evidence of immune-mediated effects associated with GE exposure in the epidemiological literature; however, the immune response is not well studied in the current database.

3.1.4.2 Evidence from controlled human exposure studies

No controlled human exposure studies related to immunological effects of GE were found in the literature.

3.1.4.3 Evidence from toxicological studies

Six animal studies investigated the potential of whole GE, filtered GE, and GEP exposure from different engines to elicit immunological responses in mice and rats. In addition, there were two *in vitro* studies examining the immunotoxicity of GEE or GEP on RAW 264.7 (macrophage) cell line, or primary macrophages (obtained from mouse, rat, or rabbit).

The potential of GE, filtered GE, or GEP exposure to induce AHR was investigated in three subacute studies (Day et al. 2008; Lee et al. 2004, 2008) and a developmental study (Reed et al. 2008) in mice via IT instillation or whole-body inhalation. AHR exacerbation was evident based on a significant increase of Penh ratio following MCh treatment in OVA-sensitized mice IT-instilled with 12 mg/kg of GEPs from a two-stroke motorcycle engine (Lee et al. 2008). However, exacerbation of AHR was not observed in OVA-sensitized and non-sensitized mice when acutely exposed (Day et al. 2008), or *in utero* and postnatally exposed (Reed et al. 2008) to whole GE (59 µg/m^3 PM, 18.8 ppm NOx, 107 ppm CO, 0.62 ppm SO_2, 15.9 mg/m^3 NMHC) and filtered GE (2.3 µg/m^3 PM, 17.8 ppm NOx, 104 ppm CO, 0.47 ppm SO_2, 25.9 mg/m^3 NMHC). Although no significant differences were observed for the exacerbation of AHR in the Day et al. (2008) study, other immunological responses were observed, including increased serum OVA-specific IgG_1 levels in OVA-sensitized mice exposed to whole GE, and increased serum OVA-specific IgG_{2a} and IgE levels in non-sensitized mice exposed to whole GE and filtered GE, respectively. Similarly, significantly increased serum total IgE levels were observed in high-dose group OVA-sensitized mice

exposed *in utero* and postnatally to whole GE and filtered GE (Reed et al. 2008); however, there is uncertainty with respect to its relevance, since the finding was noted at wk 7 after cessation of GE exposure at wk 4. Analysis of BALF cytokine levels indicated a significant increase in IL-2 in pre-OVA non-sensitized mice exposed to high-filtered GE, but decreased IL-4, IL-5 and IFN-γ were noted in post-OVA-exposed non-sensitized mice exposed to GE and/or high filtered GE (Day et al. 2008). However, no significant effects on BALF cytokine levels were seen in the Reed et al. (2008) study. Furthermore, no significant effects were observed for BALF inflammatory cells (Day et al. 2008) and for some serum immunoglobulins (Day et al. 2008; Reed et al. 2008) in OVA-sensitized mice, or for BALF IFN-γ in $ApoE^{-/-}$ mice (Lund et al. 2007). In the Day et al. (2008) and Reed et al. (2008) studies, there was an indication that the gaseous components of GE were the primary factor in eliciting several of the immunological responses, based on only filtered GE exposure eliciting the response; in certain instances, there was no lack of difference in the magnitude of the effect between whole-GE- and filtered-GE-exposure groups. Observations of pulmonary inflammatory responses and alterations of pulmonary cytokines by GE exposure are discussed in Section 3.1.2.3. Exposure to GEPs from a two-stroke motorcycle engine in mice elicited pro-allergic responses, such as increased total serum IgE, in the absence of exposure to an allergen (Lee et al. 2004). In a subsequent study (Lee et al. 2008), motorcycle GEP exposure in OVA-sensitized mice resulted in significantly increased IL-4 and TNF-α levels, as well as non-significant increases to IFN-γ and IL-5 in the BALF. Furthermore, significantly increased serum levels of OVA-specific IgE and IgG_1 were observed in sensitized mice.

AM functional changes due to GE exposure were examined in four *in vivo* studies and one *in vitro* study. In a subchronic study (Reed et al. 2008), histopathology findings revealed increased incidences of PM loading in AMs in mice and rats with high treatments of GE (see concentrations above) following 6 months of exposure. PM loading in AMs was also observed in rats from another study (Pepelko et al. 1979); however, this finding was confounded by the possibility of an infectious agent. The uptake of PM by AMs appears to alter the production of endogenous hydrogen peroxide and superoxide. Hydrogen peroxide production in unstimulated AMs was found to be decreased in male (at 6 months) and female (at wk 1 and 6 months) rats following high exposure to whole GE. In addition, superoxide production was decreased in unstimulated AMs in mid- and high-treatment male rats at 6 months and in stimulated AMs in female rats at wk 1 (Reed et al. 2008). In a subacute study (Seagrave et al. 2002), slight potency estimate reductions of superoxide responses in stimulated rat AMs were noted in rats exposed to normal-emitter vehicle gasoline emissions (engines operating at cold temperature), and slight decreases in peroxidase and superoxide responses in unstimulated AMs were noted for rats exposed to normal-emitter vehicle gasoline emissions (engines operating at ambient or cold temperature). Exposure to GEPs demonstrated a significant dose-dependent inhibition of the number of Fc receptors, anti-tumour cell toxic effect and antibody-mediated cell cytotoxicity effects in rat AM compared with control (Ye et al. 1999).

GEE or GEP effects on RAW264.7 (a murine macrophage cell line) and primary macrophages were evaluated in various *in vitro* studies. In a study by Che et al. (2010), co-incubation of RAW264.7 with GEEs resulted in the inhibition of cell proliferation and promoted apoptosis, resulting in a dose-dependent decrease in cell viability. GEE exposure also decreased immune efficiency in activated AMs (primary cells derived from adult rabbit), as evidenced by significantly decreased E-rosette formation, as well as significantly decreased AM-mediated tumour and antibody-dependent cellular cytotoxicity. In addition, E-rosette formation and AM-mediated tumour cytotoxicity activity were decreased in a dose-dependent manner. Exposure to 300 µg/ml of GEEs or GEPs from a two-stroke motorcycle engine resulted in cytotoxicity and apoptotic cell death in RAW264.7 cell line, mouse peritoneal macrophages

and rat AMs (Lee and Kang 2002). These effects were found to be attenuated by treatment with calcium chelators and antioxidants.

Although altered AM function and increased apoptotic death were induced by exposure to GE, GEPs, or GEEs, it was observed that pulmonary clearance was not impaired by subacute whole or filtered GE exposure, as demonstrated by the clearance of IT-instilled *Pseudomonas aeruginosa* in mice (Reed et al. 2008).

Overall, immunological parameters examined included allergic airway responsiveness, immunoglobulins, BALF cytokines and inflammatory cells, immune function and immunosuppression. Studies demonstrated that GEP from a two-stroke motorcycle engine could exacerbate AHR in IT-instilled, OVA-sensitized mice, but GE exposure did not exacerbate AHR in an allergic asthma mouse model. Motorcycle GEP exposure may also elicit pro-allergic responses (such as increased levels of serum immunoglobulins and pro-inflammatory BALF cytokines) in mice. However, the effect of GE on serum immunoglobulins or BALF cytokines and inflammatory cells was less clear, as a result of conflicting findings. Collectively, *in vivo* and *in vitro* findings on AM functional changes indicate that GE exposure could elicit a phagocytic response from AMs, which are important regulators of pulmonary immune response. There was also evidence that GE exposure may suppress some immune responses, as demonstrated by the attenuated peroxidase and superoxide production by AMs. In addition, suppressed AM immune functions (i.e. Fc receptors, anti-tumour cell and cell-mediated cytotoxicity) were also noted with GEP exposure. *In vitro* studies with GEEs as well as motorcycle GEPs demonstrated apoptotic cell death in primary macrophages and a macrophage cell line. In addition, immune efficiency was decreased in activated AMs following GEE exposure. Increased oxidative stress was also observed in the RAW264.7 cell line. Although AM function was impaired, pulmonary clearance was not adversely affected when challenged with a bacterium in mice exposed to GE. Further investigation is necessary in regard to the potential of immunosuppression, as well as the role and activity of immunoglobulins, cytokines and inflammatory cells, in relation to GE exposure.

3.1.4.4 Determination of causality

Overall, **it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and immunological effects**, based on insufficient evidence in the epidemiological and toxicological literature for immunological effects following GE exposure. The small number of studies evaluating the immunological effects restricts the ability to infer a causal relationship. From the toxicological studies, there is some evidence that GE exposure may augment pro-allergic responses and mixed evidence of allergic asthma induction. However, these allergic effects were not substantiated in the cross-sectional studies investigating increased risk of atopy outcomes in children from traffic-related GE surrogate exposure. Additionally, there is limited evidence of immunosuppression, although GE inhalation did not impair host defence function in an animal study.

This causality determination does not preclude evidence of adverse immunological effects of individual air pollutants to which GE contributes.

3.1.5 Reproductive and developmental effects

3.1.5.1 Evidence from epidemiological studies

There were no epidemiological studies reviewed that directly analyzed the reproductive or developmental effects associated with GE, or traffic-related GE surrogate exposure. SMRs for diseases of

the genitourinary system were provided in two cohort studies (Borgia et al. 1994; Forestiere et al. 1994), and testosterone levels were measured in a blood analysis from a cross-sectional study (Sancini et al. 2011). In addition, early life-stage exposure to traffic-related surrogates of GE may have increased susceptibility in children to adverse respiratory (Delfino et al. 2009; Nicolai et al. 2003; Pénard-Morand et al. 2010) and atopic health outcomes (Nicolai et al. 2003; Pénard-Morand et al. 2010).

The SMRs for diseases of the genitourinary system were found to be lower than expected in both taxi drivers and urban policemen; however, the number of observed cases in both cohort studies for taxi drivers (*n* = 12/2,311) and policemen (*n* = 3/3,868) were very small. In addition, the study design may not have properly accounted for confounders and selection biases (see Section 3.1.2.1.). Blood analysis revealed that traffic policemen had significantly lower mean free testosterone than the control group of indoor office workers, but the testosterone levels were not outside of the normal range for either group. One main limitation of this study was the lack of specificity in GE exposure in the traffic policemen. In studies with traffic-related surrogates of GE, an increased risk of adverse respiratory health outcomes, primarily asthma, was observed in children. In addition, a higher risk of developing allergic reactions was noted in one study, whereas the other study did not observe any significant associations between atopic outcomes with benzene. It should be noted that the examined atopic outcomes were different between the two studies.

Overall, epidemiological findings of reproductive and developmental effects due to GE exposure are very limited. The possibility that the observed findings were the result of chance, bias or confounding could not be discounted because of the limited number and quality of studies and the likely confounding by DE. Furthermore, there was no assessment of the potential long-term health consequences among children with chronic exposure to GE.

3.1.5.2 Evidence from controlled human exposure studies

No controlled human exposure studies related to reproductive or developmental effects of GE were found in the literature.

3.1.5.3 Evidence from toxicological studies

Reproductive and developmental outcomes due to GE, irradiated GE, GEP, or GEE exposure were assessed in six animal toxicity studies and two *in vitro* studies, which examined reproductive parameters, developmental AHR, oxidative stress, DNA damage to male reproductive organ, estrogen catabolism and anti-estrogenic effects (Che et al. 2009; Huang et al. 2008; Hueter et al. 1966; Lewis et al. 1967; Lin et al. 2014; Reed et al. 2008; Ueng et al. 2004; Wang et al. 2002).

In a reproductive toxicity study (Huang et al. 2008) exposure to 1:50 and 1:10 diluted GE from a two-stroke motorcycle engine resulted in significantly decreased sperm counts in the testis and epididymis, in a dose- and time-dependent manner. Subsequent studies exposing rats to 1:10 diluted GE for 4 wk also resulted in other adverse reproductive outcomes, including lower serum testosterone levels, decreased testis and epididymis weights, and histopathological effects in the testes (seminiferous tubule atrophy, moderate to severe germ cell necrosis, absent elongated spermatids, decreased spermatocytes, formation of multinuclear giant cells in damaged seminiferous epithelium). Given the sex-specific toxicity to the male reproductive system, this is a possible contributing factor for the observed decreased reproductive success (decreased male and female mating indexes, fewer gravid females, fewer implantation sites, preimplantation loss) and reduced litter size (fewer live fetuses per litter). No treatment-related effects were noted for corpora lutea count, post-implantation loss, fetal

body weight and fetal sex ratio. Furthermore, analysis of testes homogenates from ME-exposed rats revealed pro-inflammatory effects due to significantly increased cytokines (i.e. IL-6, IL-1β and COX-2) levels, and oxidative stress based on non-significant increased lipid peroxidation and GST. In addition, significantly decreased 7-ethoxycoumarin O-deethylase and SOD were noted in testes. Administration of vitamin E to GE-exposed rats demonstrated a partial attenuation of sperm count, IL-6 protein, IL-6 mRNA, IL-1β mRNA, COX-2 mRNA and serum testosterone levels. Moreover, metabolomics analysis of testicular tissue samples from rats exposed to 1:10 diluted GE showed altered amino acid levels, with betaine levels significantly increased in the hydrophilic extracts (Lin et al. 2014). The induced metabolic changes in the testes may contribute to the observed testicular toxicity.

Reproductive parameters and pup survival were also examined in female mice exposed to raw or irradiated GE in a chronic study (Hueter et al. 1966). Significant decreases in number of litters, total number of newborn, number of potential dams with at least one litter, average number of litters and survival rate of pups from birth to weaning (postnatal day or PND 21) were observed in dams exposed to two higher levels of irradiated GE treatments (with concentrations at 60 and 100 ppm CO, 20 and 36 ppm HC, 0.6 and 1.0 ppm O_3, 1.5 and 2.0 ppm NO, and 1.4 and 1.9 ppm NO_2, respectively). There were no effects on the average number of pups per litter or average birth weight resulting from exposure to irradiated GE. In addition, raw GE exposure to dams did not adversely affect the measured fertility and pup survival parameters.

As a follow-up to the Hueter et al. (1966) study, a reproductive study was conducted to further examine the effects of irradiated GE exposure during premating on fertility, fetal development and pup survival in mice (Lewis et al. 1967). Results indicated that premating exposure of males to irradiated GE (with concentrations of 20–100 ppm CO, 0–4.0 ppm NO, 0–1.5 ppm NO_2, 10–40 ppm HCs, 0–1.5 ppm O_3) resulted in fewer gravid females and slightly decreased cumulative average implantation sites and litter size. A similar decrease in cumulative average implantation sites and litter size was observed when females were switched from the premating exposure condition to a different exposure condition (clean air or irradiated GE) for mating and parturition. However, gross necropsy of reproductive tracts and histological examination of the ovaries in non-pregnant females revealed no anomalies. A significantly increased cumulative mortality rate was observed in pups exposed to irradiated GE between PND 1 and PND 8 compared with pups exposed to clean air. However, no significant differences were noted for cumulative mortality rates from PND 1 to PND 21. Furthermore, there was some evidence that increased pup mortality rates correlated with males exposed to irradiated GE during premating. No treatment-related effects for body weights in lactating dams or in pups were noted at PND 12 and 21. It is noteworthy that leaded gasoline was utilized in the generation of test atmospheres in both the Hueter et al. (1966) and Lewis et al. (1967) studies. The use of leaded gasoline may confound the interpretation of reproductive findings, since lead is a known reproductive toxicant.

In utero and postnatal exposure to GE in OVA-sensitized and non-sensitized mice did not demonstrate significant changes in developmental respiratory allergic responses and airway reactivity (Reed et al. 2008). See Section 3.1.4.3.

In a subacute study (Che et al. 2009), male rats were exposed to GEE (an extract mainly composed of 78.4% aromatic compounds, 12.3% alkanes and alkenes, <0.5% PAHs) by IT instillation. Examination of homogenized testes demonstrated oxidative stress and oxidative damage, as indicated by dose-related increased levels of malondialdehyde (lipid peroxidation) and carbonyl proteins (oxidative protein damage), respectively. Conversely, activity levels of SOD and GPx (antioxidant enzymes) were inhibited in a dose-dependent manner. In addition, testicular cell DNA damage was observed, as indicated by a

significantly increased rate of tailed cells in the mid- and high-dose group. It was also noted that the comet tails from testicular cells were significantly longer, reflecting greater DNA damage, in the high-dose group. No difference in testicle to body weight ratio was observed between GEE-exposed animals and the control group. Based on these results, there is a potential for GEE-induced oxidative stress and damage in rat testes to adversely affect fertility and the reproductive system.

In vitro studies conducted in MCF-7 cells (a human breast cancer cell line) treated with GEPs from a two-stroke motorcycle engine reported suppressed estrogen-induced cell proliferation (Ueng et al. 2004) and increased estrogen catabolism (Wang et al. 2002). GEPs increased estrogen catabolism, likely by inducing estrogenic-metabolizing CYP1A1 and CYP1B1, as well as increasing several CYP450-dependent monooxygenases, such as benzo(a)pyrene hydroxylase, 7-ethoxycoumarin O-deethylase, 7-ethoxyresorufin O-deethylase, and methoxyresorufin O-dealkylase (Wang et al. 2002). Furthermore, incubation of 17β-estradiol (E_2) with microsomes (prepared from GEP-treated MCF-7 cells) resulted in greater E_2 metabolite (2-OH-E_2 and 4-OH- E_2) formation (Ueng et al. 2004). In whole-cell estrogen binding assays, GEPs also demonstrated the ability to displace bound tritiated [^{3}H]E_2 from the estrogen receptor (ER) and increase benzo(a)pyrene hydroxylase activity (Ueng et al. 2004). However, GEPs did not displace bound tritiated [^{3}H]E_2 from recombinant human estrogen receptor α (hERα), which limits its biological relevance to humans.

The current studies provide some evidence that inhalation exposure to GE may result in adverse reproductive parameters in rats and mice. However, it should be noted that the particle levels were quite high for studies conducted with GE from a two-stroke motorcycle engine. In addition, the adverse reproductive outcomes appear to be due to sex-specific reproductive toxicity in male animals, based on the observed oxidative stress, oxidative protein damage, inflammatory responses, metabolic changes, and DNA damage in the testes. In addition, perturbed hormone levels were noted, as evidenced by decreased serum testosterone levels in motorcycle-GE-exposed rats and anti-estrogenic properties of motorcycle GEPs in MCF-7cells. No treatment-related effects on the developing immune system were observed in GE-exposed mice. The potential effect of GE exposure on reproductive outcomes warrants further investigation.

3.1.5.4 Determination of causality

Overall, **it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and reproductive and developmental effects**, based on insufficient evidence in the epidemiological and toxicological literature for reproductive and developmental effects following GE exposure. The small number of studies evaluating the reproductive and developmental effects and the limitations of the studies restricts the ability to infer a causal relationship. There is limited evidence from toxicological studies of effects in male animals exposed to high levels of GE, including adverse effects in the testes and reduced sperm counts associated with reduced reproductive success. Reduced reproductive success was also noted in an older study that may have been confounded by the use of leaded gasoline. Additionally, there is a lack of studies that evaluated developmental effects of GE exposure.

This causality determination does not preclude evidence of adverse reproductive and developmental effects of individual air pollutants to which GE contributes.

3.1.6 Central nervous system effects

3.1.6.1 Evidence from epidemiological studies

In a cohort study of urban policemen in Rome, the SMR for diseases of the nervous system was assessed (Forestiere et al. 1994). The number of observed deaths due to diseases of the nervous system was small (*n* = 9) and there was no significantly increased SMR for diseases of the nervous system among urban policemen predominantly exposed to GE resulting from their occupation. Due to the sole reliance on evidence of nervous system effects associated with GE exposure in one cohort study, the possibility of chance could not be ruled out. As previously noted, selection bias resulting from a healthy worker effect likely occurred in this cohort study. Furthermore, there was no characterization of GE exposure; consequently, there was a potential for confounding by other air pollutants, including DE. Owing to the results being drawn from one study, it was not possible to rule out chance, bias or confounding. Conclusions regarding adverse central nervous system effects and their association with GE exposure could not be drawn based on the current evidence in the database.

3.1.6.2 Evidence from controlled human exposure studies

No controlled human exposure studies related to central nervous system effects of GE were found in the literature.

3.1.6.3 Evidence from toxicological studies

The potential for GE or GEP exposure to affect neurological parameters was assessed in a neurobehavioural sound avoidance test (Stupfel et al. 1973) and a motor function test with examination of the sciatic nerve (Liu et al. 2002). Rats exposed to GE via inhalation (57.86 ppm CO, 23.46 ppm NO_2 and NO, 2.0 ppm aldehydes, <0.5 mg/L HC, 1.0 ppm NH_3) demonstrated a lower cumulative number of avoided shocks compared with control. However, major study limitations such as outdated engine technology and gasoline fuel composition are noted for this study. Decreased motor function, motor nerve conduction velocity and activity of the enzyme Na^+,K^+-ATPase in the sciatic nerve were observed in rats exposed to GE (inhalation) and GEPs (IT-instillation), and in mice exposed to GEPs (IP administration) from a two-stroke motorcycle engine. However, these neurobehavioural and neurotoxicity findings should be interpreted with caution, due to the presence of methylcyclopentadienyl manganese tricarbonyl (MMT) (a fuel additive) in the gasoline used to generate the GE and GEPs. The presence of MMT resulted in elevated manganese levels in the blood and sciatic nerve of animals, and manganese is a known neurotoxicant. Further investigations on neurological health outcomes associated with GE exposure are necessary, due to the small number of studies and major limitations with the study findings.

3.1.6.4 Determination of causality

Overall, **it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and neurological effects**, based on insufficient evidence in the epidemiological and toxicological literature for central nervous system effects following GE or traffic-related GE surrogate exposure. The small number of studies evaluating the neurological effects and the limitations of the studies restrict the ability to infer a causal relationship.

This causality determination does not preclude evidence of adverse neurological effects of individual air pollutants to which GE contributes.

4 Conclusions

Due to the important contribution of GE to air pollution in North America, stringent emission regulations have been introduced for new gasoline vehicles and engines at multiple points over the last several decades, targeting both the on-road and the off-road fleets. This has resulted in the implementation of advanced engine and emission control technologies. For example, the most recent regulations addressing light-duty on-road vehicles[1] take effect in the 2017 model year and, once fully phased in in 2025, will represent a reduction of up to 80% in per-vehicle emissions compared with previously available technologies. In addition, the quality of gasoline fuel has been improved over time, such as through the elimination of tetraethyl lead and reductions in the benzene and sulphur content, which have contributed to important population health benefits. Individual jurisdictions have also adopted additional strategies to mitigate in-use gasoline engine emissions, such as anti-idling restrictions and mandatory LDV inspection and maintenance programs. Overall, Canadian mobile source emissions, including those from gasoline engines, have decreased over the last 30 years, representing a key success in the management of air quality and the protection of human health. However, given the number of vehicles and engines in use, the age structure of the in-use fleets, and the vehicle kilometres travelled by Canadians, gasoline engines remain an important source of air pollution in Canada today. The adverse health impacts of air pollutants to which GE contributes, including $PM_{2.5}$, O_3, NO_2, benzene and PAHs are well characterized in the scientific literature and include increased risk of cardiorespiratory mortality and morbidity and of cancer. In addition, there is growing evidence indicating that air pollutant exposure is associated with the development of diabetes and adverse neurological and reproductive outcomes. The overall air pollution health impacts associated with the contribution of gasoline-powered mobile sources to air pollutants represent a public health cost to Canadian society. Those health impacts are quantitatively estimated in Part B of this document.

Gasoline-powered vehicles are universally present on Canadian roadways and are particularly concentrated in urban environments. It is reasonable to assume that almost all Canadians are regularly exposed to GE. It is very difficult to quantify general population exposure to GE as a mixture, due to differing population characteristics and behavioural patterns, the complex and variable nature of GE, and the fact that many of its constituents are emitted from other combustion sources. However, it is clear that microenvironments influenced by heavy traffic, such as those near major roads, represent scenarios where the population is exposed to higher levels of GE. Given that approximately 2, 4 and 10 million Canadians live within 50, 100 and 250 m, respectively, of a major road (Evans et al. 2011), the potential population exposure is considered substantial. Several surrogates have been used to reflect GE exposure, such as CO and benzene; however, none is unique to GE, complicating the interpretation of results. The utility of central site monitoring data is limited for estimating exposure in near-road environments or other environments disproportionately impacted by GE. Multiple modelling approaches have been used to capture the spatial variability in exposure to traffic pollutants, including proximity-based assessment, land-use regression modelling, and statistical interpolation. However, population exposure to GE specifically has not been assessed using these tools. In Part B of this assessment report, gasoline-powered vehicles and engines are considered as an emission source of individual air pollutants, and the contribution of those emissions to ambient concentrations of individual air pollutants is estimated using photochemical air quality modelling.

[1] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/DetailReg.cfm?intReg=222

Part A of the current risk assessment reviewed published studies that examined the health effects of GE exposure for literature published up to December 15, 2014 and the conclusions of IARC Monograph 105 (IARC 2013). Only studies assessing the impacts of GE as a mixture were examined in this review. The cancer and non-cancer health effects of individual pollutants in GE or produced secondarily in the atmosphere from primary GE emissions (such as $PM_{2.5}$, O_3, NO_2, benzene, 1,3-butadiene, PAHs, formaldehyde and acetaldehyde) are well-established and were considered outside the scope of Part A, as they have previously been comprehensively reviewed by Health Canada (Environment Canada and Health Canada 1993, 1994, 2000a, 2000b, 2001; Health Canada 2006, 2013, 2016a) and other international agencies. Using a weight of evidence approach, the information on GE reviewed in Part A of this document provides evidence that suggests GE emissions adversely affect human health and the respiratory system in particular. Overall, the available literature database is limited, with many studies that are relatively old. Limitations in study design, analysis and reporting hindered the interpretation of results from many epidemiological and toxicological studies. It is inherently difficult to examine the health effects of GE as a mixture in epidemiological studies, given that most occupational groups with GE exposure and the general population are co-exposed to GE and DE, and that a unique surrogate for GE exposure has not been identified.

Specifically, it is concluded that there is inadequate evidence to infer a causal relationship between GE exposure and carcinogenicity. This causality determination is based on insufficient study quantity and quality in the epidemiological and toxicological literature for the evaluation of carcinogenicity associated with GE exposure. Although there was the presence of dose-related, increased incidences of tumours in animals exposed to GE condensates and PAH fractions of GE condensates, the exposure concentrations are considered to be of greater magnitude than relevant pollutant exposure concentrations, and the routes of exposure (i.e. lung implantation and dermal) are of less relevance than inhalation exposure. Robust supporting evidence of genotoxicity and mutagenicity are demonstrated for whole GE and various sub-components of GE (e.g. GEPs and GE condensates); however, long-term inhalation exposure to GE did not result in a significant increase in tumour incidences in any of the multiple animal species examined. Overall, the weight of evidence for a causal relationship is inadequate for GE and carcinogenicity; however, the causal determination does not imply that GE is not carcinogenic. Rather it indicates that the current evidence is of inadequate quantity and/or quality to draw conclusions, due to weak GE exposure assessment methodologies, lack of control for biases and confounders, and the need for mechanistic studies to elucidate the mode of action for tumorigenesis due to GE exposure. This causality determination does not preclude the known and well-documented carcinogenicity of individual compounds found in GE, such as benzene and PAHs: rather, the conclusion reflects the studies that investigated GE as a mixture.

Regarding the potential role of GE in the development of non-cancer health endpoints, a number of causality determinations are concluded, based on the current review of the literature. The evidence is suggestive, but not sufficient to infer a causal relationship between GE exposure and adverse respiratory health outcomes, which includes increased risk of asthma in children, as well as observations of respiratory oxidative stress, inflammation, AHR exacerbation and damage in acute animal toxicity studies. Although adverse respiratory outcomes are observed, measured parameters of lung function in animals are not affected. For chronic GE exposure, there is insufficient evidence to draw conclusions, due to the small number of chronic exposure studies identified and the quality of the available studies (e.g. age of study, use of leaded gasoline). The evidence reviewed is inadequate to infer a causal relationship between GE exposure and adverse cardiovascular outcomes, based on limited study numbers and their inadequate quality in both the epidemiological and toxicological literature. The literature provides limited evidence of cardiovascular oxidative stress, inflammation, altered vasculature

and vasomotor responses, histopathological findings and altered cardiac function. Also, there are some indications from studies using an animal model of disease that GE exposure may exacerbate the development and progression of atherosclerosis. There is currently inadequate evidence to draw conclusions regarding the role of GE exposure in the development of immunological, reproductive/developmental and neurological effects. Although the database remains limited, many of the observed adverse health effects from GE exposure may be associated with oxidative stress. It is also noted that the gaseous or particulate components of GE may elicit different adverse health outcomes. The above conclusions regarding the available evidence of the role of exposure to GE as a mixture in the development of non-cancer endpoints do not preclude the extensive evidence and previous Health Canada causality determinations of the significant health effects of individual air pollutants to which GE contributes.

Quantitative risk assessment and the derivation of exposure guidance values for GE were not pursued in this document, due to the lack of sufficient evidence of causality of adverse health effects resulting from the limited literature database, as well as the current inability to quantify GE exposure in the general population.

Overall, it is concluded that gasoline-powered engines and equipment are an important source of air pollutants that have significant population health impacts in Canada, including $PM_{2.5}$, O_3 and NO_2, and that exposure to GE is ubiquitous (see Part B of this document). Further efforts to reduce GE emissions and human exposure to GE are expected to result in population health benefits. The database of studies examining the role of the GE mixture in adverse health effects (including cancer, cardiovascular, immunological, reproductive, developmental and neurological outcomes) is of inadequate quantity and quality (i.e. too limited) to infer a causal role for GE. The weight of evidence suggests that GE affects the respiratory system, which is consistent with the known health effects of air pollution to which GE contributes, but the available data examining the GE mixture itself are limited and further study is required.

5 Key uncertainties and gaps

Given the ubiquitous presence of gasoline vehicles and engines in modern society and the pervasive exposure of populations to GE over many decades, there is limited information on the health effects associated with exposure to GE as a complex mixture. Multiple key air pollutants to which GE contributes, such as ambient $PM_{2.5}$ and NO_2, have been extensively studied. Similarly, the carcinogenicity of many compounds in GE, such as benzene, PAHs and formaldehyde, is well established by international regulatory agencies. However, the potential effects of GE itself as a mixture have received relatively little attention, in terms of both epidemiological and toxicological research studies. There is substantially more information in the epidemiological literature on the health effects associated with exposure to traffic emissions (a mixture of both GE and DE), but that literature is considered outside the scope of this risk assessment, which is focussed on GE specifically and included only those traffic studies for which a GE surrogate was examined. The lack of studies on the effects of GE in humans is likely due in part to the difficulty of conducting large-scale epidemiological studies without a reliable and specific surrogate of GE exposure.

The overall evidence base reviewed here is limited by a number of factors. The relatively small number of studies examining individual health endpoints and the major limitations of some studies all hamper the interpretation of the findings. There are inconsistencies in the available evidence and key knowledge gaps for health effects associated with exposure to GE as a mixture. While a weight of evidence

approach was used to assess the causal relationships for specific health endpoints, the uncertainties and data gaps are such that chance, bias and confounding cannot be ruled out in the epidemiological literature, and key study limitations impede the interpretation of toxicological studies.

Although there is evidence of biological plausibility, genotoxicity and mutagenicity, and indications of potential carcinogenicity from GE condensates, the causal relationship for potential carcinogenicity associated with GE exposure is inadequate for drawing any conclusions based on the overall quality of the epidemiological and toxicological literature. In particular, there was uncertainty with respect to the route of exposure used (i.e. lung implantation and dermal application) in studies evaluating GE condensates, which lessened the strength of the evidence for carcinogenicity. In addition, studies to date have not reported increased tumour incidences in various animal models exposed to GE by more relevant routes of exposure, such as whole-body inhalation; this represents a gap in the mode of action for GE-induced tumorigenesis. Further mechanistic studies and large-scale epidemiological studies are needed in order to better elucidate the potential carcinogenic risk of GE.

The available evidence suggests that exposure to GE as a mixture may cause adverse respiratory effects. This is consistent with the knowledge of effects associated with ambient air pollution, which includes major contributions of emissions from mobile sources, such as gasoline engines and equipment. However, there is a relatively small body of literature that has specifically examined the adverse effects of GE exposure, which limits our understanding of the population health effects of a key pollution source that is intimately linked geographically to populations. Furthermore, the evidence from studies examining other non-cancer health outcomes, such as effects on the cardiovascular, immune, reproductive and developmental, and nervous systems, is inadequate for drawing any conclusions regarding a causal role of GE.

The majority of the epidemiological evidence in this review is derived from occupational studies, with only a few studies examining health effects in the general population. As a result, there is minimal information regarding the potential human health effects associated with GE exposure in sensitive subpopulations. A few studies examining potential adverse health effects in children have been conducted, but further research in this area is warranted. In general, further investigations are needed to study the effects of GE exposure in populations at risk, including those at different life stages and those with other pre-existing conditions.

There is a general lack of human exposure–response information for chronic non-cancer health effects associated with GE exposure in the epidemiological literature, and few high-quality chronic exposure animal studies. Consequently, there is a need for high-quality epidemiological and toxicological studies to investigate exposure–response relationships. Furthermore, additional mechanistic studies to better understand mode(s) of action for GE-induced adverse health outcomes would contribute significantly to the determination of causality.

Results from some older studies are considered confounded due to the use of leaded gasoline to generate GE, affecting the interpretation of the study results. This highlights the need to conduct more comprehensive testing of GE using modern engines and fuels.

Health Canada recognizes that there have been evolutions in gasoline engine design and emission after-treatment, largely driven by new engine emission regulations over time. Correspondingly, gasoline fuel quality has changed with the new engine designs. In addition, regulations have required changes to gasoline fuel formulation, such as removal of tetraethyl lead and lowering of benzene, in order to

minimize population exposure to toxic compounds. The GE exposures in the epidemiological and toxicological studies reviewed in this document were mostly derived from older-technology engines. It is noted that approximately one-quarter of the toxicological studies reviewed were conducted with emissions, particles or GEP extracts generated from two-stroke motorcycle engines. Furthermore, GE emissions may vary both qualitatively and quantitatively between different engine types and due to atmospheric transformation by photochemical processes. As a result, there remains uncertainty on whether different toxicological effects would be observed for GE following atmospheric reactions.

In summary, addressing these identified uncertainties and knowledge gaps will be critical to improving our understanding of the health effects associated with exposure to GE as a mixture.

Part B – Health impacts assessment of gasoline emissions

Gasoline emissions are an important primary source of CACs such as PM, NOx and CO; they also contribute to the formation of secondary pollutants in the atmosphere, including secondary particulate matter and O_3. Health Canada has previously published comprehensive weight of evidence analyses of studies that examined the health effects of individual air pollutants to which GE contributes as a source (Environment Canada and Health Canada 1993, 1994, 2000a, 2000b, 2001; Health Canada 2006, 2013, 2016a). Many of the health effects of CACs and air toxics are well characterized in the literature and the risks of adverse health outcomes associated with incremental changes in air concentrations have been quantified.

In Part B of this document, Health Canada used emission inventories and computer models to quantify the population health impacts or risks associated with the contribution of gasoline mobile source emissions to CAC (CO, NO_2, O_3, $PM_{2.5}$ and SO_2) and air toxic (acetaldehyde, benzene and formaldehyde) concentrations in Canada.[1] The gasoline mobile source emissions that were considered in this analysis include exhaust, evaporative and TWBL emissions from gasoline vehicles and engines. Evaporative gasoline emissions from stationary sites such as those from refueling stations or fuel storage facilities were not included; the effects of these will be considered in a review of gasoline fuel under the Chemicals Management Plan of Canada and reported elsewhere. The analysis presented here was conducted in a stepwise manner: (1) estimate emissions from gasoline on-road vehicles and off-road applications in Canada; (2) estimate the impact of those emissions on ambient concentrations of air contaminants across the country; and (3) estimate population health impacts or risks resulting from the incremental contribution of gasoline emissions to air pollution levels. The health impact assessment, which is complementary to the traditional risk assessment approach presented in Part A, was undertaken for calendar year 2015.

6 Mobile source gasoline emissions in Canada

ECCC developed a national emission inventory for the year 2015 (Table 6-1). Primary emissions were projected for all source categories except natural sources, with special attention being given to on-road

[1] Based on the current capabilities of national-scale air quality models, as well as Health Canada-endorsed toxicity reference values and published peer-reviewed epidemiological studies, the health impact analysis in Part B is limited to these eight air pollutants.

and off-road mobile gasoline sources.[1,2] All Canadian engine emission standards and fuel regulations planned for 2015 were considered.[3] Gasoline fuels with low sulphur (25 ppm) and benzene (less than 1%) content and no ethanol content were selected for mobile source emissions modelling. The sulphur content of ultra-low sulphur diesel was set at 10 ppm.

Table 6-1. Inventory of air pollutant emissions for anthropogenic sources in Canada in 2015

Sources	Emissions (tonnes)						
	CO	NH_3	NOx	PM_{10}	$PM_{2.5}$	SO_2	VOCs
Incineration	4 940	147	2 502	468	415	2 638	1 362
Industrial	1 466 406	15 885	595 921	173 383	82 428	673 038	668 258
Miscellaneous	4 004	2 368	18	10 056	9 967	0	233 051
Non-industrial	761 414	1 883	271 181	117 649	113 759	281 819	105 717
Open	26 270	446 944	8 395	6 327 244	998 465	2 090	283 080
Off-road transportation							
Aircraft[a, b]	33 748	7	10 765	189	184	1 142	8 976
Locomotive[b]	16 910	108	95 830	3 066	2 896	2 417	4 012
Marine	11 028	140	131 533	11 731	10 752	3 578	4 330
Off-road diesel	112 984	230	214 070	17 828	17 471	387	23 343
Off-road gasoline	2 023 395	139	35 740	6 976	6 556	185	190 376
Off-road LPG	19 501	–	4 289	78	73	–	1 034
Off-road multi-fuel	2 263	–	178	4	4	1	107
Off-road CNG	5 361	–	1 564	29	27	–	14
On-road[c]							
On-road gasoline[d]	3 069 863	22 638	141 153	5 975	2 731	1 569	141 017
HDGV	221 379	79	29 204	446	218	79	16 058
LDGT	1 343 841	9 809	62 293	2 386	1 084	772	60 846
LDGV	1 482 562	12 734	48 636	3 094	1 403	714	61 557
Motorcycles	22 081	15	1 020	48	27	3	2 556
On-road diesel[d]	63 508	343	166 919	9 057	7 133	320	14 649
HDDV	59 597	301	164 183	8 711	6 885	301	13 166
LDDT	2 510	29	2 328	255	186	15	1 279
LDDV	1 400	13	408	92	63	4	204
National total[c,d]	**7 621 595**	**490 829**	**1 680 058**	**6 683 732**	**1 252 862**	**969 184**	**1 679 326**

CNG: compressed natural gas; CO: carbon monoxide; HDDV: heavy-duty diesel vehicle; HDGV: heavy-duty gasoline vehicle; LDDT: light-duty diesel truck; LDDV: light-duty diesel vehicle; LDGT: light-duty gasoline truck; LDGV: light-duty gasoline vehicle; LPG: liquid petroleum gas; NH_3: ammonia; NOx: nitrogen oxides; PM_{xx}: particulate matter with a mass median aerodynamic diameter of *xx* µm or less; SO_2: sulphur dioxide; VOCs: volatile organic compounds

[a] Landing and takeoff

[b] Although some rail or aircraft applications consume gasoline, these are not considered in off-road gasoline applications assessed within the current assessment.

[c] TWBL emissions are included in the on-road PM_{10} and $PM_{2.5}$ estimates.

[d] Totals may differ from sum of components due to rounding.

The 2015 Canadian mobile source emission inventory combined projections from three different models: NONROAD2012C for off-road applications,[4] MOBILE6.2C for the light-duty on-road fleet and Motor Vehicle Emission Simulator version 2010a (MOVES2010a) for on-road HDVs. These models, initially developed by the US EPA, have been modified to reflect Canadian conditions (e.g. vehicle

[1] Open source emissions (such as dust from farms, construction operations and paved and unpaved roads) are dispersed over large areas in a non-point manner.

[2] Although some rail or aircraft applications consume gasoline, these were not considered in off-road gasoline applications assessed within the current assessment.

[3] The emission inventory was developed in 2012–13.

[4] Off-road gasoline applications include, for example, agricultural, mining and construction equipment.

population and age distribution, vehicle emission standards). The models provided emission rates for a series of pollutants, such as NOx, PM, SO_2 and VOCs, which were then combined with vehicle activity data. Emission factor ratios based on the SPECIATE data set from the US EPA were added for compounds that are not explicitly modelled (e.g. formaldehyde, acetaldehyde and benzene). Estimates were available for exhaust, evaporative and TWBL emissions of air pollutants on a regional and provincial or territorial basis.[1]

Table 6-2. Air pollutant emissions from the use of gasoline-fuelled on-road vehicles and off-road engines by province or territory, in 2015

	CO	NH_3	NOx	PM_{10}	$PM_{2.5}$	SO_2	VOCs
Province or territory	On-road and off-road[a] gasoline emissions (tonnes)						
Alberta	767 766	2 916	30 964	1 807	1 300	248	49 103
British Columbia	525 290	2 611	27 329	1 122	696	200	34 604
Manitoba	232 217	801	9 846	573	436	68	20 336
New Brunswick	167 287	577	4 895	404	308	45	9 876
Newfoundland and Labrador	81 167	346	2 816	221	165	28	8 197
Northwest Territories	6 758	18	264	18	14	1	652
Nova Scotia	160 628	621	4 180	391	291	47	8 518
Nunavut[b]	1 241	4	54	1	1	0	56
Ontario	1 603 378	8 680	45 612	4 506	3 175	642	93 908
Prince Edward Island	30 638	99	1 056	80	63	9	2 883
Québec	1 011 005	5 156	29 862	2 403	1 622	362	51 733
Saskatchewan	500 647	923	19 781	1 419	1 214	101	51 249
Yukon	5 237	23	234	6	3	2	275
Canada—Total[c]	**5 093 258**	**22 777**	**176 893**	**12 951**	**9 287**	**1 754**	**331 393**

CO: carbon monoxide; NH_3: ammonia; NOx: nitrogen oxides; PM_{xx}: particulate matter with an aerodynamic diameter of xx µm or less; SO_2: sulphur dioxide; TWBL: tire wear and brake lining; VOCs: volatile organic compounds

[a] Excludes aircraft, locomotive and marine emissions.

[b] Data not available for off-road mobile sources in Nunavut; considered as nil for the current assessment.

[c] Totals may differ from sum of components due to rounding.

Table 6-2 shows the 2015 emissions from the use of on-road and off-road gasoline-fuelled vehicles/equipment by province and territory. The 2015 emission inventory reflects the following Canadian vehicle or engine population and fuel use data:

- 97% of on-road LDVs composed of light-duty gasoline vehicles (LDGVs) and light-duty gasoline trucks (LDGTs);
- 12 816 000 LDGVs and 8 691 000 LDGTs;
- on-road fuel use allocated almost equally to LDGTs (52%) and LDGVs (48%);
- heavy-duty gasoline vehicles (HDGVs) totalled 690 000 units (32% of the on-road HDVs);
- HDGVs mostly composed of smaller HDVs (Classes 2b and 3; e.g. delivery and utility vehicles);
- only 1% of HDGVs included in classes 7 and 8 (e.g. commercial transport and dump trucks);

[1] On-road gasoline emissions included TWBL emissions. TWBL emissions are not routinely generated by NONROAD2012C and are not available for off-road applications. TWBL contributes only to particulate emissions.

- off-road gasoline engines estimated at 13 607 000 units (87% of off-road engines); and
- "Lawn and garden," "Recreational" and "Commercial" off-road engine categories accounted for 92% of off-road gasoline fuel use.[1]

In terms of geographical distribution, HDV emissions occur on major roadways and truck routes, and in urban and commercial areas (e.g. walk-in delivery vans); LDGV emissions are concentrated in populated areas; and off-road gasoline applications are distributed in urban and rural regions.

Table 6-3. Canadian emissions for different source categories and national contributions from on-road and off-road gasoline sources, in 2015

	CO	NH_3	NOx	PM_{10}	$PM_{2.5}$	SO_2	VOCs
Canadian source category	Emissions (tonnes)						
On-road gasoline [a]	3 069 863	22 638	141 153	5 975	2 731	1 569	141 017
Off-road gasoline	2 023 395	139	35 740	6 976	6 556	185	190 376
On-road mobile—all fuels	3 133 371	22 980	308 072	15 032	9 865	1 889	155 666
Off-road mobile—all fuels [b]	2 163 504	369	255 841	24 915	24 131	573	214 874
All sources	7 621 595	490 829	1 680 058	6 683 732	1 252 862	969 184	1 679 326
Canadian source category[c]	Contribution from mobile gasoline source emissions (%)						
On-road gasoline/on-road emissions (all fuel types) [d]	98	99	46	40	28	83	91
Off-road gasoline/off-road emissions (all fuel types) [b,d]	94	38	14	28	27	32	89
On-road gasoline/total emissions (all sources) [d]	40	5	8	<1	<1	<1	8
Off-road gasoline/total emissions (all sources) [d]	27	<1	2	<1	1	<1	11
On-road and off-road gasoline / total emissions (all sources) [d,e]	67	5	11	<1	1	<1	20

CO: carbon monoxide; NH_3: ammonia; NOx: nitrogen oxides; PM_{xx}: particulate matter with an aerodynamic diameter of xx µm or less; SO_2: sulphur dioxide; VOCs: volatile organic compounds

[a] Total includes heavy-duty gasoline vehicles, light-duty gasoline trucks, light-duty gasoline vehicles and motorcycles.
[b] Off-road all fuel type emissions exclude aircraft, locomotive and marine emissions.
[c] The contributions were determined by comparing the on-road and/or off-road gasoline source emissions with the selected Canadian source category. For example, off-road gasoline sources contribute 94% to total off-road CO emissions.
[d] On-road PM emissions include tire wear and brake lining (TWBL) emissions; off-road emissions do not. TWBL emissions contribute only to $PM_{2.5}$ and PM_{10} emissions.
[e] Totals may differ from sum of components due to rounding.

Table 6-3 includes Canadian estimates for different emission source categories, as well as the contributions from on-road and off-road gasoline sources to Canadian emissions. On-road and off-road gasoline sources contribute 67% of CO, 11% of NOx and 20% of VOC emissions from all sources included in the national inventory. Within on-road emissions, gasoline vehicles are responsible for 98%, 99%, 83% and 91% of CO, NH_3, SO_2 and VOC emissions, respectively. Contributions from gasoline applications to off-road emissions reach 94% for CO and 89% for VOCs. On-road gasoline vehicles and off-road gasoline

[1] These categories include equipment or applications such as lawnmowers, all-terrain vehicles and pleasure craft engines. The off-road gasoline fuel consumption is equivalent to 10% of the on-road gasoline fuel consumption. Gasoline fuel use projections presented herein and used for the simulations were provided by ECCC. The fuel use data align but are not identical to fuel sales data released by Statistics Canada (available at www.statcan.gc.ca/tables-tableaux/sum-som/z01/cs0002-eng.htm).

engines contribute about 27–28% of $PM_{2.5}$ emissions in their respective source category. Although relative contributions from on-road sources to SO_2 emissions are high (83%), absolute gasoline SO_2 emissions are relatively low compared with other pollutants such as NOx or $PM_{2.5}$ (which are associated with smaller relative contributions). Note that the values presented in Table 6-3 are national averages and do not account for the spatial distribution of emissions across Canada; national contributions may not adequately reflect population exposures. Owing to the concentration of on-road and off-road gasoline sources in populated areas, gasoline emissions are expected to have a greater influence on urban air pollutant concentrations than is indicated by national averages. This is relevant for all pollutants.

7 Air quality impacts of on-road and off-road gasoline emissions

The Canadian emission inventory developed for the current assessment was used as input for air quality simulations with the source-oriented model A Unified Regional Air Quality Modelling System (AURAMS). AURAMS is a prognostic tool that integrates meteorological data, emission data and specific algorithms to simulate the diffusion, transport and chemical transformation of gases and particles in the atmosphere. AURAMS is used by ECCC to study the formation of O_3, PM and acid deposition in North America, in support of air quality regulations and management decisions for Canada.

The general modelling approach was as follows:

i. Simulations initially conducted over a continental 45 km grid domain;
ii. Simulations for two nested regional domains to obtain national coverage on a 22.5 km grid;
iii. Ground-level concentrations estimated for each grid cell and Canadian census divisions (CDs) for the following pollutants and concentration metrics:[1]
    - Annual average based on:
        - hourly data for air toxics,[2] CO, NH_3, NO_2, $PM_{2.5}$, SO_2, VOCs
        - daily maximum of hourly data for CO and O_3
    - Summer (i.e. May–September)[3] average based on:
        - daily maximum of hourly data for O_3

[1] The conventional AURAMS includes the ADOM II mechanism for gas-phase chemistry, updated with organic aerosol yields based on Odum et al. (1996) and the Canadian Aerosol Module based on Gong et al. (2003a, b); it resolves 157 chemical species, including 49 gaseous species and 9 particulate chemical compounds, each divided into 12 size bins. Another version of AURAMS included the SAPRC-07 toxics mechanism. There are 136 chemical species and 601 reactions in the SAPRC-07 toxics mechanism. SAPRC-07 was generated with the Kinetic PreProcessor and uses the Rosenbrock solver Rodas3. The NO_2 photolysis rate used as the common species to scale other photolysis rates in SAPRC-07 toxics was based on Carter (2010). For more details, refer to the Supporting Document to the Human Health Risk Assessment for Gasoline Exhaust (Health Canada 2017).

[2] The version of AURAMS used for the current assessment had limited capabilities for the simulation of air toxics, such as VOCs and PAHs. AURAMS provided ambient air quality predictions for acetaldehyde, acrolein, benzene, 1,3-butadiene, formaldehyde and 1,2,4-trimethylbenzene. However, based on a performance analysis of the modelling system using Canadian air monitoring data, there was less confidence in the output for acrolein, 1,3-butadiene and 1,2,4-trimethylbenzene. As a result, and for the purposes of this health impact assessment, the term air toxics refers only to acetaldehyde, benzene and formaldehyde.

[3] O_3 formation is generally higher in summer than in winter as a result of meteorological conditions.

To distinguish the impact of gasoline emissions from other sources of air pollution, three air quality scenarios were modelled: (1) with the full Canadian 2015 emission inventory, (2) with on-road gasoline emissions removed from the Canadian inventory and (3) with on-road and off-road gasoline emissions removed from the Canadian inventory.[1] The differences in air quality between the full emission inventory scenario and the scenarios with gasoline emissions removed are assumed to represent the contribution to ambient pollutant levels from on-road or on-road and off-road gasoline emissions in Canada. A scenario targeting off-road gasoline emissions explicitly was not simulated.

7.1 Impacts associated with gasoline emissions

The following discussion focuses on air quality simulation results for O_3, $PM_{2.5}$, NO_2, CO and air toxics. For a complete analysis of model outputs, refer to the Supporting Document to the Human Health Risk Assessment for Gasoline Exhaust (Health Canada 2017).

7.1.1 Ozone

O_3 is not emitted by engines: rather it is formed in the atmosphere from gaseous precursors found in mobile source emissions—notably, NOx and VOCs. Atmospheric and meteorological conditions, such as the local concentration of NOx, temperature, and hours of sunlight, influence whether the atmosphere in a particular region is either a source or a sink of O_3.

Based on the air quality simulations undertaken, gasoline emissions contribute to both increases and decreases in summer average daily maximum O_3 concentrations across Canada.[2] It is estimated that regions around the larger urban centres, as well as areas downwind of these urban centres, experienced increases of 1–9% (maximum reached east of Vancouver) associated with gasoline emissions. Reductions in O_3 concentrations associated with on-road gasoline emissions were also modelled in most of the large urban centres, exceeding 5% in Vancouver and Montréal grid cells (maximum reduction of approximately 15% recorded in Vancouver). These seemingly opposite effects are due to the complex photochemical reactions between O_3 and NOx, and the associated impact of high levels of NOx emissions in urban centres.

Figure 7-1 shows the net contributions from on-road gasoline emissions to summer average daily maximum O_3 levels. Most of Canada is associated with an increase in O_3 concentration of 0.01–0.5 ppb. Areas with active economies and higher populations (e.g. commercial and industrial regions surrounding urban centres, such as the Windsor–Québec corridor and the Lower Fraser Valley, and suburban agglomerations) correspond to increases in concentrations of 0.5–4 ppb. On-road gasoline emissions decrease O_3 concentrations by 0.01–4 ppb within most urban centres. The highest decrease is in Vancouver; conversely, the highest increase is east of Vancouver.

The air quality impacts associated with on-road and off-road gasoline emissions combined are larger than the effects of on-road gasoline emissions only, as expected. The combined on-road and off-road gasoline emissions slightly increased the magnitude of the O_3 contributions or expanded the areas already affected by on-road gasoline emissions only (not shown). On-road and off-road gasoline

[1] Similar scenarios were not assumed for the United States or Mexico.
[2] The results indicated that on-road gasoline emissions contributed more to O_3 levels in summer compared with annual estimates. Only summer O_3 simulations are discussed in this document.

emissions decreased O_3 concentrations in urban centres in fewer grid cells compared with on-road gasoline emissions. Owing to the non-linear processes affecting O_3 concentrations, it is not possible to accurately differentiate between contributions from on-road and off-road sources. The difference between the on-road and the on-road and off-road impacts is not linked to the incremental off-road gasoline emissions, but to the impact of the combined on-road and off-road gasoline emissions. It is possible that on-road and off-road gasoline emissions shifted the NOx/VOC equilibrium in some suburban grid cells from VOC-limited (O_3 production) conditions to NOx-limited conditions.

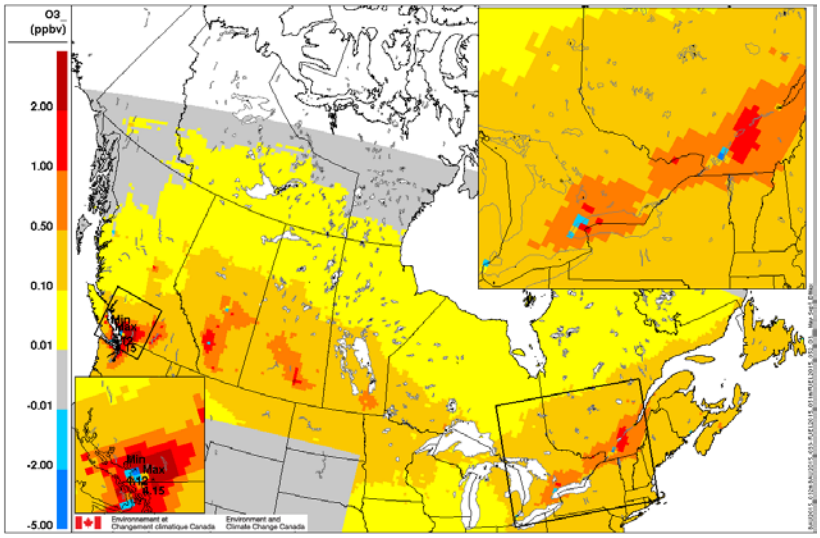

Figure 7-1. Net contributions to summer average daily maximum O_3 concentrations associated with on-road gasoline emissions in Canada in 2015

7.1.2 Fine particulate matter

On-road gasoline emissions led to a relatively small increase in the annual average $PM_{2.5}$ concentrations (between 0.1% and 5%) across Canada. Higher contributions (1–5%) were modelled in the Lower Fraser Valley area of British Columbia, the southern part of the Prairie provinces, the Windsor–Québec corridor and along the St. Lawrence River. Relative increases of 5–18% are also observed in some urban areas, such as Vancouver and Toronto, where on-road gasoline emissions are concentrated and of greater magnitude. In general, on-road gasoline emissions contributed more to $PM_{2.5}$ concentrations in urban areas than in less populated regions. Areas between and around urban centres were also affected by on-road gasoline emissions, owing to passenger vehicle traffic, the transportation of goods on major roads, and the atmospheric transport of pollutants.

Figure 7-2 shows the net contribution of on-road gasoline emissions to the annual average $PM_{2.5}$ concentrations. The results suggest that on-road gasoline emissions do not contribute greatly to annual average $PM_{2.5}$ concentrations in remote areas of Canada (i.e. between −0.01 µg/m^3 and 0.01 µg/m^3). On-road gasoline emissions contribute 0.01–0.10 µg/m^3 to $PM_{2.5}$ concentrations in populated and active economic regions (exclusive of urban centres) and 0.5–2 µg/m^3 within urban centres and on their periphery. A maximum contribution of 2.04 µg/m^3 is reported in Vancouver.

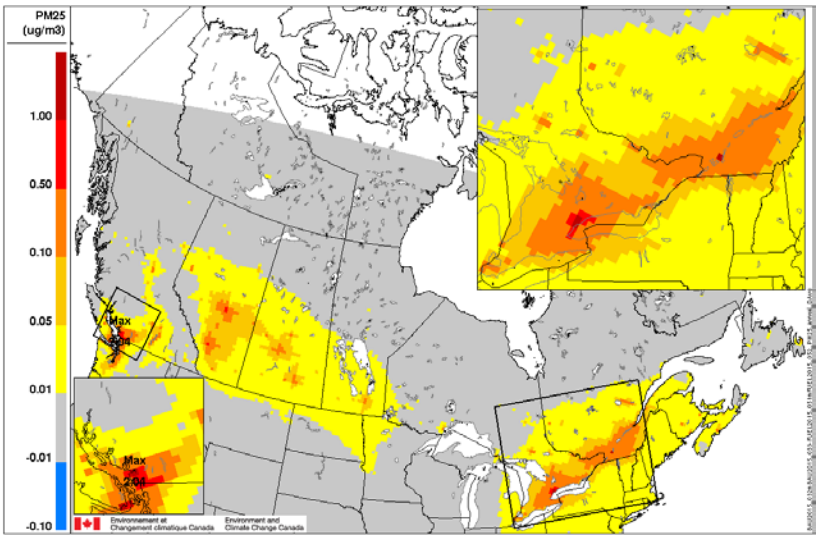

Figure 7-2. Net contributions to annual average $PM_{2.5}$ concentrations associated with on-road gasoline emissions in Canada in 2015

Differences in $PM_{2.5}$ concentrations between the on-road and the on-road and off-road scenarios were generally gradual and regular across Canada. Areas associated with higher contributions from on-road gasoline emissions were expanded when off-road gasoline emissions were included. The results did not suggest that off-road gasoline emissions affected $PM_{2.5}$ concentrations in distinctly different areas compared with on-road gasoline emissions. Slightly higher gasoline contributions were noted in urban centres and their surroundings under the on-road and off-road scenario. The maximum contribution, 2.23 µg/m^3, was observed in Vancouver.

7.1.3 Nitrogen dioxide

On-road gasoline emissions were associated with a relative increase in the annual average NO_2 concentrations of 0.01–10% across Canada, except around urban centres, where higher contributions of 10–44% were projected (e.g. Vancouver, Whitehorse, Regina, Winnipeg, Toronto and Montréal). The relative proportion of NO_2 concentrations associated with on-road gasoline emissions was notably high in the Lower Fraser Valley of British Columbia.

Figure 7-3 shows that on-road gasoline emissions contribute 0.01–0.5 ppb to the annual average NO_2 concentrations in populated regions and those with active economies and 0.5–5.5 ppb in urban centres (highest value recorded in Vancouver). On-road gasoline emissions are associated with virtually no change in annual daily NO_2 concentrations in undeveloped areas of Canada.

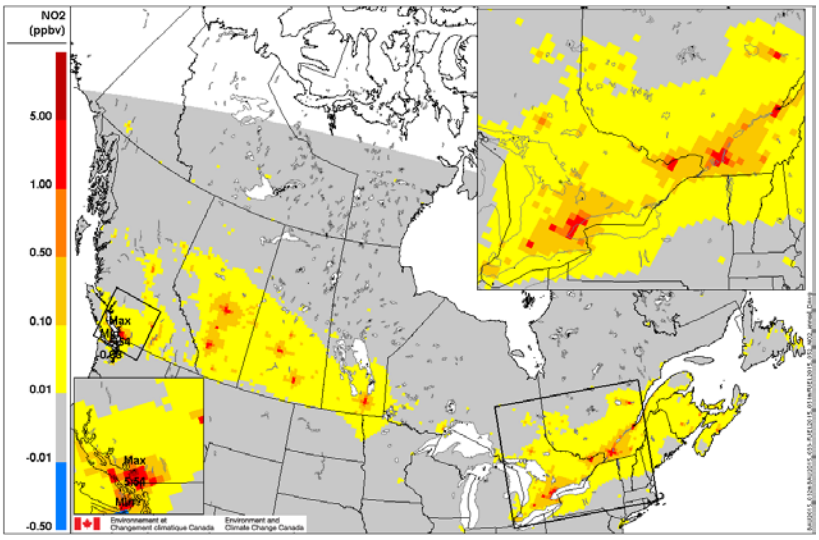

Figure 7-3. Net contributions to annual average NO_2 concentrations associated with on-road gasoline emissions in Canada in 2015

7.1.4 Carbon monoxide

Results for CO concentrations were available for the annual average of the daily maximum of hourly data (hereafter referred to as the annual average daily maximum CO) and the annual average values (not shown). Results for both metrics were very similar, with relative contributions of 1–10% over a large area of Canada and contributions of 10% to more than 60% in and around urban centres. The highest annual average daily maximum CO relative contribution, 76%, was in Edmonton. Contributions of 60% or more were also modelled in Vancouver, Calgary, Winnipeg and Montréal.

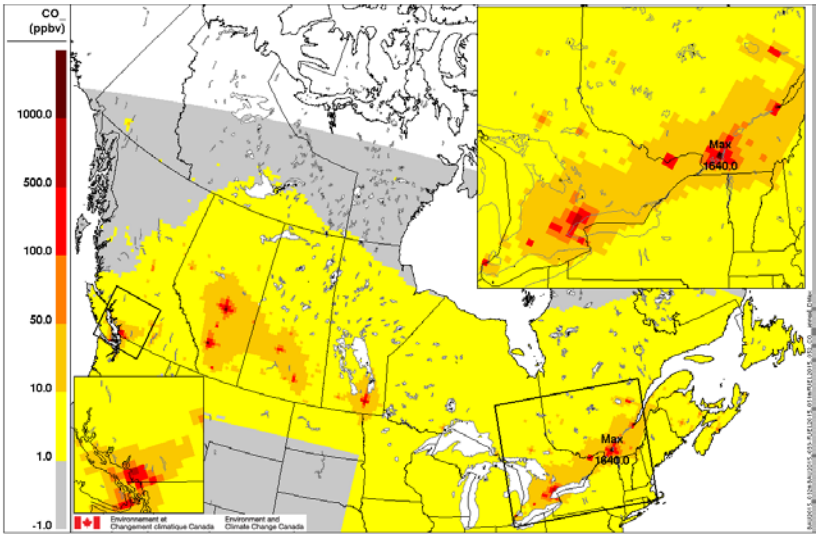

Figure 7-4. Net contributions to annual average daily maximum CO concentrations associated with on-road gasoline emissions in Canada in 2015

On-road gasoline emissions are associated with contributions of at least 1 ppb in annual average daily maximum CO concentrations over most of Canada, of 10–100 ppb in active regions (e.g. the southern regions of British Columbia and the Prairies, as well as the Windsor–Québec corridor), of 100–500 ppb

around the larger urban centres and of more than 500 ppb within these larger urban centres (Figure 7-4). A maximum contribution of 1640 ppb (or 1.64 ppm) is modelled in a Montréal grid cell. For the baseline scenario, the annual average daily maximum CO concentration for this grid cell was 2252 ppb (also the highest value modelled), indicating that on-road gasoline emissions were responsible for 73% of annual average daily maximum CO levels in Montréal.

Between the on-road gasoline emission and the on-road and off-road gasoline emission simulations, there was only a small increase in the contributions to CO concentrations, both in terms of magnitude and geographical extent. The results demonstrated the relative importance of on-road gasoline CO emissions compared with off-road gasoline emissions. A maximum contribution of 1938 ppb (or 1.94 ppm) was estimated in Montréal. Furthermore, considering that average annual daily maximum CO concentrations across Canada have ranged between 2 and 3 ppm in the last decade (Wood 2012), the results show the considerable contribution from gasoline mobile sources to ambient CO levels.

7.1.5 Air toxics

On-road gasoline emissions contributed 0.01–0.3 ppb to the annual average ambient benzene levels in the larger urban areas of Canada (maximum value recorded in a grid cell near Edmonton). Beyond urban areas, estimated contributions to benzene levels were lower than 0.01 ppb (Figure 7-5). Contributions from on-road and off-road gasoline emissions were similar to those from on-road sources only, albeit slightly greater in magnitude and geographical extent (maximum value of 0.36 ppb in a Montréal grid cell; not shown).

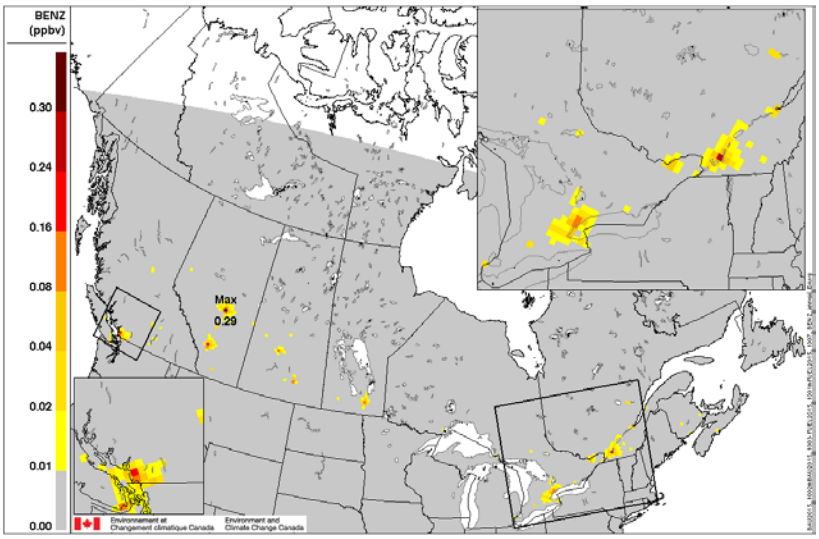

Figure 7-5. Net contributions to annual average benzene concentrations associated with on-road gasoline emissions in Canada in 2015

On-road gasoline emissions were projected to increase annual average formaldehyde concentrations in the larger urban areas, reaching a high of 0.18 ppb in an Edmonton grid cell (Figure 7-6). Only a few grid cells corresponding to urban centres show contributions greater than 0.06 ppb. On-road and off-road gasoline emissions have more impact than on-road gasoline emissions alone, both in magnitude and geographically, as expected (maximum contribution of 0.25 ppb in a Calgary grid cell; not shown).

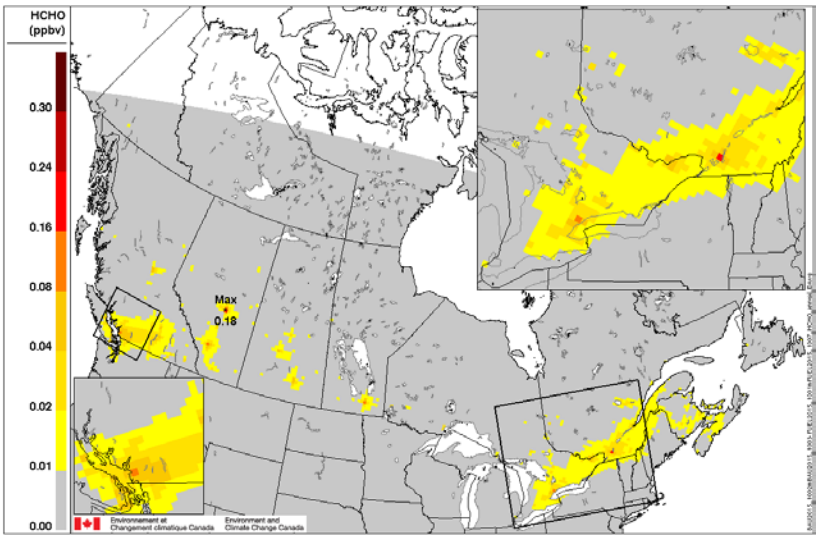

Figure 7-6. Net contributions to annual average formaldehyde concentrations associated with on-road gasoline emissions in Canada in 2015

Contributions from on-road gasoline emissions to acetaldehyde are similar to the previous figure for formaldehyde. A maximum contribution for on-road gasoline emissions of 0.12 ppb was projected near Vancouver, whereas a maximum contribution of 0.15 ppb near Calgary was associated with on-road and off-road gasoline emissions (not shown).

As for the CACs mentioned previously, differences in the distribution of the contribution of gasoline emissions to air toxic concentrations between the on-road and the on-road and off-road scenarios were generally gradual and regular across Canada and affected similar geographic areas. This suggests that on-road and off-road air toxic emissions had comparable spatial distributions.

7.2 Results by Canadian census division

The air quality impacts of gasoline emissions were also estimated at the CD level for use in the Air Quality Benefits Assessment Tool (AQBAT; see Section 8). Generally, the absolute contributions from gasoline emissions to air pollutant concentrations per CD are lower than those at the grid cell level (i.e. the 22.5 km grid results). The more extreme values observed in a single or a few grid cells are reduced when averaged across larger areas. This is especially the case outside of major urban areas, where CDs cover large geographic areas. Results from the 22.5 km grid simulations were population-weighted for each CD based on 2015 population projections.[1] The population-weighting method estimates the average exposure concentration for an individual within a geographic unit. When averaged across larger geographic units, CDs with high populations have more influence or weight than CDs with low populations. Population-weighted concentrations for all provinces and territories were determined by adding the product of a CD concentration and the fraction of the provincial population that is included in

[1] Projections by Statistics Canada based on the 2006 Census of Canada.

that CD, for all CDs in a province.[1] From the provincial and territorial population-weighted results, the same method was used to estimate the population-weighted national average.

The national and provincial average population-weighted contributions from gasoline emissions to CO, NO_2, summer O_3 and $PM_{2.5}$ concentrations are provided in Table 7-1. There are variations among provinces and pollutants, but similar trends are observed. Greater impacts are observed in the more populated provinces, such as British Columbia, Ontario and Québec. In general, the results agree with the emissions data in Table 6-2 and also reflect the contributions presented in previous figures. Notwithstanding some limitations, the results indicate that on-road gasoline emissions contribute approximately 70–90% of the incremental ambient CO, NO_2 and $PM_{2.5}$ concentrations associated with on-road and off-road gasoline emissions combined. The national population-weighted air toxic results also suggest that on-road gasoline emissions contribute 60% or more of the incremental ambient air toxic concentrations associated with on-road and off-road gasoline emissions in Canada (not shown). A direct comparison between the on-road and on-road and off-road contributions is inappropriate for O_3 owing to the influence of precursors and photochemical reactions in the atmosphere.

8 Health impacts assessment of on-road and off-road gasoline emissions

In order to quantitatively assess the Canadian population health impacts of individual constituents of gasoline emissions (i.e. exhaust and non-exhaust emissions) and of individual compounds produced secondarily in the atmosphere from gasoline emission constituents, two approaches were used. Firstly, the health impacts associated with the contribution of emissions from gasoline vehicles and engines to ambient levels of CACs were estimated based on evidence from the scientific literature that quantifies the incremental risk of an adverse outcome for a given change in air pollutant concentration. Secondly, cancer and non-cancer risks associated with the contribution of gasoline emissions to ambient concentrations of individual air toxics were estimated based on toxicity reference values in previously published risk assessments or air quality guidelines.

8.1 Population health impacts associated with criteria air contaminants

Population health impacts for a given change in ambient CAC levels associated with on-road and off-road gasoline emissions in Canada were estimated using the AQBAT, a Health Canada model that estimates annual population health and welfare benefits or costs. The AQBAT includes health impact information for $PM_{2.5}$, O_3, CO, NO_2 and SO_2 in the form of concentration–response functions (CRFs) derived from published peer-reviewed epidemiological studies pertaining to Canadian and other populations.[2] The health effects assessed in the AQBAT include both morbidity and mortality outcomes.

[1] For example, if a province includes three CDs, the population-weighted concentration (C_{pw}) is determined by:

$$C_{pw} = (CD_{d1} \times CD_{pop1} \div PT_{pop}) + (CD_{d2} \times CD_{pop2} \div PT_{pop}) + (CD_{d3} \times CD_{pop3} \div PT_{pop})$$

where CD_{dx} is the concentration of CDx, CD_{popx} is the population of CDx and PT_{pop} is the population of the province.

[2] A CRF is a probabilistic value expressed as the average per capita excess risk of an adverse outcome (e.g. asthma symptom days) per unit increase in ambient pollutant concentration (e.g. per 1 $\mu g/m^3$ of $PM_{2.5}$).

Table 7-1. Contributions from on-road and off-road gasoline emissions to national and provincial mean population-weighted concentrations for $PM_{2.5}$, NO_2, summer O_3 and CO, in 2015 – AURAMS

Region—population[a]	Modelled mean population-weighted concentrations[b] Baseline concentrations and relative contributions from on-road and on-road and off-road (OROF) gasoline emissions											
	Annual average						Annual average daily maximum					
	$PM_{2.5}$			NO_2			Summer O_3			CO		
	Baseline ($\mu g/m^3$)	On-road (%)	OROF (%)	Baseline (ppb)	On-road (%)	OROF (%)	Baseline (ppb)	On-road (%)	OROF (%)	Baseline (ppm)	On-road (%)	OROF (%)
Alberta—3 995 100	4.80	3	5	4.4	8	8.5	45.1	2	2	0.28	33	40
British Columbia—4 888 059	4.61	9	11	3.6	29	30	39.6	2	3	0.31	38	43
Manitoba—1 300 664	4.02	3	5	5.3	22	23	37.8	1	2	0.51	59	66
New Brunswick—768 857	2.26	1	2	0.6	11	13	35.5	1	1	0.19	5	8
Newfoundland and Labrador—510 193	2.00	1	1	0.4	5	6	31.9	<1	1	0.17	3	3
Nova Scotia—967 182	2.78	1	2	0.7	10	12	35.7	1	1	0.18	6	9
Ontario—14 127 882	6.45	7	8	5.2	14	17	44.2	1	2	0.47	39	54
Prince Edward Island—148 740	3.49	1	1	0.6	14	15	35.0	1	1	0.18	5	7
Québec—8 212 175	7.65	5	6	6.6	17	19	35.8	<1	2	0.68	55	66
Saskatchewan—1 067 999	2.27	2	4	1.1	11	15	39.4	1	2	0.19	12	18
Canada—36 101 253	**5.80**	**6**	**7**	**4.8**	**16**	**18**	**40.7**	**1**	**2**	**0.45**	**43**	**55**

CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; OROF: on-road and off-road gasoline emissions; $PM_{2.5}$: fine particulate matter or particulate matter with an aerodynamic diameter of 2.5 µm or less; ppb: parts per billion; ppm: parts per million

[a] Values for the Northwest Territories, Nunavut and the Yukon are not shown. The values were generally very low and difficult to interpret.
[b] Concentrations in $\mu g/m^3$ and ppm rounded to two decimals; concentrations in ppb rounded to one decimal; percentages rounded to unity.
[c] For O_3 concentrations, summer is defined as the period from May to September.

Note: The table must be read as follows: In Canada, the population-weighted annual average daily maximum CO concentration is 0.45 ppm. On-road gasoline emissions contribute 43% (0.19 ppm) to the population-weighted CO concentration, whereas on-road and off-road gasoline emissions contribute 55% (0.25 ppm).

The health endpoints, their acute or chronic nature, the associated CRFs and the applicable population group(s) (e.g. age-specific groups) are predefined within the AQBAT and represent Health Canada-endorsed values drawn from the health science literature. Health impacts were estimated for individual geographic areas, represented by 285 CDs of varying geographical and population sizes.[1]

The AQBAT also includes economic valuation estimates for the health outcomes in the model. Economic valuation estimates consider the potential social, economic and public welfare consequences of the health outcomes, including medical costs, reduced workplace productivity, pain and suffering, and the effects of increased mortality risk. For more details on the AQBAT, refer to the Supporting Document to the Human Health Risk Assessment for Gasoline Exhaust (Health Canada 2017) or the AQBAT User Guide (Judek et al. 2012).

AQBAT simulations were conducted to estimate the annual health impacts in Canada, in 2015, associated with (1) on-road gasoline emissions and (2) on-road and off-road gasoline emissions. The values from the AQBAT simulations are interpreted as the incremental population health impacts associated with gasoline emissions. Negative values indicate a benefit in terms of health outcomes and the monetary valuation associated with gasoline emissions, whereas positive values reflect a cost. Economic valuation estimates are the mean estimates, expressed in 2013 Canadian dollars.

The 2015 national AQBAT health impact estimates are shown in:

- Table 8-1 by pollutant for on-road gasoline emissions (run no. 1);
- Table 8-2 by pollutant for on-road and off-road gasoline emissions (run no. 2);
- Table 8-3 by health endpoint for run no. 1 and run no. 2; and
- Table 8-4 by province and territory for all pollutant premature mortality for run no. 1 and run no. 2.

On-road gasoline emissions are associated on average with 700 premature mortalities in 2015 (Table 8-1). Incremental premature mortalities are driven by the mortality risk associated with chronic exposures to $PM_{2.5}$ (480 premature mortalities) and summer O_3 (37 premature mortalities)[2] and acute exposures to NO_2 (140 premature mortalities) and CO (43 premature mortalities). It is estimated that on-road gasoline emissions decrease premature mortalities associated with acute exposure to annual O_3 (5 avoided premature mortalities).[3] On-road gasoline emissions are also associated with a considerable number of morbidity outcomes, such as acute respiratory symptom days, restricted activity days and asthma symptom days. The total economic cost of incremental health outcomes associated with on-road gasoline emissions in 2015 is $5.4 billion. This amount primarily reflects premature mortalities valued at $5.0 billion. Although the monetary value associated with morbidity endpoints is low compared with that

[1] 2015 population projections by Statistics Canada; three remote northern CDs are not included in AQBAT.
[2] Summer O_3 was defined as the period from May to September, inclusively.
[3] Elevated NOx emissions from on-road gasoline sources in urban areas can increase O_3 scavenging and atmospheric radical removal by NO and NO_2, respectively (e.g. European Commission 1999), leading to a decrease in ambient O_3 concentrations.

associated with mortalities, they represent an impact on Canadian population health and quality of life.

Gasoline emissions from on-road and off-road sources combined (AQBAT run no. 2) are associated on average with health impacts of approximately 940 premature mortalities annually, owing to incremental mortality risks from chronic exposures to $PM_{2.5}$ (620 premature mortalities) and summer O_3 (74 premature mortalities) and from acute exposures to NO_2 (160 premature mortalities), CO (55 premature mortalities) and annual O_3 (34 premature mortalities) (Table 8-2). The total economic cost of the health outcomes for AQBAT run no. 2 is $7.3 billion, largely owing to premature mortalities (valued at $6.8 billion).

Chronic exposure IHD mortality (44–46% of all mortalities), acute exposure mortality (26% of all mortalities) and chronic exposure lung cancer mortality (13–14% of all mortalities) account for a majority of estimated premature mortalities (Table 8-3).[1]

Benefits or damages are not distributed equally across provinces, territories and CDs, largely because of different human populations, varying air quality conditions and variations in the contribution from gasoline emissions to ambient pollutant concentrations. The highest damages and counts are generally associated with the most populated provinces (Table 8-4). For example, on-road gasoline emissions are generally associated with greater impacts in Ontario, Québec and British Columbia. Within each province or territory, the large majority of impacts are associated with a few populated CDs that correspond with the larger metropolitan areas (e.g. Greater Vancouver, Edmonton, Calgary, Winnipeg, Peel, Toronto, York and Montréal). The large fraction of population health impacts that is allocated to the more populated CDs in each province reflects several factors, such as population size and distribution, on-road vehicle activity and emissions, vehicle fleet characteristics, baseline air pollutant concentrations and meteorology.

[1] Premature mortalities associated with acute exposure are considered to affect all ages, whereas other premature mortality endpoints apply only to adults.

Table 8-1. Mean change in the frequency of health outcomes and monetary valuation ($, thousands) associated with on-road gasoline emissions in Canada in 2015—AQBAT

Health outcome[a]	$PM_{2.5}$	O_3	O_3 summer	CO	NO_2	SO_2	All pollutants[b]
All mortalities	480 $3 500 000	−5 −$34 000	37 260 000	43 $300 000	140 $1 000 000	1 $8 000	700 [320/1 500] $5 000 000 [$2 100 000/ $12 000 000]
Hospital admissions	91 [c]	–	20 [c]	290 $2 000	–	–	400 [140/660] $2 000
Emergency room visits	250 $930	–	100 $280	–	–	–	350 [240/470] $1 200
Acute respiratory symptom days	1 900 000 $17 000	–	300 000 $4 200	–	–	–	2 200 000 [340 000/4 000 000] $21 000
Asthma symptom days	130 000 $8 900	–	29 000 $2 000	–	–	–	160 000 [49 000/270 000] $11 000
Restricted activity days	1 000 000 $65 000	–	–	–	–	–	1 000 000 [590 000/1 400 000] $65 000
Child acute bronchitis episodes	3 100 $1 300	–	–	–	–	–	3 100 [0/6 900] $1 300
Adult chronic bronchitis cases	720 $300 000	–	–	–	–	–	720 [0/1 400] $300 000
Sum of damages—All endpoints[b]	$3 800 000 [$1 200 000/ $10 000 000]	−$34 000 [−$60 000/ −$14 000]	$270 000 [$77 000/ $560 000]	$310 000 [$810/ $1 100 000]	$1 000 000 [$270 000/ $2 100 000]	$8 000 [$380/$19 000]	$5 400 000 [$2 400 000/$12 000 000]

AQBAT: Air Quality Benefits Assessment Tool; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: fine particulate matter or particulate matter with an aerodynamic diameter of 2.5 µm or less; SO_2: sulphur dioxide

[a] Counts of health outcomes and damage estimates ($, thousands) are rounded to the nearest integer with a maximum of two significant figures. Damages are in 2013 Canadian dollars. Column and row totals may not match because of rounding.

[b] The 2.5th/97.5th percentile count or valuation estimates are provided in square brackets.

[c] No damages are presented for $PM_{2.5}$ and summer O_3 hospital admissions alone, as valuation estimates for emergency department visits associated with $PM_{2.5}$ and summer O_3 take into account the probability and valuation of subsequent admissions to hospital.

Table 8-2. Mean change in the frequency of health outcomes and monetary valuation ($, thousands) associated with on-road and off-road gasoline emissions in Canada in 2015—AQBAT

Health outcome[a]	$PM_{2.5}$	O_3	O_3 summer	CO	NO_2	SO_2	All pollutants[b]
All mortalities	620 $4 500 000	34 $240 000	74 $530 000	55 $400 000	160 $1 100 000	1 $8 300	940 [460/2 000] $6 800 000 [$2 900 000/$15 000 000]
Hospital admissions	120 [c]	–	40 [c]	360 $2 500	–	–	520 [190/840] $2 500
Emergency room visits	330 $1 200	–	200 $540	–	–	–	530 [330/720] $1 700
Acute respiratory symptom days	2 400 000 $22 000	–	580 000 $8 200	–	–	–	3 000 000 [640 000/5 500 000] $30 000
Asthma symptom days	160 000 $11 000	–	55 000 $3 900	–	–	–	220 000 [68 000/380 000] $15 000
Restricted activity days	1 300 000 $83 000	–	–	–	–	–	1 300 000 [750 000/1 800 000] $83 000
Child acute bronchitis episodes	4 000 $1 300	–	–	–	–	–	4 000 [0/8 900] $1 700
Adult chronic bronchitis cases	920 $380 000	–	–	–	–	–	920 [0/1 800] $380 000
Sum of damages—all endpoints[b]	$5 000 000 [$1 600 000/ $13 000 000]	$240 000 [$100 000/ $420 000]	$550 000 [$160 000/ $1 100 000]	$400 000 [$1 000/ $1 400 000]	$1 100 000 [$290 000/ $2 400 000]	$8 300 [$440/ $20 000]	$7 300 000 [$3 400 000/$16 000 000]

AQBAT: Air Quality Benefits Assessment Tool; CO: carbon monoxide; NO_2: nitrogen dioxide; O_3: ozone; $PM_{2.5}$: fine particulate matter or particulate matter with an aerodynamic diameter of 2.5 µm or less; SO_2: sulphur dioxide

[a] Counts of health outcomes and damage estimates ($, thousands) are rounded to the nearest integer with a maximum of two significant figures. Damages are in 2013 Canadian dollars. Column and row totals may not match because of rounding.

[b] The 2.5th/97.5th percentile count or valuation estimates are provided in square brackets.

[c] No damages are presented for $PM_{2.5}$ and summer O_3 hospital admissions alone, as valuation estimates for emergency department visits associated with $PM_{2.5}$ and summer O_3 take into account the probability and valuation of subsequent admissions to hospital.

Table 8-3. Comparison of national count estimates by health endpoint in 2015 based on results for on-road gasoline emissions and for on-road and off-road gasoline emissions

Health endpoint	Pollutant	On-road	OROF	Difference[b]
Mortality[a]				
Acute exposure mortality	CO	42	55	13
Acute exposure mortality	NO_2	140	160	15
Acute exposure mortality	O_3	-5	34	38
Acute exposure mortality	SO_2	1	1	0
Chronic exposure respiratory mortality	O_3 summer[c]	37	74	37
Chronic exposure cerebrovascular mortality	$PM_{2.5}$	26	34	8
Chronic exposure COPD mortality	$PM_{2.5}$	34	44	10
Chronic exposure IHD mortality	$PM_{2.5}$	320	420	92
Chronic exposure lung cancer mortality	$PM_{2.5}$	98	130	28
Total acute exposure mortality[a]	CO, NO_2, O_3, SO_2	180	250	66
Total chronic exposure mortality[a]	O_3 summer, $PM_{2.5}$	520	690	170
Total mortality[b]	All pollutants	700	940	240
Morbidity[a]				
Acute respiratory symptom days	O_3 summer, $PM_{2.5}$	2 200 000	3 000 000	820 000
Adult chronic bronchitis cases	$PM_{2.5}$	720	920	200
Asthma symptom days	O_3 summer, $PM_{2.5}$	160 000	220 000	62 000
Cardiac emergency room visits	$PM_{2.5}$	73	95	21
Cardiac hospital admissions	$PM_{2.5}$	56	72	16
Child acute bronchitis episodes	$PM_{2.5}$	3 100	4 000	880
Elderly cardiac hospital admissions	CO	290	360	74
Minor restricted activity days	O_3 summer	68 000	130 000	65 000
Respiratory emergency room visits	O_3 summer, $PM_{2.5}$	280	430	150
Respiratory hospital admissions	O_3 summer, $PM_{2.5}$	56	86	30
Restricted activity days	$PM_{2.5}$	1 000 000	1 300 000	280 000

CO: carbon monoxide; COPD: chronic obstructive pulmonary disease; IHD: ischemic heart disease; NO_2: nitrogen dioxide; O_3: ozone; OROF: on-road and off-road gasoline emissions; $PM_{2.5}$: fine particulate matter or particulate matter with an aerodynamic diameter of 2.5 µm or less; SO_2: sulphur dioxide

[a] Health counts are rounded to the nearest integer and given to a maximum of two significant figures.
[b] Difference may not calculate as expected because of rounding.
[c] May–September only
[d] Percentage differences are rounded to one decimal, as calculated from unrounded values; percentage differences may not calculate as expected because of rounding.

Table 8-4. All pollutant ($PM_{2.5}$, O_3, NO_2, CO) premature mortality damages and counts associated with on-road gasoline emissions and on-road and off-road gasoline emissions in Canada in 2015

Province/Territory—2015 population	Counts[a]	Damages ($, thousands)[a]	Counts[a]	Damages ($, thousands)[a]
	On-road		OROF	
Alberta—3 995 100	32	230 000	44	320 000
British Columbia—4 888 059	130	900 000	140	1 000 000
Manitoba—1 300 664	18	130 000	25	180 000
New Brunswick–768 857	3	21 000	4	28 000
Newfoundland and Labrador—510 193	1	6 500	1	8 200
Northwest Territories—45 541	<1	14	<1	27
Nova Scotia—967 182	4	29 000	5	39 000
Nunavut—34 101	<1	2	<1	3
Ontario—14 127 882	310	2 200 000	430	3 100 000
Prince Edward Island—148 740	<1	3 500	1	4 700
Québec—8 212 175	200	1 400 000	270	2 000 000
Saskatchewan—1 067 999	7	47 000	11	80 000
Yukon Territory—34 760	<1	17	<1	17
Canada—36 101 253	**700**	**5 000 000**	**940**	**6 800 000**

OROF: on-road and off-road gasoline emissions

[a] Counts of health outcomes and damage estimates are rounded to the nearest integer with a maximum of two significant figures. Damages are in 2013 Canadian dollars.

8.2 Population health risks associated with air toxics

AURAMS with the SAPRC-07 system provides reliable estimates for acetaldehyde, benzene and formaldehyde ambient concentrations across Canada. The air toxic concentration results were combined with toxicity reference values corresponding with the air toxics considered, when available, to estimate population risks.

8.2.1 Lifetime excess cancer risk associated with exposure to toxics

The lifetime excess cancer risk associated with a carcinogenic pollutant is estimated by multiplying its inhalation unit risk value by its air concentration, as follows:

$$R_{ij} = [c]_{ij} \times IUR_j \qquad \text{(equation 1)}$$

R_{ij} is the estimated lifetime excess cancer risk from pollutant *j* at location *i*, $[c]_{ij}$ is the concentration (in $\mu g/m^3$) of pollutant *j* at location *i* and IUR_j is the inhalation unit risk for a 70-year lifetime for pollutant *j* (in units per $\mu g/m^3$).[1]

The IUR is defined as the upper-bound lifetime excess cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 $\mu g/m^3$ in air.[2] For example, an IUR value of 2×10^{-6} per $\mu g/m^3$ is interpreted as two excess cancer cases per 1 million people if they are exposed daily and for a lifetime to 1 $\mu g/m^3$ of a pollutant in air.

[1] A 70-year life expectancy is a common default value used in environmental risk assessment (Zhou et al. 2015).
[2] https://ofmpub.epa.gov/sor_internet/registry/termreg/searchandretrieve/termsandacronyms/search.do

The cancer risk (R_{ij}) is a unitless number expressed as a probability (Zhou et al. 2015). The lifetime excess cancer risk methodology is used to estimate the cancer risk from exposure to air toxics, and it represents a valuable measure for comparisons among potential risks from varied sources and emissions (South Coast Air Quality Management District 2014). In the current study, the cumulative cancer risks reflect the level of concern associated with gasoline emissions. Lifetime excess cancer risks are compared with benchmarks, such as one in 100 000. An excess cancer risk of less than one in 100 000 is considered essentially negligible. Cancer risks are considered additive across multiple pollutants (Golder Associates Ltd. 2013); thus, cumulative (i.e. total individual lifetime) cancer risks may be estimated.

Table 8-5 shows the national lifetime excess cancer risk associated with gasoline emissions for the three toxics of interest, using Health Canada unit risks. Of note, Health Canada has determined that acetaldehyde and formaldehyde are threshold carcinogens. Thus, Health Canada does not endorse a linear inhalation unit risk value for these two air toxics. A quantitative cancer assessment cannot be performed for acetaldehyde owing to dose–response model limitations. Nonetheless, the non-cancer reference concentration for acetaldehyde that is shown in Table 8-6 is protective of cancer, as this non-cancer effect represents an early precursor of cancer, and cancer development is not expected if the adverse effect is prevented.[1]

Table 8-5. Canadian average excess cancer risk estimates for lifetime exposure to ambient air toxic concentrations using Health Canada unit risks, based on AURAMS simulations for 2015

Air toxic		Acetaldehyde	Benzene	Formaldehyde	
National population weighted annual average concentration					
Baseline—all sources	µg/m^3	0.880	0.436	0.923	
Contribution—on-road gasoline emissions	µg/m^3	0.038	0.129	0.044	
Contribution—on-road and off-road gasoline emissions	µg/m^3	0.066	0.187	0.071	
Canadian average excess cancer risk					Cumulative[c]
Unit risk[a] ((µg/m^3)$^{-1}$)		n.a.[b]	3.3×10^{-6}	n.a.[b]	
Baseline—All sources		-	1.44×10^{-6}	~2.3×10^{-10}	1.44×10^{-6}
Contribution—on-road gasoline emissions		-	4.26×10^{-7}	<2.3×10^{-10}	4.26×10^{-7}
Contribution—on-road and off-road gasoline emissions		-	6.17×10^{-7}	<2.3×10^{-10}	6.17×10^{-7}

n.a.: not applicable (threshold carcinogen)

[a] Health Canada. 2010. Federal Contaminated Site Risk Assessment in Canada. Part II: Health Canada Toxicological Reference Values (TRVs) and Chemical-Specific Factors, Version 2.0. Available at: www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/contaminated-sites/federal-contaminated-site-risk-assessment-canada-part-health-canada-toxicological-reference-values-trvs-chemical-specific-factors-version-2-0.html; Water and Air Quality Bureau, personal communication, Health Canada, 2015

[b] Health Canada has determined that acetaldehyde and formaldehyde are threshold carcinogens.(Environment Canada and Health Canada 2001; Health Canada 2004a; www.canada.ca/en/health-canada/services/publications/healthy-living/residential-indoor-air-quality-guideline-acetaldehyde.html).

[c] Cumulative cancer risk for lifetime exposures to acetaldehyde, benzene and formaldehyde. May not calculate as expected because of rounding.

[1] Residential indoor air quality guideline: acetaldehyde. Available at www.canada.ca/en/health-canada/services/publications/healthy-living/residential-indoor-air-quality-guideline-acetaldehyde.html.

Based on available data, the predicted additional risks of upper respiratory tract cancer for non-smokers, associated with an 80-year continuous exposure to levels of formaldehyde between 0.001 and 0.1 ppm (1.2 and 120 µg/m^3), range from 2.3×10^{-10} to 2.7×10^{-8}, respectively (Environment Canada and Health Canada 2001).

Contributions to ambient air toxic levels from on-road gasoline emissions or on-road and off-road gasoline emissions combined are associated with individual and cumulative lifetime cancer risks lower than 1×10^{-5}. Thus, on average across Canada, gasoline emissions are considered to contribute negligibly to lifetime exposure cancer risks for ambient levels of acetaldehyde, benzene and formaldehyde (individually and cumulatively). Furthermore, based on the modelling results and the selected lifetime cancer unit risk values, average baseline Canadian concentrations for these three air toxics are considered to contribute negligibly to lifetime exposure excess cancer risks.

Cumulative cancer risks associated with on-road or on-road and off-road gasoline emissions were lower than 1×10^{-5} in all CDs. Cumulative cancer risk estimates exceeded 1×10^{-6} ($1.25–2.61 \times 10^{-6}$) in only five CDs corresponding with urban centres (i.e. Montréal, Toronto, Winnipeg and Vancouver areas) or regions directly downwind (owing to the atmospheric transport of pollutants released from gasoline sources in urban centres). On a provincial basis, the cumulative lifetime cancer risk estimates associated with on-road and off-road gasoline emissions are lower than 1×10^{-5} or 1×10^{-6}.

8.2.2 Non-cancer inhalation risks

In order to examine the impacts of gasoline emissions on the non-cancer health effects associated with ambient concentrations of acetaldehyde, benzene and formaldehyde, this analysis makes use of published reference concentrations (RfCs) for those compounds. RfCs are defined by multiple risk assessment agencies as estimates of continuous inhalation population exposures that are likely to be without appreciable risks of deleterious effects over a lifetime, including among sensitive subpopulations.[1]

In this health impact assessment, a hazard quotient (HQ) is calculated for each pollutant and at each location, by dividing the modelled concentration by its RfC according to:

$$HQ_{ij} = [c]_{ij} / RfC_j \qquad \text{(equation 2)}$$

HQ_{ij} is the hazard quotient for pollutant j at location i, $[c]_{ij}$ is the concentration (µg/m^3) of pollutant j at location i and RfC_j is the RfC for pollutant j. HQ calculations are conducted using exposure concentrations for each CD covered by the modelling domain and averaged over provinces, territories or Canada. A total non-cancer hazard index (HI) is determined by summing the HQs for each pollutant at a location, for a specific target system (assumption of dose additivity; ATSDR 2004). For the current assessment, effects for different systems and different modes of action were combined, which results in a conservative assumption, overestimating the risk. Note that the HI index is not a numerical risk estimate but a decision index. An HI of less than one is generally not expected to be a concern for health, whereas values above one indicate exposure concentrations that may present a health concern. Furthermore, an HI of 0.2 or less for single pathways (in this case, inhalation) is considered negligible (Health Canada 2004b). Table 8-6 summarizes the RfCs that Health Canada has defined. The Department

[1] RfCs are also referred to as Reference Exposure Levels or RELs by other agencies or authors.

has not defined a non-cancer RfC for benzene; the cancer RfC of 3.0 µg/m^3 (for a risk of 1×10^{-5}) is considered protective for non-cancer effects. For the purpose of calculating non-cancer cancer risks, the annual non-cancer RfC for benzene defined by the Office of Environmental Health Hazard Assessment (OEHHA) was used.

The modelled baseline ambient concentrations across Canadian CDs for acetaldehyde, benzene and formaldehyde were lower than the RfCs included in Table 8-6. The maximum modelled contributions from on-road and off-road gasoline emissions to ambient air toxic concentrations across CDs are 0.17 µg/m^3 for acetaldehyde (Toronto), 0.79 µg/m^3 for benzene (Montréal) and 0.22 µg/m^3 for formaldehyde (Montréal).[1] Calculated HQs for the three air toxics in these and other Canadian CDs are lower than one using Health Canada and CalEPA RfCs (not shown). The HQ exceeded 0.2 only for benzene. In general, the modelling results suggest that the contributions from gasoline emissions to ambient concentrations of acetaldehyde, benzene and formaldehyde represent an acceptable non-cancer inhalation health risk, including in urban CDs.

Table 8-6. Non-cancer reference concentrations and target organ systems for air toxics modelled with AURAMS

Organization	Exposure	Metric	Acetaldehyde	Benzene	Formaldehyde
Health Canada	Annual	µg/m^3	280[b] Respiratory (histological)	n/a	50[c] Respiratory (asthma)
OEHHA[a] / CalEPA	Annual	µg/m^3		3 hematologic	

CalEPA: California Environmental Protection Agency; IRIS: Integrated Risk Information System; n/a: not available; OEHHA: Office of Environmental Health Hazard Assessment; US EPA: United States Environmental Protection Agency

[a] OEHHA acute, 8 h and chronic reference exposure levels (RELs) as of June 2016 (www.oehha.ca.gov/air/allrels.html). Exposure averaging time for acute RELs is 1 h. Chronic RELs are designed to address continuous exposures for up to a lifetime; the exposure metric used is the annual average exposure.

[b] Residential indoor air quality guideline: acetaldehyde (www.canada.ca/en/health-canada/services/publications/healthy-living/residential-indoor-air-quality-guideline-acetaldehyde.html)

[c] Residential indoor air quality guideline for formaldehyde (www.canada.ca/en/health-canada/services/publications/healthy-living/residential-indoor-air-quality-guideline-formaldehyde.html)

8.3 Discussion

Gasoline-powered engines and vehicles are an important source of air pollutant emissions that can potentially affect population health, particularly in high-traffic urban areas. Due to the prevalence of gasoline-powered vehicles, the Canadian population is regularly exposed to gasoline emissions in the environment. Although the available scientific literature database examining the health effects of GE as a mixture is too limited to infer a causal role for GE emissions in adverse health outcomes (refer to Part A), the many adverse health impacts of primary (e.g. $PM_{2.5}$, CO, NO_2 and SO_2) and secondary (e.g. O_3) air pollutants associated with gasoline use are well documented in the health science literature (e.g. Crouse et al. 2012; Fann et al. 2012; Health Canada 2013, 2016a; US EPA 2009). Furthermore, there is biological plausibility of potential GE-induced carcinogenicity, since known human carcinogens (e.g. benzene and PAHs) are constituents of the GE mixture.

[1] The maximum modelled contributions from on-road and off-road gasoline emissions to ambient concentrations on a grid cell basis were 0.153 ppb (0.275 µg/m^3) for acetaldehyde, 0.357 ppb (1.24 µg/m^3) for benzene and 0.248 ppb (0.332 µg/m^3) for formaldehyde (Health Canada 2017). These values are also lower than the RfCs in Table 8-6.

Air pollutants are responsible for population health impacts in Canada and elsewhere, including cardiorespiratory mortality, hospital admissions and emergency room visits. The RRs of mortality associated with air pollution that have been observed in epidemiological studies are generally low compared with other risk factors such as smoking; however, the risks apply to millions of people. Health Canada has estimated that approximately 5 600 deaths were attributable to above-background $PM_{2.5}$ exposure in Canada in 2011 (approximately 8% of deaths),[1] as well as 1 400 hospital admissions and 3 900 emergency department visits (Stieb et al. 2015). These figures increase to nearly 10 000 deaths, 2 200 hospital admissions and 7 800 emergency department visits annually when O_3 and NO_2 are also considered (D. Stieb, personal communication, Health Canada, 2016).

The objective of the AQBAT analysis undertaken in Part B of the current assessment was to estimate the contribution of gasoline emissions to air pollution health impacts (via CACs) in Canada. On-road gasoline emissions were estimated to account for 700 premature mortalities across Canada, as well as morbidity outcomes, valued at $5.4 billion in total. On-road and off-road emissions were associated with approximately 940 premature mortalities as well as morbidity outcomes, with a total monetary cost of $7.3 billion. Health impacts associated with gasoline emissions are projected to be larger than those estimated for diesel emissions using the same methodology. Previous estimates showed that, on average in Canada, on-road diesel emissions were responsible for 320 premature mortalities while on-road and off-road diesel emissions (excluding rail and commercial marine applications) were responsible for 710 premature mortalities in 2015 (Health Canada 2016b, c).

The majority of the premature mortalities attributed to gasoline emissions were associated with $PM_{2.5}$ and NO_2 concentrations, with lower contributions from O_3 and CO. Cardiovascular mortalities accounted for more than half of the total mortalities, followed by lung cancer and respiratory mortalities. Gasoline emissions, through their influence on ambient $PM_{2.5}$ and O_3 concentrations, were also associated with acute respiratory symptom days, restricted activity days, asthma symptom days, hospital admissions, emergency room visits, child acute bronchitis episodes and adult chronic bronchitis cases across Canada.

Overall, the results suggest that on-road gasoline emissions had a greater impact than off-road gasoline emissions for all pollutants and endpoints combined; off-road gasoline emissions were responsible for approximately one-third as many impacts as on-road gasoline emissions. Notwithstanding some inherent uncertainties, the lower health impacts associated with off-road gasoline emissions are to be expected, owing to lower fuel use and a larger fraction of off-road emissions being distributed in rural and less populated areas. Given the recent emission standards that apply to the on-road gasoline fleet, the relative contribution to gasoline emissions from the off-road gasoline sector may increase in the future.

Regional differences in population health impacts were observed. Health effects associated with gasoline emissions were larger in more populated provinces (e.g. Ontario, Québec and British Columbia) and CDs (e.g. Montréal, Toronto and Greater Vancouver), and in areas with greater on-road or off-road gasoline activity (e.g. urban centres and major highways). Proximity to population may be more correlated to premature mortality estimates than pollutant emission magnitude, based on the weight of the population variable in the health impact function (Turner et al. 2015).

[1] Based on IHD, cerebrovascular disease, COPD and lung cancer (refer to Stieb et al. 2015).

The approach used to quantify the effects of long-term exposure on mortality in the AQBAT was selected to follow as closely as possible that employed in the Global Burden of Disease analysis, which evaluates effects according to four causes of death based on multiple worldwide studies.[1] The AQBAT model used for the current assessment was based on the best and most robust data that were available when the simulations were conducted. Since then, new epidemiological studies have been published that include different, new or revised risk estimates reflecting associations between exposure to atmospheric pollutants and health endpoints. For example, Crouse et al. (2012) investigated associations between long-term exposure to ambient $PM_{2.5}$ concentrations and cardiovascular mortality in Canadian adults. They observed associations at concentrations that were predominantly lower than concentrations reported in previous studies. Crouse et al. (2012) defined hazard ratios (HRs) from all-cause non-accidental mortalities and from IHD mortality for each 10 $\mu g/m^3$ increase in $PM_{2.5}$ concentration that differed from the values or endpoints used in the AQBAT. A sensitivity analysis was conducted in the current assessment using the HRs and endpoints from Crouse et al. (2012) instead of the values currently in the AQBAT. The modified IHD mortality HR led to higher but similar values compared with the original AQBAT simulations for both scenarios (maximum difference of 9%). The regular version of the AQBAT does not include an all-cause non-accidental $PM_{2.5}$ mortality endpoint. Chronic exposure premature mortality associated with $PM_{2.5}$ is represented by four endpoints in the AQBAT: chronic exposure cerebrovascular mortality, chronic exposure chronic obstructive pulmonary disease (COPD) mortality, chronic exposure IHD mortality and chronic exposure lung cancer mortality. The AQBAT estimates using the modified all-cause $PM_{2.5}$ mortality HR increased national $PM_{2.5}$ mortality impacts by 57% compared with aggregated $PM_{2.5}$ mortalities (four causes) in the original analysis. The larger estimate of attributable deaths was not necessarily due to the all-cause $PM_{2.5}$ mortality HR; the baseline mortality rate for all internal causes in Crouse et al. (2012) was approximately 3-fold higher than the sum of baseline rates for the four specified causes.[2] Ultimately, the original analyses reported in this assessment reflect the CRFs presently endorsed by Health Canada. As the original AQBAT values presented here are lower than estimates based on the Crouse et al. (2012) study, the premature mortality estimates from the current assessment may be considered conservative.

Nationally, the contributions from on-road and off-road gasoline emissions to ambient concentrations of acetaldehyde, benzene and formaldehyde corresponded with lifetime excess cancer risks of less than 1×10^{-5}. Lifetime excess cancer risks higher than 1×10^{-6} and less than 1×10^{-5} for benzene were observed only in a few urban CDs, including Winnipeg, Toronto and Montréal. Thus, the results suggested that incremental ambient concentrations of these air toxics attributable to gasoline emissions contribute negligibly to excess cancer risks in Canada.

Since Health Canada considers acetaldehyde and formaldehyde to be threshold carcinogens, and owing to the low baseline ambient concentrations that were modelled for these air toxics in Canada, the estimated total lifetime excess cancer risk in Canada due to ambient air concentrations of the three air toxics examined in this analysis is attributable almost exclusively to benzene. Gasoline vehicles and engines are responsible for most of the mobile source benzene emissions in Canada, as well as a large fraction of ambient benzene levels, especially in urban areas.

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[1] For more information on the global burden of disease analysis method, refer to the World Health Organization publications available online at: www.who.int/topics/global_burden_of_disease/en/

[2] The HRs for the four AQBAT mortality causes in relation to $PM_{2.5}$ are equal to or greater than that for all internal causes in Crouse et al. (2012).

For non-cancer inhalation risks, HI estimates suggested that the contribution from on-road and off-road gasoline emissions to ambient concentrations of acetaldehyde, benzene and formaldehyde represents an acceptable health risk; even the modelled ambient baseline concentrations that consider air toxic emissions from all sources were considerably below available RfCs.

The cancer and non-cancer risks associated with air toxics from gasoline emissions in the current assessment were estimated from modelled ambient concentrations for acetaldehyde, benzene and formaldehyde exclusively. As mentioned previously, gasoline emissions include other air pollutants that are known human carcinogens (e.g. PAHs) as well as air toxics that are expected to contribute to non-cancer health effects (e.g. toluene, ethylbenzene, xylenes). The inclusion of additional air toxics in this analysis could contribute to the identification of increased population risks associated with exposure to gasoline emissions. However, additional pollutants could not be evaluated due to limitations in the ambient air quality modelling process. Hence, the population risk estimates from the current assessment may be considered an underestimate.

9 Key uncertainties and gaps

The modelling conducted in the current assessment made use of the best available tools and data for Canadian scenarios. For practical reasons, assumptions and simplifications were required at each step, which introduced uncertainties in the analysis. In terms of emission projections, imperfect spatial and temporal predictions may arise for a variety of general reasons, such as simplified algorithms, limited vehicle fleet data and errors in forecasting future economic activity. The use of three similar but distinct models to estimate emissions from different segments of the mobile source population added to the uncertainty; however, an inter-model comparison was beyond the scope of this assessment. To assess some of the limitations, modelling data were analyzed in parallel to engine or vehicle emission testing data, emission inventories and air quality data in order to corroborate results with as many sources of information as possible.

In terms of air quality modelling, examples of limitations and uncertainties include the quality of the meteorological and emission data, the horizontal grid resolution, the precision of spatial surrogates and the accurate representation of the numerous and complex atmospheric reactions. For air toxics, air monitoring data are often limited in terms of both monitoring sites and time period. Historical monitoring data are not available for most air toxics, and the monitoring has been done at only a few monitoring sites across Canada. Thus, air quality simulations are limited for air toxics because the model output cannot be thoroughly validated by air monitoring data.

Including air pollutants in quantitative benefits assessment is a non-trivial task and requires the development and use of RRs or CRFs. The main prerequisite is the consideration that causality exists between exposure to a specific air pollutant and one or several health outcomes. An extensive exposure assessment is also necessary to define RRs and CRFs, such as through long-term air monitoring data collected at geographically distributed sites.

The AQBAT includes a limited number of CRFs related to CACs. The CRFs are based on robust scientific data and are reviewed continually (e.g. H. Shin, personal communication, Health Canada, 2013; Shin et al. 2016). Other health outcomes associated with exposure to CACs (e.g. reproductive and developmental outcomes) have been reported in the literature (Health Canada 2013; US EPA 2009), but not all health effects of air pollution are adequately quantified to be included in the analysis. The available epidemiological data do not support the inclusion of pollutants other than the selected CACs.

As more robust pollutant-specific health data become available, more specific CRFs will be considered for addition to the AQBAT. However, even with the inclusion of more pollutants and CRFs, $PM_{2.5}$ and to a lesser extent the other CACs considered in AQBAT would likely remain the most important contributors to health impacts. There is high confidence in the selected CRFs, but it is expected that existing uncertainties pertaining to CRFs lead to underestimations of air quality health impacts.

Human health outcomes and the economic values associated with them are provided by CD in the AQBAT. The exposure assessment, based on AURAMS modelling, was conducted over a national grid with a resolution of 22.5 km. CDs generally include several fractions of grid cells or entire grid cells. A horizontal grid resolution of 22.5 km may reflect ambient concentrations appropriately for areas with low variability in emissions, such as rural or undeveloped areas, and for chemical species that are characterized as regional pollutants (e.g. O_3 and $PM_{2.5}$). However, within-city variations in air concentrations can be considerable, especially near traffic sources, resulting in greater exposures for near-roadway populations (Jerrett et al. 2005b; Özkaynak et al. 2013). Air concentrations in urban areas vary on a scale of a few metres for local-scale pollutants (e.g. NO, UFPs). Owing to the coarse grid resolution and the area-weighting approach adopted for the current assessment, the CD-based values likely underestimate road-scale exposures. Alternatively, coarser resolutions can overestimate exposures for a fraction of the population included in urban CDs or grid cells but residing at a distance from roadways. Overall, it is expected that extreme low and high pollutant concentration values were diluted following the weighting and that there is potential misclassification of population exposures. The magnitude and direction of the bias owing to this exposure misclassification are difficult to estimate without a thorough sensitivity analysis, which was beyond the scope of the current assessment.

It is important to consider that the CRFs in the AQBAT were derived from epidemiological studies that assessed population health effects based on monitoring data collected at centrally located sites (except Crouse et al. 2012). These epidemiological studies did not use high-resolution exposure data, and population health impact studies based on higher resolution exposure estimates have more recently been undertaken. Few epidemiological studies have applied spatially refined estimates of daily ambient concentrations in studies of population health effects. The ability to develop higher resolution exposure surfaces and to combine these with detailed population health data is a recent development (e.g. Crouse et al. 2012; Özkaynak et al. 2013; Sarnat et al. 2013; Stieb et al. 2015). The development and use of spatially and temporally refined ambient concentration data may enable greater detection of associations between air pollution and health effects compared with exposure estimates based on central site data, particularly for traffic-related pollutants (Dionisio et al. 2013; Sarnat et al. 2013). The goal of refined approaches is to reduce exposure error and its resulting bias, in order to provide more power to detect potential epidemiologic associations of interest (Baxter et al. 2013). The ability for improved exposure assessments in future air pollution epidemiology studies will reduce uncertainty in health risk assessments of ambient air pollution (Sarnat et al. 2013) and will allow for more detailed analyses of the influence of model grid resolution on population health impacts.

The air toxic risk estimates reflected an evaluation of potential risk according to current understandings of health effects, and they represent the risk associated with the modelled contribution of gasoline emissions to ambient levels of the three selected air toxics only. The potential risks should not be interpreted as actual rates of disease in the exposed population.

10 Conclusions

The air quality scenarios modelled with AURAMS and the AQBAT were selected in order to provide an indication of the potential air quality and health impacts associated with gasoline fuel use in on-road and off-road applications in Canada. On-road and off-road gasoline applications are an important source of air pollutant emissions (e.g. 11% of NOx emissions, 67% of CO emissions and 20% of VOC emissions), especially in populated urban areas, where a large fraction of the Canadian population resides and where personal vehicle use is also important. Within all mobile source emissions, gasoline vehicles and engines contribute large fractions of CO, NO_2, $PM_{2.5}$ and VOC emissions.

Air quality modelling results indicated that gasoline emissions influence ambient concentrations of CO, NO_2, O_3 and $PM_{2.5}$. On-road gasoline emissions contribute to air pollutant concentrations in urban areas (e.g. Greater Vancouver, Calgary, Winnipeg, Toronto and Montréal) and along major transportation routes. The impact on ambient air pollutant concentrations of off-road gasoline emissions appears more widely distributed geographically, affecting air quality in both rural and urban areas, but the effect is lower in magnitude than that of on-road gasoline emissions.

The health effects of individual air pollutants are well recognized by Health Canada and internationally. The current health impact analysis clearly showed that on-road and off-road gasoline emissions, via their contributions to ambient concentrations of CACs, lead to population health impacts and societal costs in Canada. On-road gasoline emissions are associated with 700 mortalities (valued at $5.0 billion), where 69%, 20%, 6%, and 5% of the estimated mortalities are attributable to ambient $PM_{2.5}$, NO_2, CO, and O_3, respectively. On-road and off-road gasoline emissions are associated with 940 mortalities (valued at $6.8 billion), where 66%, 17%, 11% and 6% of the estimated mortalities are attributable to ambient $PM_{2.5}$, NO_2, and O_3 and CO, respectively. The mortality endpoints considered result from both acute and chronic exposure to air pollutants, and include cardiovascular, respiratory and lung cancer mortalities. Gasoline emissions are also associated with acute respiratory symptom days, restricted activity days, asthma symptom days, hospital admissions, emergency room visits, child acute bronchitis episodes and adult chronic bronchitis cases across Canada.

The AQBAT simulations defined for the current assessment suggest that on-road gasoline emissions contribute considerably more (i.e. 2–3 times more) to health impacts than off-road gasoline emissions. This is not unexpected owing, for example, to the higher number of on-road vehicles, the greater volume of fuel used by on-road vehicles and the proximity of on-road sources to large populations. The results also indicate that both on-road and off-road gasoline applications contribute to health impacts in major Canadian urban centres. Importantly, not all health impacts that have been associated with CACs in the scientific literature can be quantified with the AQBAT; hence, the quantitative estimates of population health impacts provided in this analysis are assumed to represent an underestimate of the full effects of gasoline emissions-related air pollution.

A similar health impact analysis was previously undertaken for on-road and off-road diesel emissions in Canada, for calendar year 2015 (Health Canada 2016b, c). For that assessment, it was estimated that on-road diesel emissions were associated with 320 premature mortalities and combined on-road and off-road diesel emissions were associated with 710 premature mortalities. Approximately two-thirds of mortalities were attributable to ambient $PM_{2.5}$ and one-third to ambient NO_2 in both cases. Hence, the population health impacts from gasoline emissions are estimated to be greater than those from diesel emissions. Furthermore, although primary $PM_{2.5}$ emissions from the on-road and off-road diesel fleet are higher than those from the on-road and off-road gasoline fleet (26 528 tonnes and 9 287 tonnes,

respectively; see Table 6-1), the health impact modelling estimated a higher number of premature mortalities from ambient $PM_{2.5}$ associated with gasoline emissions (620) than from diesel emissions (460). A similar finding is seen when considering on-road gasoline emissions (480 $PM_{2.5}$ mortalities) compared with on-road diesel emissions (250 $PM_{2.5}$ mortalities). This finding highlights the important contribution of gasoline emissions to ambient air pollution, including the contribution of NOx and VOCs to the secondary production of $PM_{2.5}$. It also highlights that the geographic distributions of gasoline emission sources and human populations are closely aligned, increasing population exposures. Although emissions from heavy-duty on-road vehicles (dominated by diesel engines) and light-duty on-road vehicles (dominated by gasoline engines) were modelled with two different models (MOVES and MOBILE6.2C, respectively) in both the gasoline and diesel emission health impact analyses, the findings that larger population health impacts are associated with gasoline emissions than with diesel emissions are expected to hold. This represents an important conclusion of this report.

It is important to note that recent amendments to the *On-Road Vehicle and Engine Emission Regulations,*[1] *Sulphur in Gasoline Regulations,*[2] and *Off-Road Small Spark-Ignition Engine Emission Regulations*[3] will result in reductions in air pollutant emissions from gasoline engines over the next decade and associated population health benefits. Specifically, it has been estimated that the combined national effect of the first two of these regulations on on-road vehicle emissions will result in 40 fewer premature mortalities in 2020 and 200 fewer premature mortalities in 2030.[4] These amendments were not reflected in the current analysis, which targeted calendar year 2015.

Gasoline emissions contain multiple air toxics, including benzene, 1,3-butadiene, formaldehyde, acetaldehyde and PAHs, the carcinogenic effects of which are recognized by Health Canada and international agencies. Cancer and non-cancer inhalation risk estimates for modelled ambient levels of acetaldehyde, benzene and formaldehyde suggested that gasoline emissions contribute negligibly to total risk levels from ambient concentrations in Canada. This analysis did not address the impact of gasoline-powered sources on personal exposures to these air toxics or on their concentrations in microenvironments influenced by engine emissions. Hence, the conclusions drawn apply only to the risks associated with modelled ambient concentrations. Additional analyses and data are required to include more air toxics in future assessments and to improve cancer and non-cancer inhalation risk estimates.

This health impact analysis was undertaken to provide Canadian jurisdictions, regulators and policy makers with a comprehensive evaluation of the potential health impacts of gasoline emissions. This assessment of gasoline emissions in Canada is the first Canada-wide study of the contribution of gasoline emissions to air quality and human health impacts. As such, it represents a baseline for discussions on the health consequences of gasoline use in on-road and off-road sources in Canada. This assessment, which used a similar approach as the Human Health Risk Assessment for Diesel Exhaust released by Health Canada in 2016, also provides the first nationwide comparison of health impacts associated with gasoline and diesel emissions in Canada. It can be used to inform further efforts to

[1] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=65
[2] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/DetailReg.cfm?intReg=18
[3] http://www.ec.gc.ca/lcpe-cepa/eng/regulations/detailReg.cfm?intReg=81
[4] http://canadagazette.gc.ca/rp-pr/p2/2015/2015-07-29/html/sor-dors186-eng.php

mitigate emissions and the population health impacts associated with mobile source emissions in this country. Owing to continual changes in terms of emission estimates and source characterization, modelling methodology improvements and updates, population dynamics and epidemiological findings, the current 2015 estimates may not be representative for an extended period of time. However, these results will remain informative and provide a relevant Canadian baseline for future analyses of fuel-related health impacts.

Overall, it is concluded that air pollutants from gasoline sources continue to pose a risk to human health in Canada.

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