A screening-level risk assessment of petrol exposures in New Zealand

A report to the Institute of Environmental Science and Research, Ltd.

May 2015

J. Fowles
E. Silver

Laurelton Research
Tox-Logic Consulting, LLC

A SCREENING-LEVEL RISK ASSESSMENT OF PETROL EXPOSURES IN NEW ZEALAND

Prepared as part of a Ministry of Health
contract for scientific services

by

J Fowles

E. Silver

May 2015

Client Report FW15029

A SCREENING-LEVEL RISK ASSESSMENT OF PETROL EXPOSURES IN NEW ZEALAND

Rob Lake
Manager, Risk and Response Group

Chris Nokes
Project Leader

Toxicology Consulting
Peer Reviewer

GLOSSARY 3

EXECUTIVE SUMMARY 7

INTRODUCTION 9

Purpose of report 9

Background 9

Literature search 10

Approach 10

HAZARD ASSESSMENT 13

Acute toxicity 14
Surveillance data 15
Sensitisation 18

Mutagenicity 18

Reproductive/developmental toxicity 18

Non-cancer chronic toxicity 18
Summary of non-cancer effects 20

Carcinogenicity 21
Non-occupational studies 22
Occupational studies 23
Childhood cancer 25
Summary of carcinogenicity 26

DOSE RESPONSE ASSESSMENT 28

EXPOSURE ASSESSMENT 32

Acute exposures 32
Scenario 1: Filling the car petrol tank 32
Scenario 2: Filling the lawn-mower petrol tank 33
Scenario 3: Child/toddler exploration 35

Chronic exposures 35
Scenario 4: Filling the car petrol tank 35
Scenario 5: Filling the lawn-mower petrol tank 39

RISK CHARACTERISATION 42

Acute 42
Scenario 1 – Filling the car petrol tank 42
Scenario 2 – Filling the lawn-mower petrol tank 42

Scenario 3 – Child/toddler exploration 42

Chronic **43**
Scenario 4 – Filling the car petrol tank 43
Scenario 5 – Filling the lawn-mower petrol tank 44

DISCUSSION **46**

Risk management/risk reduction **47**

UNCERTAINTIES IN THIS REPORT **50**

CONCLUSIONS **52**

APPENDIX B. CALCULATIONS OF HAZARD QUOTIENTS AND HAZARD INDICES **54**

REFERENCES **58**

Glossary

Acute toxicity	1. *Adverse effects* of finite duration occurring within a short time (up to 14 d) after administration of a single *dose* (or *exposure* to a given *concentration*) of a test substance or after multiple doses (exposures), usually within 24 h of a starting point (which may be exposure to the *toxicant*, or loss of reserve capacity, or developmental change, etc.) 2. Ability of a substance to cause *adverse effects* within a short time of dosing or *exposure*
Acute Myelogenous Leukaemia (AML)	A cancer of the blood cells, stemming from unregulated proliferation of white blood cells from the bone marrow. AML is also known as acute non-lymphocytic leukaemia (ANLL).
Adverse effect	A change in biochemistry, physiology, growth, development morphology, behaviour, or lifespan of an organism which results in impairment of functional capacity or impairment of capacity to compensate for additional stress or increase in susceptibility to other environmental influences
Aromatic hydrocarbons	Organic chemical components of petrol, normally referring to benzene, toluene, ethylbenzene, and xylene (BTEX). As distinct from aliphatic hydrocarbons.
Aspiration pneumonia	Disease resulting from damage to the deep lung following accidental inhalation of liquid hydrocarbons or similar chemicals
Cancer Potency	Also termed the potency slope factor expressed usually in $(mg/kg\ BW/day)^{-1}$. When multiplied by the estimated daily dose in mg/kg BW/day, gives a unitless expression of cancer risk. Related to this is the unit risk, which is the upper-bound excess lifetime cancer risk estimated to result from continuous exposure to an agent at a concentration of 1 microgram per cubic meter ($\mu g/m^3$) in air.
Cancer Risk	An expression of the probability of additional cancers to occur, above a background incidence. Often expressed in terms of added cases per million or 100,000 people.
CLP	Classification and labelling proposal in industry REACH registration dossiers found online and submitted to the European Chemicals Agency in 2010 and 2013.
CNS	Central Nervous System
Dermal	Cutaneous, pertaining to the skin
Developmental Toxicity	Harmful effects caused by chemicals on the developing foetus or new-born

DNEL	Derived No Effect levels – practical thresholds for the onset of adverse effects for use in risk assessments. DNELs are usually industry-derived values.
Dose	Total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue
Dose response	Association between dose and the incidence of a defined biological effect in an exposed population
Dose response assessment	Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population. Dose–response assessment is the second of four steps in risk assessment.
Exposure assessment	Evaluation of the exposure of an organism, system, or (sub)population to an agent (and its derivatives). Exposure assessment is the third step in the process of risk assessment.
Exposure Scenario	A contrived situation representing assumptions about exposure conditions that are intended to reflect typical and/or worst case potential exposure events
Haematology	The study of blood components
Harm	An adverse effect. Damage or adverse effect to a population, species, individual organism, organ, tissue, or cell
Hazard identification	The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population. Hazard identification is the first stage in hazard assessment and the first of four steps in risk assessment.
Hazard Quotient	The ratio of a single chemical exposure to its relevant health-based hazard value.
Hazard Index	A summed ratios of the estimated exposure dose of one or more chemicals with similar targets or mechanisms, to their respective health based hazard values (see Hazard Quotient) that serve as practical thresholds for prevention of adverse effects. An HI in excess of 1.0 indicates a potential risk of adverse effects to occur to some fraction of the population.
Incidence	Number of occurrences of illness commencing, injury, or of persons falling ill, during a given period in a specific population usually expressed as a rate
Injury	Any physical harm or damage serious enough to warrant medical treatment by a health professional either at the scene or in a hospital or primary care practice
Irritant	Producing inflammation or irritation
Myelodysplastic Syndrome (MDS)	A disease stemming from alteration of white blood cell balance in the blood. Considered a precursor condition to leukaemia.

Napthas	Refers to a range of hydrocarbons from 5 to 12 carbons in length, with varying boiling points. Petrol or gasoline is a naphtha mixture.
No observed adverse effects level (NOAEL)	Greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure
Oral	Pertaining to or via the mouth
Petrol	Also known as gasoline, is produced from crude petroleum oil through a distillation and refining process
ppm	Parts per million (weight to volume in air). Converted to mg/m^3 through the use of ideal gas law: for benzene 1 ppm = 3.19 mg/m^3 at standard temperature and pressure (25°C, 1 atm).
RfD or RfC	Reference Dose or Reference Concentration – Practical thresholds for risk assessment purposes to indicate the potential for the onset of adverse effects, accounting for variabilities in the human population, uncertainties in animal-human extrapolations, and other factors. These are often US EPA-derived.
Risk characterisation	The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions. Risk characterization is the fourth step in the risk assessment process.
Toxicological endpoints	An observable or measurable biological event or chemical concentration (eg, metabolite concentration in a target tissue) used as an index of an effect of a chemical exposure
UN GHS	United Nations Global Harmonized System for the classification of hazardous substances
US EPA	United States Environmental Protection Agency

Executive summary

Petrol is a widely used commodity in New Zealand. The high use rate and volatility lead to frequent exposures. Petrol ranks highly among hazardous substance related injuries resulting in hospitalization in New Zealand and internationally. Between 2007 and 2011, there were four recorded deaths caused by petrol toxicity in New Zealand. Petrol is also among the highest ranked substances in New Zealand in acute hospitalisations from hazardous substance exposures, with 58 hospitalisations in 2012. To explore the toxicological risks from domestic use, we constructed exposure scenarios for motorists while refuelling, for home gardeners refuelling equipment, and for child exploratory play. Hazard indices (HIs), using reference concentrations from the US Environmental Protection Agency (EPA), and the California EPA for typical acute and chronic exposures, were derived that show a potential risk of developmental haematological effects in acute exposure scenarios (HIs= 2 and 3), but no significant risks in chronic long term exposure. These risks of systemic health effects are due to the benzene component in petrol, averaging 0.74 to 0.78% from 2012 to 2014. The additional risk of cancer from weekly or bi-weekly exposures to petrol fumes and small liquid petrol spills containing benzene on skin while refuelling an automobile over a lifetime was estimated to be approximately 8 in 1,000,000 to 60 in 1,000,000, using published cancer potency values for benzene of 0.015 or 0.1 $(mg/kg\text{-}d)^{-1}$. Refuelling a lawn-mower twice per month, year round, for 50 years similarly results in a range of cancer risk from 4 in 1,000,000 to 50 in 1,000,000 depending on the effective control of spillage. Benzene concentrations in the air at petrol stations from overseas studies were used as surrogates for New Zealand data. This represents an important data gap that could influence our conclusions significantly. Data from the Ministry of Business, Innovation, and Employment on benzene content of New Zealand petrols are broadly consistent with overseas data, but the specific control systems operating in petrol stations may not be comparable. This assessment provides a precautionary approach to the estimated potential exposures and risks from petrol exposures. Further exploration of key variables will allow for a more precise estimate of these risks.

For child exploratory settings, any oral exposure to petrol carries a serious risk of aspiration pneumonia, as does the case of mouth-siphoning of petrol. It is therefore important to keep petrol securely away from access by toddlers and children.

Petrol sniffing and solvent abuse represent an additional dimension to the acute and chronic chemical injury risks from petrol, but this is outside the scope of this report.

[Intentionally Blank]

Introduction

Purpose of report

The purpose of this report is to describe exposures and risks to the New Zealand public from incidental exposures to petrol formulations commercially for sale. The report specifically does not include diesel or aviation fuels, nor any combustion products resulting from the normal use of these fuels. The report does not address occupational exposures or risks from petrol, nor does it address intentional injuries from exposures to petrol such as suicides. Injuries from explosions and burns are also outside the scope of this assessment.

Background

Petrol, also known as gasoline in some countries, is produced from crude petroleum through the distillation and refining process. According to the US Agency for Toxic Substances and Disease Registry (ATSDR), there are typically more than 150 chemicals in petrol, including small amounts of benzene, toluene, xylene, ethylbenzene, and trace amounts of some contaminants, such as lead. How the petrol is made determines which chemicals are present and at what concentrations in the mixture. The actual composition varies with the source of the crude petroleum, the manufacturer, and the time of year (ATSDR 1995).

There are different petroleum-derived hydrocarbon fuels. The petrol discussed in this risk assessment is that mixture of petroleum-derived hydrocarbons used as fuel for engines in automobiles and other vehicles, such as motorbikes and equipment such as lawn-mowers. Other types of distillate fuels, such as diesel and jet fuels, and fuel oils, are not included in this risk assessment.

New Zealand consumed, per capita, 508 kg of petrol, measured in oil equivalents in 2011 (World Bank 2014). In terms of country rankings, this figure places New Zealand at 10th out of 136 countries for which data were reported for that year (Table 1). As a high volume consumer product, the frequency and amount of use of petrol creates many potential exposures in a typical day.

Petrol has a high vapour pressure and rapidly evaporates at normal ambient temperatures. Small spills of petrol in filling stations can therefore contribute to significant air concentrations. For example, it has been reported that the concentration of petrol in air at a filling station during the filling of an automobile petrol tank was up to 99 ppm (ATSDR 1995).

Table 1. Petrol use per capita (kg/person): The top 10 countries out of 136 reported, ranked by 2011 standings.

Country	2009	2010	2011
United States	1126	1146	1106
Canada	889	903	886
Kuwait	854	1028	809
Luxembourg	755	690	696
Saudi Arabia	635	651	686
Oman	628	666	639
Brunei	576	587	603
Qatar	604	637	599
Australia	614	593	580
New Zealand	531	525	508

* Data from the World Bank, 2014.

Petrol, as a low viscosity hydrocarbon mixture, also represents a significant health hazard if ingested, through incidental aspiration (ECHA 2010). No threshold is known below which there is no risk of aspiration pneumonia from oral ingestion of petrol. Therefore, mouth-siphoning of petrol can lead to serious pulmonary toxicity, including pneumonia, as well as transient central nervous system (CNS) effects.

The purpose of this risk assessment is to characterise the acute and chronic health risks from petrol exposures to non-occupationally exposed New Zealanders under conditions of typical use, or in anticipated accidental exposure scenarios.

Literature search

We reviewed a broad range of epidemiological and toxicological literature on cancer and non-cancer endpoints associated with various types of exposures to petrol. PubMed was used as the major search engine to identify papers, and was supplemented by searches with google and google scholar, and by reviewing the references of key papers. Many search terms were used, including various combinations of “petrol”, “gasoline”, “epidemiology”, “hazards”, “cancer”, “benzene”, “humans”, and “petrol sniffing”. Many hundreds of papers were identified in this manner and about 150 were reviewed in detail for this report. In addition to peer-reviewed published literature, we used regulatory dossiers from the European Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) registration programme to identify and describe animal and human data that may be otherwise unpublished.

Approach

For non-cancer toxicological endpoints, a hazard index (HI) approach was employed, comparing estimated exposures from likely scenarios, with industry Derived No Effect Levels (DNELs) from the REACH registration of the petrol mixture, the summation of individual component Reference Concentrations (RfCs) from the US Environmental Protection Agency (EPA), or Reference Exposure Levels (RELs) from the California EPA

for the major chemicals in petrol, providing an overall HI or hazard quotient for acute and chronic exposure scenarios.

The general form of the HI equation is:

1) HI = Exp/DNEL (for the whole petrol mixture), or

2) HI = Sum [HQ_1 + HQ_2… HQ_n] (ie, summed component HQs for the mixture)

and $HQ_n = C_n/RfC_n$

Where:

DNEL = Derived No Effect Level (dose or concentration units)
Exp = Estimated dose in mg/kg/d, or the estimated concentration in mg/m^3
C_1 = Estimated dose of chemical component 1
RfC_1 = Reference Concentration of chemical 1

According to the California EPA's Office of Environmental Health Hazard Assessment (OEHHA 2009), the estimation of cancer risk from benzene in petrol uses the "multistage" polynomial (US EPA 1986, 2005; Anderson et al 1983), based on the cancer induction mechanisms from the original Armitage and Doll model of cancer induction and progression. This linear approach has been extensively used by the US EPA, the State of California, and other agencies to model the risk of developing cancer over a lifetime. In mathematical terms, the probability of dying with a tumour (P) induced by an average daily dose (d) is:

$A(d) = 1 - \exp[- (q1d1 + q2d2 + \cdots + qkdk)]$,

Where: $A(d) = P(d) – P(0) / 1-P(0)$

is the extra risk over background at dose d.

Since petrol is classified as a Category 1B carcinogen under REACH, and because benzene, a known human carcinogen (IRIS 2003; ATSDR 2007; IARC 2012), is a component of petrol, a detailed cancer risk assessment of exposure to benzene during automobile refuelling, including an exposure assessment for benzene, was conducted.

Due to the presence of multiple potency values for benzene, we have presented the cancer risks in terms of a range that includes the lowest and highest potency value. At the more conservative end, we used a cancer potency factor for benzene of 0.1 per mg/kg-day, based the California EPA's Office of Environmental Health Hazard Assessment (OEHHA 2003). A less conservative value that was also used is the US EPA reported cancer potency factor range of 0.015 – 0.055 per mg/kg-day. Many publications that were reviewed in the course of preparing this report used a cancer potency factor of 0.0273 per mg/kg-day, apparently citing a US EPA value that is no longer shown in the IRIS database (IRIS 2003), and may have been removed as early as 1991 (see http://www.epa.gov/iris/subst/0276.htm#revhis). Because we can find no

support for using this value at present, it has not been used in our analysis. However, it does fall within the range of cancer potency factors used in this report.

Multiplication of the average daily inhalation dose over 70 years (mg/kg-day) with the cancer potency factor $(mg/kg\text{-}day)^{-1}$ was performed to give inhalation cancer risk (unitless). It is common to employ a Unit Risk value in units of $(\mu g/m^3)^{-1}$ for the estimation of cancer risk from chronic inhalation exposures. However, due to the discontinuous and episodic nature of the inhalation exposures (minutes/day), we elected to estimate inhalation daily doses and use the systemic oral cancer potency to derive cancer risk. The question of route specificity is moot since both potencies relate to the same endpoint and draw upon the same database. The potential cancer risk was then multiplied by 10^5 (or 10^6) in order to present a risk as the chances per 100,000 (or per million) of developing cancer. This method is described in US EPA (US EPA 2005) and California EPA's Office of Environmental Health Hazard Assessment (OEHHA 2003) guidelines for health risk assessments of carcinogens.

Hazard assessment

Petrol is a hydrocarbon chemical product with a variable composition. Regulations exist which prescribe limits on the components of petrol in New Zealand. The Engine Fuel Specifications Regulations 2011 (SR 2011/352, as at 4 October 2013) provide the following descriptions of petrol components in Table 2:

Table 2. Petrol Component Specifications in New Zealand, according to the Engine Fuel Regulations 2011.

Component(s)	Limits (Maxima)	Test method
Sulphur (mg/kg)	50	ASTM D5453
Existent gum (mg/100 mL)	5	ASTM D381
Lead (mg/L)	5	IP 224
Benzene (%)	1	ASTM D5528
Ethanol (%)	10	ASTM D4815
Total aromatics (%)	45	ASTM D5580
Other oxygenates (%)	1	ASTM D4815
Olefins (%)	18	ASTM D1319
Manganese (%)	2	ASTM D3831
Phosphorous (%)	1.3	ASTM D3231

http://www.legislation.govt.nz/regulation/public/2011/0352/latest/whole.html

Two notable components of petrol from a toxicological perspective are benzene and lead. Lead was banned from petrol in New Zealand in 1996, but since petroleum can contain naturally occurring traces of lead, the Fuel Regulations 2011 still contain an allowable level of 5 mg/L (5 ppm). Blood lead levels in New Zealand have correspondingly fallen since the early 1990's. Benzene levels in New Zealand petrol have similarly decreased since the 1990's, with formulations now able to achieve an impurity level nearly down to 0.1% (Table 3).

Information available from the Ministry for Business, Innovation, and Employment's routine analyses of petrol for quality assurance purposes indicate that the benzene concentration of petrols in New Zealand are typically below 1%, averaging 0.74 and 0.78 during 2013–2014 and 2012–2013, respectively, while toluene and C8 hydrocarbon (xylenes and ethylbenzene) concentrations vary but are typically near 10% (Table 3) (MBIE 2014). Trace oxygenate additives are not considered in this report.

Table 3. Petrol aromatic components in New Zealand 2012–2014 (MBIE, 2014a)[1]

Petrol Component(s)	Mean % (2012–2013)	Mean % (2013–2014)	Range % (2012–2014)
Benzene (%)	0.78	0.74	0.13–0.98
Toluene (%)	11.5	10.4	3.1–30.3

[1] *Trading Standards, division of Ministry of Business, Innovation and Employment, which runs the national programme on fuel quality, supplied data on aromatic content in petrol. Trading Standards produces an annual report which gives a high level overview of the quality of the fuel supply in New Zealand.*

Ethylbenzene + Xylenes (%)	10.7	9.8	1.2–15.9

n = 100 (2012−2013), n = 103 (2013−2014)

Acute toxicity

Petrol is not considered to be acutely hazardous by any route of exposure, according to the criteria developed by the United Nations Globally Harmonized System (UN GHS) classification scheme (ECHA 2010). However, despite this lack of classification, ATSDR describes the acute toxicity of petrol as being potentially lethal to children when swallowed, in amounts as small as 10–15 g (approximately 500–1500 mg/kg) (ATSDR 2014). In adults, 20–50 g (approximately 300–800 mg/kg) can cause severe intoxication. Table 4 summarises all of the toxicological hazard classifications for petrol, according to the UN GHS system, under REACH. The acute toxicity hazard of petrol stems from the ingestion of low viscosity hydrocarbons, which can lead to accidental aspiration and pulmonary toxicity (Table 4).

The European REACH regulations required the submission of a risk assessment dossier by the manufacturing industries, and disclosure of toxicological data for each toxicological endpoint required for substances produced at different volumes. For petrol, the REACH dossier contains the industry's hazard classification of various commercial mixtures of low boiling point naphthas sold in Europe (shown in Table 4).

Table 4. Toxicological hazard classifications of gasolines or petrols[1], according to UN GHS classification scheme (ECHA 2010)

Hazard	GHS Classification under REACH
Skin irritation	Skin irritation 2 (H315: Causes skin irritation)
Aspiration	Asp. Tox. 1 (H304: May be fatal if swallowed and enters airways.)
Reproductive toxicity	Repr. 2 (H361: Suspected of damaging fertility or the unborn child
Germ cell mutagenicity	Muta. 1B (H340: May cause genetic defects.)
Carcinogenicity	Carc. 1B (H350: May cause cancer.)
Specific target organ toxicity – single exposure	STOT single exp 3 (H336 – May cause drowsiness or dizziness)

[1]CLP 5. Low boiling point naphtha, defined as: flashpoint <23°C and initial boiling point >35°C, benzene ≥0.1%, n-hexane ≥3% OR toluene ≥3% OR toluene ≥3% and n-hexane ≥3%.

Surveillance data

Petrol related acute injuries and deaths occur in New Zealand, as shown in the most recent available data in Table 5. In terms of hospital admissions, petrol consistently ranks near the top among all chemical categories for age groups until 54 years of age, and, notably, first place in the under age 14 categories. Its prominence in the 0–4 year age group indicates that exploration exposures, such as that described in this report, likely do occur with frequency. For deaths, Coronial Services data from 2007-2011 show that while petrol ranks less highly among chemical-related deaths than among hospitalisations, it still causes occasional fatalities.

Similarly, National Poisons Centre data from the US indicate that occasional major injuries and fatalities from petrol or gasoline occur (Table 6). The US data from 2009 to 2013 reveal a low rate of petrol related calls among adults (0.49–0.62% of total human exposures). By comparison, in New Zealand, 269 child exploratory exposure calls (0.28% of actual human exposures recorded) were made to the National Poisons Centre (NPC) between 2009 and 2012, while there were 528 adult unintentional exposures (0.55% of actual human exposures), and 15 adult intentional exposures (0.016% actual exposures) (Lee, personal communication, 2015).

That similar annual fatality total cases for petrol exist for New Zealand and the US (i.e. both countries had 4 total fatalities over a 5 year period), suggests that there is a far higher mortality rate from petrol exposures in New Zealand. However, caution should be used with this conclusion as the US national data are derived from poisons centres, and it is unclear if all petrol-related fatalities nationwide in the US would be reported through this means. On the other hand, the New Zealand fatality numbers are reported through the national coronial data which should be comprehensive.

Table 5. Acute injuries and fatalities from petrol in New Zealand

Age group	Hospitalisations (2012)[1]	Rank	Deaths (2007–2011)[2]
0 to 4	8	1	0
5 to 14	12	1	1
15 to 24	7	4	1
25 to 34	13	1	0
35 to 44	11	3	1
45 to 54	4	4	1
55 to 64	2	7	0
65+	1	8	0

[1] From the National Minimum Dataset (# of events)
[2] From the National Coronial Services Data

Table 6. Incidents of gasoline (petrol) poisoning reported to US Poison Centres 2009-2013

Year[1]	Exposures reported		Age (years)				Reason					Outcome[2]				
	Total	Gasolines	<6	6-12	13-19	>19	Unknown	Unint	Int	Other	Adv Rxn	None	Minor	Mod	Major	Death
2009	2,479,355	15,219	3439	845	1470	7563	1513	13,678	979	75	54	1980	5012	427	11	0
2010	2,384,825	15,123	3051	877	1463	7865	1441	13,555	988	73	45	2034	4964	412	14	1
2011	2,334,004	14,036	2565	748	1323	7414	1543	12,383	1026	110	38	1712	4651	435	15	2
2012	2,275,141	13,086	2425	706	1190	6896	1345	11,417	991	80	23	1623	4102	345	12	0
2013	2,188,013	11,024	2100	663	977	5855	1040	9669	818	91	25	1413	3551	308	13	1

Unint = unintentional exposures, including passive environmental exposure, occupational exposure, therapeutic error or unintentional misuse
Int = intentional exposures, including suspected suicide and improper or incorrect use of a substance for a purpose other than its intended purpose
Adv Rxn = adverse reaction, an adverse event occurring with normal, prescribed, labelled, or recommended use of the product, as opposed to overdose, misuse, or abuse, including allergic, hypersensitive and idiosyncratic reactions
Mod = moderate
[1] Report references: Bronstein et al 2010; Bronstein et al 2011; Bronstein et al 2012; Mowry et al 2013; Mowry et al 2014
[2] Minor = The patient developed some signs or symptoms as a result of the exposure, but they were minimally bothersome and generally resolved rapidly with no residual disability or disfigurement. A minor effect is often limited to the skin or mucus membranes.
Moderate = The patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement
Major = The patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement

Sensitisation

Petrol has been evaluated for sensitisation potential in 43 animal skin sensitisation studies, and found to be negative (Table 7 and Table 8).

Mutagenicity

Petrol, benzene, toluene, xylene, and ethylbenzene have been evaluated for genotoxic effects in numerous test systems (Table 6 and Table 8). While petrol is generally negative for mutagenicity in bacterial systems, positive results in some mammalian and other animal systems for both petrol and benzene lead to a Category 1B classification under GHS for mutagenicity (ECHA 2010; NESCAUM 1989).

Reproductive/developmental toxicity

Animal studies on petrol, benzene, and toluene have all shown significant effects on the developing foetus (ECHA 2010; NESCAUM 1989). Increases in resorptions, decreased foetal body weight, and delays in skeletal ossification are all outcomes that have been observed with one or more of these materials (Table 6) (NESCAUM 1989). Human data on reproductive or developmental outcomes are more limited. Some women who breathed high levels of benzene for many months had irregular menstrual periods and a decrease in the size of their ovaries (CDC 2013). Petrol is classified under REACH as Reproductive Toxicity Category 2 using the UN GHS classification scheme (Table 4). Benzene is included in California's Proposition 65 list of chemicals known to cause reproductive toxicity, and toluene is considered a developmental toxicant (OEHHA 1997).

Non-cancer chronic toxicity

Benzene in petrol is harmful to the bone marrow and can decrease the number of red blood cells, leading to anaemia. It can also cause excessive bleeding and affect the immune system, increasing the chance for infection. A full review of the vast literature on this substance is not presented here. Epidemiological and experimental studies suggest that benzene exposure can lead to numerous non-cancerous health effects associated with functional aberration of vital systems in the body. These include reproductive, immune, nervous, endocrine, cardiovascular, and respiratory illnesses (Bahadar et al 2014). Doses and concentrations at which some of these effects have been reported to occur are shown in Table 7.

In everyday use, the odour of petrol can trigger migraine headaches in some individuals (Silva-Néto et al 2014). After spills or accidents, many more people can be expected to suffer adverse effects of petrol exposure. After 7000 tonnes of unleaded petrol were discharged into the English Channel after a tanker collision in 1997, the vapour plume was carried across England to Wales, resulting in widespread irritation of the eyes, skin, and upper respiratory tract (Welch et al 1999).

Fifteen workers were exposed to concentrations averaging >60 ppm (192 mg/m^3) benzene during removal of residual fuel from shipping tankers (Midzenski et al 1992). The maximum level was approximately 653 ppm (2,129 mg/m^3). Volatilization of benzene from the residual fuel was the suspected source of benzene. Twelve workers reported mucous membrane irritation. Eleven reported neurotoxic symptoms. Workers with more than two days of acute exposure were significantly more likely to report dizziness and nausea. Blood cell analyses over a four-month period after exposure found haematologic abnormalities consistent with benzene exposure in nine workers, with white blood cell counts below normal in four workers. After one year, six workers had persistent abnormalities; an additional worker, with normal haematologic parameters initially, later developed an abnormality consistent with benzene exposure. Many large granular lymphocytes were found in the peripheral blood smears of six of the workers.

More recently, a study of 60 petrol station workers and 28 control subjects found significant decreases in lymphocyte and monocyte cellular receptors CD80 and CD86, increased production of interleukin-8, and decreased delta-aminolevulinate dehydratase (ALA-D) enzyme activity (Moro et al., 2015). These effects were seen after controling for confounding variables, and at benzene exposures below the 8-hour occupational exposure limit of 0.5 ppm (1.6 mg/m^3).

In the US, several studies have described increases in exposures to petrol reported to poison control centres after hurricanes (Cox et al 2008; Forrester 2009; Kim et al 2013). Opportunities for petrol exposure are increased when people are looking for it to power vehicles during times of petrol shortages, and portable petrol-driven electric generators, which have become widespread. Siphoning petrol by mouth is reported in a majority of these cases.

Numerous animal chronic toxicity studies have been conducted on unleaded petrol (Table 7). A difficulty with interpretation of animal data lies in the apparently unique metabolism and distribution of benzene in humans, resulting in increased human susceptibility to the formation of haematologic cancers compared with what is observed in rat or mice models. In one major study, petrol vapour was administered by inhalation to Fischer 344 rats and B6C3F mice for 6 hours/day, 5 days/week for up to 113 weeks at concentrations of 322, 1402, and 9869 mg/m^3 (MacFarland et al 1984). No consistent, compound-related changes were seen in mortality, hematology or clinical chemistry parameters in either species. A significant reduction in body weight gain was seen in both sexes of rats and in male mice at the highest concentration tested. An exposure-related increase in liver nodules and masses was seen in female mice exposed to the highest concentration. In addition, male rats at all petrol concentrations exhibited primary kidney neoplasms, correlated histopathologically with an increase in the incidence and severity of regenerative epithelial changes and dilated tubules containing proteinaceous material. These kidney effects in male rats are indicative of alpha-2u-globulin nephropathy. Alpha-2u-globulin nephropathy, also known as hyaline droplet nephropathy, results from the formation of complexes with a naturally-occurring protein in the kidneys of male rats. These complexes can accumulate in the proximal renal tubule and are known to produce species-specific histopathological changes of no known relevance to human health.

Summary of non-cancer effects

Although a number of toxicological findings in animal studies point to systemic effects from petrol, the most sensitive effects appear to be species-specific kidney pathology of questionable relevance to humans. Human data on non-cancer effects of the principal components of petrol, including benzene, toluene, ethylbenzene, and toluene, are numerous, with benzene being a particularly potent and hazardous component.

Table 7. Summary of toxicity studies on petrols summarised in the European REACH regulations (ECHA, 2010)

Toxicity Endpoint	Number of studies	Dose Range of NOAEL or Acute LD_{50} (mg/kg bw)	Comment
Acute (oral LD50)	44	>4500–14063	Not acutely toxic by oral route
Acute (inhalation LC50, 4 h)	40	>4420–>8530	Not acutely toxic by inhalation
Acute (dermal LD50)	45	>1900–>6000	Low acute toxicity
Irritation (skin)	114	Irritating	Reversible irritation
Irritation (eye)	45	Not irritating	
Sensitisation (skin)	43	Not sensitising	
Repeat dose (oral) 28 d studies	5	<500	Hydrocarbon nephropathy in male rats after 28 days
Repeat dose (inhalation) Chronic	22	1402 mg/m^3 (chronic) 10000 mg/m^3 (90 day) 9840 mg/m^3 (28 day) 10032 mg/m^3 (28 day) 1970 mg/m^3 (90 day)	Decrease body weight gain in mice and rats Local airway effects No effects at top dose No effects at top dose Increased liver and kidney weight
Repeat dose (dermal)	52	0.5 mL <200 mg/kg	Local irritation/keratosis Dermal irritation
Mutagenicity	35	Not mutagenic	
Reproductive toxicity	4	NOAEC >20,000 mg/m^3	No effects aside from kidney and liver pathology of questionable relevance to humans
Developmental toxicity	8	NOAEC >23940 mg/m^3 (rats) NOAEC = 540 mg/m^3 (mice); NOAEL > 1000 mg/kg (dermal)	No effects on foetal development in rats. High dose effects in mice from inhalation (cleft palate, reduced bw, delayed ossification). Benzene content unknown

Toxicity Endpoint	Number of studies	Dose Range of NOAEL or Acute LD_{50} (mg/kg bw)	Comment
Carcinogenicity	12	50 µL/day not generally carcinogenic by dermal route; mice inhalation studies found liver tumours in females; rat kidney tumours in males	Benzene content unknown

The toxicological endpoints of most interest for non-cancer repeated dose effects are CNS effects, haematological toxicity and developmental toxicity. Non-cancer DNEL and Reference Exposure Levels for the benzene, toluene, and xylene were used to characterize the local and systemic risks from chronic petrol exposures.

Carcinogenicity

Petrol is classified as a Category 1B Carcinogen under the European REACH system (Table 4) (ECHA, 2010). Benzene is a known human carcinogen according to WorkSafe New Zealand (formerly the Department of Occupational Safety and Health in the Department of Labour), and is present in refined petrol at varying concentrations, required to be less than 1% in New Zealand (Engine Fuel Specifications Regulations 2011). Company product information sheets online describe benzene levels in some formulations as less than 3%, but do not provide greater specificity. However, analytical data provided by MBIE (2014a) indicate that typical benzene concentrations in New Zealand petrol from 2012 to 2014 were approximately 0.7–0.8% by weight, with 0.98% representing the highest reported concentration (MBIE 2014a). As no threshold for the carcinogenicity of benzene is known to exist, even small incidental exposures to petrol on a chronic basis can be assumed to carry some cancer risk.

Benzene is widely recognized as causing human leukaemia (Rinsky et al 1987; Hayes et al 2001; IARC 2012). Some other components of petrol, notably ethylbenzene and methyl tertiary butyl ether (MTBE) possess carcinogenic properties, based on studies in laboratory animals (Mehlman 1996). However, it is not clear from the nature of the types of cancers seen in animals, if ethylbenzene and MTBE represent human carcinogens. Hematologic research and advances in stem cell biology, molecular genetics, and computational biology have provided new insight into the events that lead to benzene-induced leukaemogenesis. This has resulted in an increasing appreciation of a group of relatively obscure hematologic disorders now known as myelodysplastic syndromes (MDS). MDSs are disorders of the hematopoietic stem cell in the bone marrow (related to myeloid lineage) and are debilitating, often fatal and sometimes precursors to leukaemia. These conditions are associated with progressive bone marrow failure, but are not characterised by increases in the number of circulating cells as seen in myeloproliferative or leukaemic diseases, and share certain common features of abnormal maturation and development of haematopoietic precursor cells in the bone marrow (Tefferi et al 2009; Irons et al 2014).

Many biomarkers have been identified and validated to investigate benzene exposure, susceptibility, and early effects (Smith and Rothman 2000; Arnold et al 2013). Furthermore, numerous publications have described increases in biomarkers of genetic damage in petrol station attendants, consistent with the carcinogenic effects of benzene (Rekhadevi et al 2011; Singaraju et al 2012; Fustinoni et al 2012; Moro et al., 2015). For brevity, this body of literature is not discussed in detail in this report.

The primary persistent disease in benzene myelotoxicity is MDS, which precedes cytogenetic injury. Acute myeloid leukaemia (AML) arises as a secondary event, subsequent to evolution of the leukaemia-initiating cell phenotype within the altered bone marrow microenvironment (Irons et al 2014). AML is also known as acute non-lymphocytic leukaemia (ANLL), particularly in publications from China. Other types of leukaemia have also been widely studied in relation to benzene exposure, including Hodgkin's lymphoma (HL), non-Hodgkin lymphoma (NHL), multiple myeloma (MM), acute lymphocytic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL).

A recent review of the benzene epidemiological literature (Smith 2010) concluded that benzene adversely affects the blood-forming system at concentrations at or below 1 ppm, and that there is no evidence of a threshold. The consensus clearly shows that benzene causes AML and MDS, even at relatively low doses, and that AML often arises secondary to MDS (Smith 2010).

There is a very large body of epidemiologic literature describing petrol exposures and cancer. The vast majority of this literature involves occupational exposures to petrol, which are outside the scope of this report.

Non-occupational studies

Smoking is a source of benzene exposure. For non-smokers, most benzene exposure is derived from vehicle exhaust or petrol vapour emissions (Wallace 1996). There are published papers describing community risks of cancer and other illnesses after exposure to petroleum refinery emissions (Barregard et al 2009) or communities living in neighbourhoods near petrol stations who may be exposed to large amounts of petrol vapour from exhaust (Brender et al 2011), as well as in children born in such environments (Miligi et al 2013), but the volatile organic products of combustion that are present in these exposures are outside of the scope of this report.

Two papers were identified which investigated cancer risk in community residents of an area in northeastern Pennsylvania, US, affected by the Tranguch Gasoline Spill which occurred in the early 1990s (Patel et al 2004; Talbott et al 2011). These reports described a statistically significant increase in total leukaemia, and specifically, acute myelogenous leukaemia (AML), among the community living in the area that was exposed to petrol vapour leaking through underground storage vessels.

A hospital-based case-control study of over 400 newly diagnosed MDS patients was conducted to examine the relation of lifestyle, environmental, and occupational factors to risk of MDS in China (Lv et al 2011). Occupational benzene was a risk factor for MDS (OR=3.73; 95% CI 1.32–10.51), and risk factors of MDS subtype refractory cytopenia

with multiple dysplasia (RCMD) were occupational exposures to benzene (OR=5.99; 95% CI 1.19–30.16) and petrol (OR=11.44; 95% CI 1.31–100.03). Although this is not an occupational study *per se*, it did identify occupational risk factors for MDS.

Occupational studies

Although occupational exposures and risks are outside the scope of this report, the majority of what is known about the cancer risks of petrol and its components in humans has been learned from occupational studies, and this informs the non-occupational risk assessment. However, the literature in this area is prone to bias and unreliable analyses. As a result, a careful, but brief, review of the occupational epidemiology literature is warranted.

Quantitative evaluations of benzene-associated risk for cancer have relied primarily on findings from a cohort study of highly exposed (>200 ppm-years) rubber workers in the US (Rinsky et a, 1987). Later, an epidemiologic investigation in China showed that significant excesses of AML and AML/MDS were observed at average exposures of less than 25 ppm-years, with evidence of a doubled risk for AML/MDS at average exposure levels under 10 ppm-years benzene (Hayes et al 2000). This analysis was based on a cohort of 75,000 benzene-exposed workers compared to 35,000 unexposed workers employed from 1972 through 1987. In contrast to many other occupational cohorts, both men and women were included in the study population (Hayes et al 1997, 2000).

Some models predict that excess cases of cancer will occur at benzene 8-hour time-weighted average (TWA) concentrations below 1 ppm (Infante 1992). Until recently, there was little direct information on common exposure to predominantly less than 1 ppm benzene in modern occupational environments (Schnatter et al 1996).

Two recent papers describe the pooled study of three updated case–control studies, nested within three cohorts of male petroleum workers from Australia, Canada, and the UK (Schnatter et al 2012; Rushton et al 2014). In the pooled study, 8-hour-shift average benzene exposure concentrations were largely under 1 ppm. Relatively low-level exposure to benzene (<10 ppm-years) experienced by petroleum distribution workers was associated with an increased risk of MDS but not AML (Schnatter et al 2012; Rushton et al 2014). The authors explain that MDS cases in early literature were likely grouped with, or misclassified as, aplastic anaemia, myeloproliferative diseases, or other leukaemias. Cumulative benzene exposure showed a monotonic dose-response relationship with MDS (highest vs lowest tertile, >2.93 vs ≤0.348 ppm-years, OR = 4.33, 95% CI 1.31–14.3) (Schnatter et al 2012). In contrast to the patterns for MDS, the AML results were not consistent across the three studies. Categorical analyses showed increased risks for AML with several exposure metrics. Risks for tanker drivers, particularly at terminals, were similarly raised in both MDS and AML. However, the AML patterns were unclear, and the authors conclude that the data do not persuasively demonstrate an association between benzene and AML. The authors suggest that MDS may be the more relevant health risk for lower exposure (Rushton et al 2014).

Prior to the pooling of data from these three cohorts, each cohort had been described in numerous publications over the years, along with another cohort from the US

(Schnatter et al.1996; Rushton et al 1997; Wong et al 1999; Glass et al 2003). In reports describing the individual cohorts, little evidence of an effect of low benzene exposure was seen in Canada, the UK or the US (Schnatter et al 1996; Rushton et al 1997; Wong et al 1999). These studies may have lacked sufficient power individually to detect a small effect for low exposure to benzene (mainly 0.1–1.0 ppm) (Schnatter et al 1996).

In the Australian Health Watch study (Glass et al 2003), higher levels of benzene exposure were seen (above 2 ppm-years), and the exposure assessment performed in this cohort is considered to be extremely well done (Smith 2010). Benzene exposure in this cohort was demonstrated to be a risk factor for acute nonlymphocytic leukaemia and chronic lymphocytic leukaemia. No association with non-Hodgkin's lymphoma and multiple myeloma was detected. The risk of leukaemia was increased at cumulative exposures above 2 ppm-years and with intensity of exposure of the highest exposed job over 0.8 ppm (Glass et al 2003).

The Australian, Canadian, and UK cohorts were reviewed for quality and comparability by independent researchers who concluded that the exposure assessments and data analyses were done appropriately (Miller et al 2010). The US cohort was not included in this data review because the reviewers were unable to access materials from the US cohort. These researchers concluded that the evidence of an increased risk at higher exposures in Australia was convincing, that the results are consistent with some effect of benzene at higher lifetime exposures, and described plans for the pooled analysis in order to increase the power to detect an effect at low exposures to benzene (Miller et al 2010).

In the US, Schwartz et al (1987) reported an excess of deaths from leukaemia among automobile mechanics and gasoline station attendants in the US. These may be attributable to a variety of substances, including petrol vapour, benzene, solvents, lubricating oils and greases, and asbestos (from brake and clutch repair) as well as welding fumes and car and truck exhaust (Schwartz 1987). In a more recent study from the US, a favourable mortality experience was seen for crude oil production workers compared with the US population, which may represent a healthy worker effect (Divine et al 2000). However, a significant increase for acute myelogenous leukaemia deaths was seen in analyses restricted to people who were first employed before 1940 and who were employed in production and pipeline jobs for more than 30 years. No information was available about the benzene content of the crude oil over time or oil fields. Additionally, it is not known whether benzene was used as a solvent or cleaning agent in oil field work (Divine et al 2000).

In Nigeria, significant degrees of anaemia, neutropenia, and thrombocytopenia were observed in roadside vendors compared with control subjects (Niazi et al 1997). Study subjects included 118 roadside vendors of petrol, 57 mechanics working in small workshops, 38 attendants serving at modern petrol stations, and 129 control subjects who were not occupationally exposed to petrol. The authors observed that petrol products were used by some workers as solvents and skin cleansers, and also siphoned by mouth (Niazi et al 1997).

Review papers from the occupational literature yield conflicting conclusions. Jamall et al. reviewed the literature to determine whether exposure to benzene at refineries

handling gasoline might result in cancer risk under routine conditions for a working lifetime (Jamall et al 2008). The authors found that benzene exposures required to induce a measurable carcinogenic response exist, but are substantially greater than exposures likely to be encountered from exposure to gasoline at contaminated properties (0.5–1.0 ppm benzene in air on a TWA basis; Jamall et al 2008).

Several reviews and pooled analyses were identified that found no association between benzene and various leukaemias, lymphomas, and multiple myeloma (Raabe et al 1996; Wong et al 1997; Keenan et al 2013). However, there are some earlier suggestions by some of the same authors that somewhat contradict these negative findings. For example, Wong et al reported in 1989 that refinery employees, particularly those employed before the 1940s, may have been at increased risk of leukaemia, and that cancer of other lymphatic tissue may also be elevated (Wong et al 1989). Infante (2001) points out that analyses of the Wong cohort that begin follow-up before 1950 cannot be relied upon for estimating causes of death because of biases introduced into this cohort when the company removed records of some worker deaths that occurred before 1950. In another example, researchers from ChemRisk wrote in 2010 that the only malignant hematopoietic disease that has been clearly linked to benzene exposure is AML (Galbraith et al 2010). However, a 2013 ChemRisk meta-analysis finds no strong and consistent association between AML and benzene (Keenan et al 2013). Only 30 studies out of 67 identified were included in the meta-analysis (Keenan et al 2013), which may introduce bias.

Another recent meta-analysis, by Vlaanderen et al (2011) came to a different conclusion (Vlaanderen et al 2011). These authors conducted a meta-analysis of 41 occupational cohort studies (out of 44 identified), and found support for an association between occupational benzene exposure and risk of multiple myeloma (MM), acute lymphocytic leukaemia (ALL), and chronic lymphocytic leukaemia (CLL). They found that the evidence for an association with NHL is less clear, which may be due to the disease heterogeneity within the NHL group of diseases (Vlaanderen et al 2011).

Neasham et al (2011) investigated occupational risks for lymphomas in the European Prospective Investigation into Cancer and Nutrition (EPIC). Over 300,000 subjects were followed up for an average of nine years. Hodgkin's lymphoma was associated with gasoline station occupation (HR=4.59, 95% CI 1.08–19.6) (Neasham et al., 2011). A recent review and meta-analysis (Kane et al 2010) reviewed 22 cohorts and 13 case-control studies that described the risk of NHL among workers in the downstream petroleum industry, and found no association with NHL, while another (Steinmaus et al 2008) reviewed 22 studies in total and did find an association. Additionally, the authors noted that the effects of benzene on NHL might be missed in occupational studies if certain biases, such as the healthy worker effect, are not accounted for (Steinmaus et al 2008).

Childhood cancer

An association between childhood leukaemia and parental exposure to benzene has been considered compelling by some authors (Zeise et al 2000) based on occupational studies of paternal and maternal exposures and animal studies of benzene induced DNA

damage to sperm. However, the hypothesized association remains poorly quantified in human epidemiological studies.

Multiple studies have shown an increase in childhood leukaemia risk in relation to air pollution sources emitting benzene, such as petrol stations and traffic (Brosselin et al 2009; Smith 2010), which again is outside the scope of this report. However, in Australia, researchers found no evidence that non-occupational refuelling of a vehicle with petrol in the year before or during pregnancy increased the risk of ALL in the offspring (Bailey et al 2011). In a U.K. case-control study of childhood leukaemia, McKinney et al (2008) found significant risks of acute lymphoblastic leukaemia (ALL) with self-reported maternal occupational exposure to petrol. However, when the authors restricted the analyses to good-quality, validated exposure assessment data, this association did not persist (McKinney et al 2008). A case-control study of childhood leukaemia in China did find an association between self-reported occupational exposure to benzene and petrol (Shu et al 1988).

Summary of carcinogenicity

The consensus of our literature review shows that benzene exposure can be considered to be causally associated with AML and MDS in humans upon chronic exposure, even at relatively low doses (i.e. <1 ppm), and that AML often arises secondary to MDS. Additionally, petrol itself is classified as a Category 1B carcinogen and Category 1B mutagen due to animal and human toxicology and epidemiological data (Table 4). As a result, a cancer risk analysis is warranted.

[Intentionally Blank]

Dose response assessment

Hazard threshold values are available for petrol and several of its main components, including benzene, toluene, ethylbenzene, and xylene. These values are shown in Tables 8 and 9, with cancer potency values from the US EPA and California EPA (OEHHA) shown in Table 9. Key toxicological non-cancer endpoints include CNS effects, haematological and immunological effects, and membrane irritation.

Derived No Effect Levels (DNELs) have been established in the European REACH chemical registration process for petrol (Table 8). DNELs are derived from a key NOAEL or LOAEL point of departure (POD) typically, with Assessment Factors (AFs) modifying the POD to account for variabilities in extrapolation of experimental results in homogenous laboratory animal populations, to heterogeneous human populations. The PODs and DNEL values for petrol are shown in Table 8.

Table 8. Summary of available non-cancer DNELs for petrol for the general population*

Source	Value (mg/m^3)	LOAEC/NOAEC (mg/m^3)	Endpoint
Acute (local effects) 15 min	640	2400	Irritation of nose and throat in humans
Acute (systemic effects) 15 min	1200	4320	Neuromuscular effects in humans
Chronic (local effects)	180	10,000	Nasal discharge in rats (6 hour/day, 5 day/week)

* CONCAWE low boiling point naphtha REACH Chemical Safety Report, 2012

For individual components of petrol, RfCs, RELs, and Minimal Risk Levels (MRLs) exist to aid in general population risk assessments (Table 10).

While it is not the purpose of this report to examine all derived values internationally and the detailed technical assessments and methodologies that underpin each, the acute REL for benzene is briefly summarized below for illustrative purposes:

"Reference Exposure Levels are based on the most sensitive, relevant health effect reported in the medical and toxicological literature. Acute Reference Exposure Levels are levels at which infrequent one-hour exposures are not expected to result in adverse health effects (see Section 5 of the Technical Support Document (OEHHA 2008)). Studies of developmental toxicity usually use repeat exposures in utero, either throughout gestation or during organogenesis. The acute REL for benzene is based on a developmental study (Keller and Snyder 1988) in which pregnant mice were exposed 6 hours per day during days 6 through 15 of gestation. However, developmental toxicity may occur in response to just one exposure during a specific window of susceptibility. A literature search found 133 single-day exposure developmental toxicity studies involving 58 chemicals (Davis et al 2009). The same endpoints observed in repeat dose studies are often observed with single exposures, an acute effect. The acute REL derived above is a level not to be exceeded in any

one hour period, which is the default application for acute RELs based on developmental studies (OEHHA 2008)

In the key study, which OEHHA earlier used to develop a Proposition 65 MADL for benzene (OEHHA 2001), a monotonic dose response was seen for early nucleated red cells in 2 day neonates. The LOAEL was 5 ppm. A NOAEL was not detected."

Table 9. Acute 1-hour REL derivation parameters from OEHHA 2014.

PARAMETER	**VALUES AND RESULTS**
Key Study	Keller and Snyder, 1988
Study population	Pregnant mice
Exposure method	Inhalation of 0, 5, 10, or 20 ppm
Exposure continuity	6 hours/day
Exposure duration	10 days (day 6-15 gestation)
Critical effects	Decreased nucleated red cell counts
LOAEL	5 ppm (16 mg/m3)
NOAEL	Not found
Human Equiv. Concentration	5 ppm
Time adjustment factor	Not done
LOAEL uncertainty factor	SQRT10
Interspecies uncertainty factor	2 x SQRT10
Intraspecies uncertainty factor	10 x SQRT10
Database uncertainty factor	1
Cumulative uncertainty factor	600
Acute Reference Exposure Level	8 ppb (27 μg/m^3)

Table 10. Summary of available non-cancer hazard values for benzene, ethylbenzene, toluene, and xylene for the general population

Source	Value	LOAEC/NOAEC	Endpoint
Benzene	mg/m^3	mg/m^3	
OEHHA REL (acute 1-hr) ATSDR MRL (acute) (<14 days)	0.027 0.028	16	Immunological findings in foetal and neonatal mice
USEPA RfC (chronic)	0.03	8.2 (BMCL)	Decreased lymphocyte count in workers
ATSDR (chronic)	0.003	0.1 (BMCL)	B-cell counts in workers
OEHHA REL (chronic)	0.003	1.9	Human haematology
Ethylbenzene			
USEPA RfC (chronic)	1	434	Developmental toxicity in rats and rabbits
OEHHA REL (chronic)	2	65 (NOAEC)	Nephrotoxicity, hepatotoxicity in rodents
Toluene			
OEHHA REL (acute 1-hr)	37	370	Respiratory, CNS, eyes
OEHHA REL (chronic)	0.3	190 (NOAEC)	CNS, respiratory, developmental effects
USEPA RfC (chronic)	5	46	Neurological effects
Xylenes			
OEHHA REL (acute 1-hr)	22	430	Respiratory, eye irritation
OEHHA REL (chronic)	0.7	50 (LOAEC)	CNS, respiratory, developmental effects
USEPA RfC (chronic)	0.1	48	CNS effects

REL = Reference Exposure Level; MRL = Minimal Risk Level; RfC = Reference Concentration

Table 11. Summary of cancer potency slope values for benzene and ethylbenzene

Source	Potency Value(s)	Comments
Benzene		
US EPA	0.015–0.055 $(mg/kg\text{-}day)^{-1}$	Based on leukaemia in workers (Rinsky et al 1987)
OEHHA	0.1 $(mg/kg\text{-}day)^{-1}$	Based on leukaemia in workers
Ethylbenzene		
OEHHA	8.7×10^{-3} $(mg/kg\text{-}day)^{-1}$	Based on the incidence of kidney cancer (renal tubule adenoma or carcinoma) in male rats

Note: The World Health Organization (WHO) has an inhalation Unit Risk value for benzene of 6×10^{-6} $(\mu g/m^3)^{-1}$ (WHO 2000). This value falls within the range of Unit Risks from the US EPA ($2.2–7.8 \times 10^{-6}$ $(\mu g/m^3)^{-1}$.

The cancer potency values in Table 11 provide a basis for calculating cancer risk from discontinuous episodic exposures, once a chronic internal dose is determined. The US EPA and the WHO have determined potency values that are generally consistent with each other and within a similar range.

Susceptible populations

Infants and children may be at higher risk to benzene toxicity generally, due to their smaller body weight, their stage of development, and less developed liver detoxification mechanisms. According to the 2014 technical review of benzene toxicity by OEHHA (2014),

"*CYP2E1, a principal enzyme in the pathway of benzene metabolism which produces toxic metabolites, has not been detected early in human fetal liver (Vieira et al 1996) and rises to only 10-20 percent of the adult level by the third trimester (Johnsrud et al 2003). However, since many detoxifying enzymes are also low during this period (McCarver and Hines 2002), bone marrow toxicity from benzene metabolites could occur in the fetus. The variation in CYP2E1 levels between the third trimester fetus and the adult is also compatible with the default value of 10 for toxicokinetic variability among humans."*

However, a greater acute concern about infants and children is their exploratory nature, and this is likely an explanation of the high rates of hospitalisations in Table 5 for the under 4 year old age groups.

Striking variations have been noted in benzene toxicity among workers with comparable levels of occupational exposure (Smith 2010). The reasons underlying this variation are unknown, and probably include both genetic and environmental factors, including gender, age, amount of adipose tissue, routes of exposure, physical activity, co-exposures, smoking, alcohol consumption, and dietary habits. Many genetic factors have been suggested to play a possible role in benzene toxicity, including candidate genes related to metabolism, such as cytochrome P450 genes (CYP2E1, CYP2F1 and CYP2A13), NAD(P)H:quinone oxidoreductase 1 (NQO1), myeloperoxidase (MPO), glutathione-S-transferases (GSTs) including GSTT1 and GSTM1, and microsomal epoxide hydrolase (mEH); genes involved in DNA repair and genomic maintenance (BLM, TP53, RAD51, WDR79, and WRN); and cytokine and chemokine genes (VEGF, IL-1A, IL-4, IL-10, IL-12A, VCAM1, and TNF) (Smith 2010). When considering a risk reduction strategy, attention should be paid to the fact that some people may be more vulnerable to benzene toxicity than others, for reasons that are not yet fully understood.

Exposure assessment

We considered five exposure scenarios based on known use patterns and hospitalisation/injury statistics in New Zealand: Three acute scenarios and two chronic, which capture the following situations:

Acute Scenarios:

1) Filling the car petrol tank (inhalation + dermal)
2) Filling the lawn-mower petrol tank (inhalation + dermal)
3) Child/toddler exploration (oral + inhalation + dermal)

Chronic Scenarios:

4) Filling the car petrol tank (inhalation + dermal)
5) Filling the lawn-mower petrol tank (inhalation + dermal)

Due to the nature of scenario 3, effectively obviating the need to consider dose thresholds for effects from a public health perspective, these were not quantitatively assessed.

Dermal contact is expected to contribute insignificantly to an overall dose in some scenarios because the quantity of petrol contacting the skin is expected to be small, and because petrol constituents in the vapour phase are poorly absorbed percutaneously (REACH 2010). For example, the dermal absorption of toluene from vapour is approximately 1% of the amount absorbed by inhalation (REACH 2010). When contacted as liquid, petrol constituents are also poorly absorbed dermally if allowed to evaporate from the skin. However, if evaporation is impeded, then the fraction absorbed can be substantial, but this is considered irrelevant to the exposure scenarios presented. The child exploratory scenario does include dermal absorption, as it is conceivable the amount of spilled material and surface area could be significantly more than in the other scenarios. Other toxicokinetic properties of percutaneously absorbed petrol constituents, once in the systemic circulation, are similar to the same substances absorbed by inhalation.

Oral ingestion also normally contributes little to overall dose, as petrol is not intended for consumption. However, if ingested, most of the constituents are well absorbed from the gastrointestinal tract, and 100% absorption can be assumed (US EPA 1999).

Acute exposures

Scenario 1: Filling the car petrol tank

In this scenario, an adult refuels a car once per week for three minutes of refuelling time. The REACH exposure assessment for petrol describes measurements of petrol vapours in petrol use situations up to a high value of 728 mg/m^3 (CONCAWE, 2012). Inhalation exposures were calculated to give the equivalent concentrations for longer periods (15 minutes, and 1 hour) using a modification of Haber's Law ($C^n \times T = K$), where C is concentration, T is time, n is a derived or assumed value based on empirical

results, and K is a constant value. This conversion allows the comparison of air concentrations to acute DNELs and RELs to enable a direct estimate of risk. Only acute inhalation hazard values are available for comparison in the acute scenarios, thus dermal exposures are only considered qualitatively in terms of contribution to overall dose and risk in this scenario. Oral exposures are considered negligible in this scenario (CONCAWE, 2012).

Time adjustments for 3 minute durations in petrol station air to 15 minutes or 60 minutes were done as follows:

$C_1^n \times T_1 = C_2^n \times T_2$

Example: $(728\ (mg/m^3))^1 \times 3\ min = C_2^1 \times 15\ min$

$C_2 = 146\ mg/m^3$

Inhalation exposure parameters for acute car refuelling scenario are shown in Table 12.

Table 12. Inhalation exposure parameters for acute car refuelling scenario

Parameter	Value	Unit	Reference
C_{air} – P (Petrol Conc. in air)	728	mg/m^3	CONCAWE 2012
C_{air} - B (Benzene Conc. in air)	2.9		Egeghy 2000
C_{air} – T (Toluene Conc. in air)	40.9		Est. from MBIE 2014
C_{air} – X (Xylene Conc. in air)	79.2		Est. from MBIE 2014
IR (Inhalation rate)	0.023	m^3/min	US EPA Handbook 2011
RT (Refuelling time)	3	minutes	Egeghy 2000; CONCAWE 2012
Equiv. 15-min conc. (Petrol)	146	mg/m^3	Using Haber's Law of time adjustment for acute toxicity from 3 minute to 15 or 60 min
Equiv. 60 min conc. (Benzene)	0.15		
Equiv. 60 min conc. (Toluene)	2.1		
Equiv. 60 min conc. (Xylenes)	4.0		
Fraction absorbed	0.5		50% absorption assumed

Scenario 2: Filling the lawn-mower petrol tank

Consumers can be exposed to petrol through inhalation from vapour evaporation/ displacement or dermal contact from spillage when they are refuelling their garden equipment. Dermal and inhalation routes are relevant to this case. In this scenario, assumptions of bi-weekly refuelling a tank in an indoor location are designed to be conservative.

Dermal exposure was determined using the formulae:

$$A_{derm} = C_{derm} \times BIO_{derm} \times N_{events}$$

$$U_{derm\ pot} = \frac{A_{derm} \times Fabsorp}{BW}$$

Where:

C_{derm} = Concentration in the product (g/cm^3)

A_{derm} = External exposure to skin (g/event)

$U_{derm\ pot}$ = Potential dermal uptake rate (g/kg body weight/day)

BIO_{derm} = Bioavailability for dermal exposure (default = 1)

N_{events} = Number of events per period (usually, events/day)

BW = Body weight, in kilograms. Body weights for any average New Zealand adult (15+ years, 5th and 50th percentile) were taken from the 2009 Adult Nutrition survey (52.7 kg and 77.1 kg) (University of Otago and Ministry of Health 2011).

F_{abs} = Factor to quantify absorption

Dermal exposure parameters for acute lawn-mower refuelling scenario are shown in Table 13. Inhalation exposure parameters for acute lawn-mower refuelling scenario are shown in Table 14.

Table 13. Dermal exposure parameters for acute lawn-mower refuelling scenario

Parameter	Value	Unit	Reference
C_{liq-P} (Petrol conc. in liquid)	100	%	MBIE 2014
C_{liq-B} (Benzene conc. in liquid)	0.78		
C_{liq-T} (Toluene conc. in liquid)	10.4		
C_{liq-X} (Xylenes conc. in liquid)	20.2		
A_{derm} (Exposure to skin)	5	g/event	Assumed spillage is approximately 2x that of car spills (Wixtrom and Brown 1992)
Fraction absorbed (F_{abs})	0.01		ECHA 2010 – conservative default
ED (Exposure duration)	50	years	estimated years of lawn care
RY (Refuelling days per year)	26	per year	estimated (once/ 2 weeks for a year)
BW (Body weight) 5%	52.7	kg	NZ NNS 2009
50%	77.1		
AT (averaging time period)	70	years	OEHHA 2003
Conversion Factor	365	days/year	
Acute Dermal Dose – P	6.5–9.5 x 10^{-1}	mg/kg-day	Dependent upon body weight percentile (5% or 50%)
Acute Dermal Dose – B	5.1-7.4 x 10^{-3}		
Acute Dermal Dose – T	6.7–9.9 x 10^{-2}		
Acute Dermal Dose – X	1.3–1.9 x 10^{-1}		
Lifetime Dermal Dose – P	3.3–4.8 x 10^{-2}	mg/kg-day	Dependent upon body weight percentile (5% or 50%)
Lifetime Dermal Dose – B	2.8–3.8 x 10^{-4}		
Lifetime Dermal Dose – T	3.4–5.0 x 10^{-3}		
Lifetime Dermal Dose – X	6.7–9.8 x 10^{-3}		

[1] Assumes 1% absorption

B = benzene; P = Petrol; T = Toluene; X = Xylenes

Table 14. Inhalation exposure parameters for acute lawn-mower refuelling scenario

Parameter	Value	Unit	Reference
C_{air} – P (Petrol Conc. in air)	728	mg/m^3	CONCAWE 2012
C_{air} - B (Benzene Conc. in air)	2.9		Egeghy 2000
C_{air} – T (Toluene Conc. in air)	40.9		MBIE 2014
C_{air} – X (Xylene Conc. in air)	79.2		MBIE 2014
IR (Inhalation rate)	0.023	m^3/minute	EPA Exposure Factor Handbook Table 6-41
RT (Refuelling time)	2	minutes	CONCAWE 2012
EF (Exposure factor)	0.5		Assumes 50% absorption
Equiv. 15-min conc. (Petrol)	97	mg/m^3	Using Haber's Law of time adjustment for acute toxicity from 2 minute to 15 or 60 min
Equiv. 60 min conc. (Benzene)	0.1		
Equiv. 60 min conc. (Toluene)	1.4		
Equiv. 60 min conc. (Xylenes)	2.6		

Scenario 3: Child/toddler exploration

In this scenario, a single event of a toddler gaining access to uncontrolled areas of the garage or other storage areas around the house for petrol is assumed. Exposure computations are not deemed to be useful in the event of ingestion due to the severe hazard of ingestion of even small quantities of liquid with aspiration of petrol. Severe pulmonary toxicity can result from aspiration of just a few millilitres of this hydrocarbon mixture. This risk scenario is therefore hazard-driven, and risk management practices and public health messaging should ideally be directed to reduce the likelihood of this scenario from occurring.

Chronic exposures

Scenario 4: Filling the car petrol tank

Self-service petrol customers can be exposed to petrol through inhalation from vapour evaporation or dermal contact from spillage when they are refuelling their cars or similar vehicles. Use of a vapour recovery system at the pump can be expected to reduce the exposure concentration. The REACH registration of gasolines calculated the air concentration, based on physical/chemical properties as 728 mg/m^3 in a reasonable worst case scenario. Typical measurements are reported to be 110 mg/m^3 (CONCAWE, 2012). We have used the higher concentration assumption (728 mg/m^3) in this screening risk assessment.

Since benzene is a component of petrol that has been identified as a known human carcinogen (IRIS 2003; ATSDR 2007; IARC 2012) a cancer risk assessment for exposure to benzene during car refuelling was conducted. Three studies were identified that described benzene exposure assessment to the general public during automobile refuelling (Vainiotalo et al 1999; Egeghy et al 2000; Esteve-Turrillas et al 2007). These studies are described in Table 14. Vainiotalo et al and Esteve-Turrillas et al used static samplers in the areas where customers stand while pumping petrol and Egeghy et al.

(2000) outfitted study participants with personal samplers to be worn while they pumped petrol. All three of these reports describe a wide variability in exposure levels across samples, which the authors attribute to type of fuel, refuelling time, season, and atmospheric conditions (Egeghy et al 2000; Esteve-Turrillas et al 2007). Notably, Egeghy et al analysed the largest number of samples, and describe remarkable variability in benzene concentrations, with 95% of the estimated values falling within a 274-fold range. This variability was comprised entirely of the within-person component of variance (representing exposures of the same subject at different times of refuelling). In other words, environmental factors such as fuel octane grade, duration of exposure, and season of the year were the most important predictors of benzene levels, rather than individual level factors such as body size, behaviour (eg, always facing away from the nozzle when refuelling), or vehicle type (Egeghy et al 2000). A mean value of 2.9 mg/m^3 was concluded by the authors and a three minute typical duration time (Table 15).

Data from the New Zealand Ministry for Business, Innovation and Employment (MBIE 2014) indicate that the benzene content of petrols is typically 0.74-0.78% based on 2012–2014 data. Using the REACH risk assessment measurement of 728 mg/m^3 for total petrol vapour at petrol stations, a rough estimate of benzene concentrations in air at New Zealand petrol stations would be in the range of 5-6 mg/m^3, less than 2-fold different from the published value from Egeghy et al (2000). While this estimate would serve as a more health cautious air concentration than the 2.9 mg/m^3 value from Egeghy et al a higher degree of uncertainty surrounds this value, due to the different volatility of benzene compared with other hydrocarbons.

Table 15. Reported short-term measurements of benzene air concentrations during refuelling at petrol stations

Reference	Country	Duration (min)	N samples	Mean (mg/m^3)	Max (mg/m^3)
Vainiotalo 1999	Finland	2	8*	0.90	Not reported
Esteve-Turrillas 2007	Spain	2-6	6	2.04	4.90
Egeghy 2000	United States	3	130	2.90	36

*Each sample consisted of 20–21 refuellings

Other reports assessing consumer exposure to benzene during car refuelling have used exposure estimates from occupational studies, with results similar to those shown in Table 13 (Lynge et al 1997; Duarte-Davidson et al 2001). Duarte-Davidson et al (2002) estimated benzene exposure to the UK general public of 0.93 mg/m^3 with evaporative controls, and 3.7 mg/m^3 without. Lynge et al (1997) cites studies of workers in Finland, Sweden and Norway during the period 1980 to 1995 with benzene exposures during refuelling ranging from 1.6 to 3.3 mg/m^3 (using pumps not equipped with vapour recovery). Other investigations of occupational exposure to benzene at the petrol pump (CONCAWE 1987, 1994; Glass et al 2010) found a very wide range of benzene exposures, from 0.16 to 5.2 mg/m^3, which is also consistent with the values shown in Table 15.

We used an exposure duration (ED) value of 50 years. People in New Zealand may begin driving at age 16, so 50 years seems like a reasonable estimate of exposed years and may even be an underestimate, as adults may continue to drive and refuel well into

their 70s or beyond. The C_{air} value (air concentration of benzene per refuelling) of 2.9 mg/m^3 benzene was taken from Egeghy et al (2000) (Table 15). This value is slightly larger than other values and was chosen because it was based on the largest number of observations. The air inhalation (AI) value of 0.023 m^3/minute was taken from the US EPA Exposure Factors Handbook (2011) for adult males performing car maintenance (Table 6-41). This value is similar to, but slightly higher, than another possible value also obtained from the US EPA Exposure Factors Handbook (2011) for an adult performing light activity (Table 6-28). The value listed there is 0.6 m^3/hour, which corresponds to 0.01 m^3/minute. We have used an estimated refuelling time of three minutes based on Egeghy et al (2000) and consistent with that used by CONCAWE. Finally, body weights from the New Zealand National Nutrition Survey were used (52.7 kg (5th percentile) and 77.1 kg (50th percentile) and a lifetime averaging time period (70 years) was used, as is standard in cancer risk assessments and described in OEHHA (2003). The general formula used to estimate the chronic lifetime daily inhalation dose is:

$$Inhalation\ exposure\ IE = \frac{C \times IR \times EF \times RT}{BW} \text{RY} \times (\text{ED/AT})$$

Where:

C	=	Concentration of petrol (mg per m^3 of air).
IR	=	Inhalation rate (m^3/min). IR was taken from the USEPA exposure factors handbook (2011) for 3–5.9 year-old children sitting (Table 6-40).
RT	=	Refuelling time (min)
EF	=	exposure factor, weight percent of product ingredient absorbed. Complete absorption was assumed
n	=	number of exposure events per day.
RY	=	Number of days/year
ED/Life	=	Number of years in lifespan
BW	=	body weight, in kilograms.

Similarly, for dermal exposure:

$$A_{derm} = C_{derm} \times BIO_{derm} \times N_{events}$$

$$U_{derm\ pot} = \frac{A_{derm} \times Fabsorp}{BW} \times \text{RY} \times (\text{ED/AT})$$

Where:

C_{derm}	=	Concentration in the product (g/cm^3)
A_{derm}	=	External exposure to skin (g/event)
$U_{derm\ pot}$	=	Potential dermal uptake rate (g/kg body weight/day)
BIO_{derm}	=	Bioavailability for dermal exposure (default = 1)
N_{events}	=	Number of events per period (usually, events/day)
RY	=	Number of refuelling days/year
ED/Life	=	Number of years refuelling in lifespan
AT	=	Averaging time - typical lifespan assumed 70 years
F_{abs}	=	Factor to quantify absorption

Combined exposures in car and lawn-mower refuelling scenarios were calculated:

Combined exposure = Average dose from inhalation (IE) + Dermal ($U_{derm\ pot}$)

Inhalation exposure parameters for the chronic car refuelling scenario are shown in Table 16, and dermal exposure parameters are shown in Table 17.

Table 16. Inhalation exposure parameters and dose estimates for chronic car refuelling scenario

Parameter	Value	Unit	Reference
C_{air} – P (Petrol Conc. in air)	728	mg/m^3	CONCAWE 2012
C_{air} - B (Benzene Conc. in air)	2.9		Egeghy 2000
C_{air} – T (Toluene Conc. in air)	40.9		Based on % Toluene from MBIE 2014
C_{air} – X (Xylene Conc. in air)	79.2		Based on % Xylenes from MBIE 2014
AI (Air inhalation)	0.023	m^3/minute	EPA Exposure Factor Handbook Table 6-41
RT (Refuelling time)	3	minutes	Egeghy 2000, CONCAWE 2012
ED (Exposure duration)	50	years	estimated years of driving and refuelling
RY (Refuelling events/year)	52	per year	CONCAWE 2012
BW (Body weight)	52.7 (5%) 77.1 (50%)	kg	NZ NNS 2009
EF (Exposure factor)	0.5		50% absorption assumed
AT (averaging time period)	70	years	OEHHA 2003
Conversion Factor	365	days/year	
Daily Inhalation Dose – P	3.3–4.8 x 10^{-1}	mg/kg-day	Calculated from the above
Daily Inhalation Dose – B	1.3–1.9 x 10^{-3}		
Daily Inhalation Dose – T	1.8–2.7 x 10^{-2}		
Daily Inhalation Dose – X	3.5–5.2 x 10^{-2}		
Chronic Inhalation Dose – P	3.3-4.8 x 10^{-2}	mg/kg-day	Averaged 50/70 yr and 52/365 days/yr
Chronic Inhalation Dose – B	1.3–1.9 x 10^{-4}		
Chronic Inhalation Dose – T	1.9–2.7 x 10^{-3}		
Chronic Inhalation Dose – X	3.6–5.3 x 10^{-3}		

B = benzene; P = Petrol; T = Toluene; X = Xylene

Table 17. Dermal exposure parameters and dose estimates for chronic car refuelling scenario

Parameter	Value	Unit	Reference
C_{liq-P} (Petrol conc. in liquid) C_{liq-B} (Benzene conc. in liquid) C_{liq-T} (Toluene conc. in liquid) C_{liq-X} (Xylenes conc. in liquid)	100 0.74-0.78 10.4 20.2	%	MBIE, 2014
Aderm (Exposure to skin)	1 - 2.5	g/event	Wixtrom and Brown, 1992
Fraction absorbed (Fabs)	1	%	ECHA, 2010
ED (Exposure duration)	50	years	estimated years of driving and refuelling
RY (Refuelling days per year)	52	per year	estimated (once/ 2 weeks for a year)
BW (Body weight)	52.7 (5%) 77.1 (50%)	kg	NZ NNS, 2009
AT (averaging time period)	70	years	OEHHA 2003
Conversion Factor	365	days/year	
Daily Dermal Dose – P Daily Dermal Dose – B Daily Dermal Dose – T Daily Dermal Dose – X	$1.3–4.7 \times 10^{-1}$ $9.6–3.7 \times 10^{-3}$ $1.3–4.9 \times 10^{-2}$ $2.6–9.6 \times 10^{-2}$	mg/kg-day	Calculated from the above
Chronic Dermal Dose – P Chronic Dermal Dose – B Chronic Dermal Dose – T Chronic Dermal Dose – X	$1.3–4.8 \times 10^{-2}$ $9.8 \times 10^{-5}–3.8 \times 10^{-4}$ $1.4–5.0 \times 10^{-3}$ $2.7–9.8 \times 10^{-3}$	mg/kg-day	Considers 50/70 years and 26/365 days/year

B = benzene; P = Petrol; T = Toluene; X = Xylene

Scenario 5: Filling the lawn-mower petrol tank

In this scenario, an adult filling a lawn-mower petrol tank, taking 2 minutes per operation, twice per month, year round, is assumed. Overall vapour petrol concentrations in the indoor area of the operation are assumed to be the same as that in a petrol station. An assumption of 5 g liquid spillage onto the hands, due to poor controls and no personal protection is assumed.

Inhalation exposure parameters for the chronic lawn-mower refuelling scenario are shown in Table 18. Dermal exposure parameters for the chronic lawn-mower refuelling scenario are shown in Table 19.

Table 18. Inhalation exposure parameters for the chronic lawn-mower refuelling scenario

Parameter	Value	Unit	Reference
C_{air} – P (Petrol Conc. in air)	728	mg/m^3	CONCAWE 2012
C_{air} - B (Benzene Conc. in air)	2.9		Egeghy 2000
C_{air} – T (Toluene Conc. in air)	40.9		
C_{air} – X (Xylene Conc. in air)	79.2		
AI (Air inhalation)	0.023	m^3/minute	EPA Exposure Factor Handbook Table 6-41
RT (Refuelling time)	2	minutes	CONCAWE 2012
EF (Exposure factor)	0.5		Assumes 50% absorption
ED (Exposure duration)	50	years	estimated years of lawn care
RY (Refuellings per year)	26	per year	CONCAWE 2012
BW (Body weight)	52.7 (5%) 77.1 (50%)	kg	NZ NNS 2009
AT (averaging time period)	70	years	OEHHA 2003
Conversion Factor	365	days/year	
Daily Inhalation Dose – P	2.2-01 – 3.2E-01	mg/kg-day	Calculated from the above
Daily Inhalation Dose – B	8.7E-04 – 1.3E-03		
Daily Inhalation Dose – T	1.2E-02 – 1.8E-02		
Daily Inhalation Dose – X	2.4E-02 – 3.5E-02		
Chronic Inhalation Dose – P	1.1E-02 – 1.6E-02	mg/kg-day	Considers 50/70 years and 26/365 days/year
Chronic Inhalation Dose – B	4.4E-05 – 6.4E-05		
Chronic Inhalation Dose – T	6.2E-04 – 9.1E-04		
Chronic Inhalation Dose – X	1.2E-03 – 1.8E-03		

B = benzene; P = Petrol; T = Toluene; X = Xylene

Table 19. Dermal Exposure Parameters and Dose Estimates for Chronic Lawn-Mower Refuelling Scenario

Parameter	Value	Unit	Reference
C_{liq-P} (Petrol conc. in liquid)	100	%	MBIE, 2014
C_{liq-B} (Benzene conc. in liquid)	0.74-0.78		
C_{liq-T} (Toluene conc. in liquid)	10.4		
C_{liq-X} (Xylenes conc. in liquid)	20.2		
Aderm (Exposure to skin)	2.5-–5	g/event	Assumed spillage is approximately 2x that of automobile spills (Wixtrom and Brown, 1992)
Fraction absorbed (Fabs)	1	%	ECHA, 2010
ED (Exposure duration)	50	years	estimated years of lawn care
RY (Refuelling days per year)	26	per year	estimated (once/ 2 weeks for a year)
BW (Body weight)	52.7 (5%) 77.1 (50%)	kg	NZ NNS, 2009
AT (averaging time period)	70	years	OEHHA 2003
Conversion Factor	365	days/year	
Daily Dermal Dose – P	$3.2–9.5 \times 10^{-1}$	mg/kg-day	Calculated from the above
Daily Dermal Dose – B	$2.4–7.4 \times 10^{-3}$		
Daily Dermal Dose – T	$3.4–9.9 \times 10^{-2}$		
Daily Dermal Dose – X	$6.5 \times 10^{-2}–1.9 \times 10^{-1}$		
Chronic Dermal Dose – P	$1.6–4.8 \times 10^{-2}$	mg/kg-day	Considers 50/70 yr and 26/365 days/yr
Chronic Dermal Dose – B	$1.2–3.8 \times 10^{-4}$		
Chronic Dermal Dose – T	$1.7–5.0 \times 10^{-3}$		
Chronic Dermal Dose – X	$3.3–9.8 \times 10^{-3}$		

[1] Assumes 10% absorption

B = benzene; P = Petrol; T = Toluene; X = Xylene

Risk characterisation

Acute

Hazard indices show an acute risk of haematological effects (HI = 3, 2) from benzene exposure in the acute refuelling scenarios (Scenario 1 and 2). Local irritation, CNS, and developmental effects are not expected to present significant risks (Table 20 and 21).

Scenario 1 – Filling the car petrol tank

Table 20. Acute Non-cancer Risk Estimates from Automobile Refuelling Scenario

Parameter	Value	Unit	Comments
Equiv. 15-min conc. (Petrol)	326	mg/m^3/15 min	From Table 11 (Haber's Law)
Equiv. 60 min conc. (Benzene)	0.65	mg/m^3/60 min	
Equiv. 60 min conc. (Toluene)	9.1	mg/m^3/60 min	
Equiv. 60 min conc. (Xylenes)	17.7	mg/m^3/60 min	
Hazard Index – Acute Local irritation	0.1	Unitless	Calculated
Hazard Index – Acute Haematology	3		
Hazard Index – Acute CNS	0.1		
Hazard Index – Acute Developmental	0.1		

Scenario 2 – Filling the lawn-mower petrol tank

Table 21. Acute non-cancer risk estimates from lawn-mower refuelling scenario

Parameter	Value	Unit	Comments
Equiv. 15-min conc. (Petrol)	266	mg/m^3/15 min	From Table 12 (Haber's Law)
Equiv. 60 min conc. (Benzene)	0.53	mg/m^3/60 min	
Equiv. 60 min conc. (Toluene)	7.5	mg/m^3/60 min	
Equiv. 60 min conc. (Xylenes)	14.5	mg/m^3/60 min	
Hazard Index – Acute Local irritation	0.04	Unitless	Calculated
Hazard Index – Acute Haematology	2		
Hazard Index – Acute CNS	0.04		
Hazard Index – Acute Developmental	0.04		

Scenario 3 – Child/toddler exploration

The risks from any access to open or uncontrolled containers of petrol to a child are significant due to the possibility of oral ingestion and aspiration hazards of the material. Therefore, child access to containers of petrol should avoided. No safe dose or exposure for this scenario could be identified. The occurrence of significant numbers of hospitalisations in young children exposed to petrol is evidence that this risk represents a demonstrable public health concern.

Chronic

Scenario 4 – Filling the car petrol tank

Cancer risks

The average daily dose from combined inhalation and dermal routes of exposure was multiplied by the cancer potency factor to obtain a unitless risk number, and then multiplied by 10^5 (or 10^6) to obtain the cancer risk per 100,000 (or 1,000,000). The range of slope factors given by California EPA and the US EPA is 0.015–0.1 $(mg/kg\text{-}d)^{-1}$. For this screening risk assessment, both potencies help form the range of cancer risks.

Based on internationally reported benzene air concentrations of 2.9 mg/m^3 (Egeghy et al 2000, Table 15), and using a 50-year exposure period, the 50^{th} percentile of New Zealand body weight (77.1 kg), and assuming a spill volume of 1 mL onto the skin and a cancer potency value of 0.015 $(mg/kg\text{-}d)^{-1}$ a cancer risk of 8 per 1,000,000 is obtained. Using the 5^{th} percentile of New Zealand body weight (52.7 kg), a 2.5 mL spill onto the skin, and a cancer potency of 0.1 $(mg/kg\text{-}d)^{-1}$ a cancer risk of 6 per 100,000 is obtained.

Tables 22 summarizes the chronic risk estimates for the car refuelling scenarios.

Table 22. Chronic risk estimates for the car refuelling scenarios

Parameter	Value	Unit	Comments
Combined Inh + Derm - Petrol	$8.1–9.7 \times 10^{-2}$	mg/kg/day	Range of doses reflect body weights from 5% to 50% NZ adult BW.
Combined Inh + Derm – Benzene	$5.1–5.7 \times 10^{-4}$		
Combined Inh + Derm – Toluene	$6.9–7.7 \times 10^{-3}$		
Combined Inh + Derm – Xylene	$1.3–1.5 \times 10^{-2}$		
Hazard Index – Chronic Haematology	< 0.1	Unitless	No significant risk identified
Hazard Index – Chronic Developmental	< 0.1		
Hazard Index – Chronic CNS	< 0.1		
Cancer Risk Estimate	$8 \times 10^{-6}–6 \times 10^{-5}$	Unitless	8 to 60 in 1,000,000

The potential for ethylbenzene, as a suspected carcinogen, to contribute to the cancer risk, exists, but has not been taken into account in this risk assessment, as specific data for ethylbenzene content of New Zealand petrols was not available at the time of this report.

Scenario 5 – Filling the lawn-mower petrol tank

Table 23 summarizes the chronic risk estimates for the lawn-mower refuelling scenarios.

Table 23. Chronic risk estimates for the lawn-mower refuelling scenarios

Parameter	Value	Unit	Comments
Combined Inh + Derm - Petrol Combined	$4.4–4.9 \times 10^{-2}$	mg/kg/day	Range of doses reflect body weights from 5% to 50% NZ adult BW.
Inh + Derm – Benzene	$3.0–3.2 \times 10^{-4}$		
Combined Inh + Derm – Toluene	$4.1–4.3 \times 10^{-3}$		
Combined Inh + Derm – Xylene	$7.9–8.4 \times 10^{-3}$		
Hazard Index – Chronic Haematology	< 0.1	Unitless	No significant risk identified
Hazard Index – Chronic Developmental	< 0.1		
Hazard Index – Chronic CNS	< 0.1		
Cancer Risk Estimate	$4 \times 10^{-6} – 3 \times 10^{-5}$	Unitless	4 to 30 in 1,000,000

[Intentionally Blank]

Discussion

The exposure scenarios in this report illustrate the influence of numerous variables on non-cancer and cancer risk estimates. We found that, while acute, one-hour time adjusted, non-cancer risks from benzene exposures are expected to be significant in car and lawn-mower refuelling scenarios, chronic non-cancer risks were not significant. While it may seem incongruent for acute risks to be significant when chronic risks are not, this is in fact quite possible given that the toxicity values compared are based on different endpoints, and exposures are averaged across different timeframes. Thus it is possible to have a scenario with a one-hour exposure being unacceptably high during that one hour period, yet when averaged across a 24-hour day, 7 day/week period and compared with a different daily continuous toxicity value, the risk becomes insignificant. In this assessment, the acute REL value for benzene from the California EPA based on a rodent study finding of impaired developmental hematology, is a key driving factor in the HI values exceeding 1.0. A similar acute MRL value is available from ATSDR, but in this case, the value is intended for a 24-hour averaging period. In support of the rodent acute finding, a recent publication found subtle markers of immunological effects to occur in petrol station workers exposed to benzene at concentrations that were within acceptable workplace standards (Moro et al., 2015). Acute and chronic effects on reproduction and development as well as on the nervous system are not expected to reach significance under the scenarios developed.

The cancer risk range estimated from chronic car or lawn-mower refuelling of 0.4 to 3 in 100,000 is based on an assumed average air estimate of 2.90 mg/m^3 benzene air concentration where the consumer is refuelling, based on overseas data from Egeghy et al (2000) and supported by data from Vainiotalo et al (1999) and Esteve-Turrillas et al (2007). This air concentration is not from a New Zealand source, and thus uncertainty remains about this as a surrogate measure. Seasonal variations have been shown to influence air concentrations. In a study of non-smoking volunteers from four Australian cities (Hinwood et al 2007), pumping petrol in winter was associated with increased exposure to benzene, toluene, ethylbenzene, and xylenes (BTEX). In summer, only benzene exposure increased with refuelling. The authors suggest that in the summer, petrol volatility may overtake the influence of combustion (Hinwood et al 2007). In an analysis of the US Relationships of Indoor, Outdoor, and Personal Air (RIOPA) study and, to a lesser extent, the 1999–2000 data from the National Health and Nutrition Examination Survey (NHANES), BTEX, MTBE, and styrene exposures were associated with pumping petrol (Batterman et al 2014). However, in analyses from NHANES alone, pumping petrol was associated with increased exposures to toluene, ethylbenzene, and xylene, but was not an important determinant of benzene exposure (Symanski et al 2009).

The contribution of ethylbenzene to overall cancer risk was not quantified in this report, as specific ethylbenzene air concentration data were unavailable. Ethylbenzene is a suspected carcinogen, and, if the C8 composite value from MBIE (2014a) were taken to be entirely comprised of ethylbenzene, the addition of ethylbenzene to the petrol cancer risk estimate would increase the cancer risk significantly compared with that reported in this assessment.

A recent paper from Australia (Edokpolo et al 2014) describes a comprehensive evaluation of the adverse health effects of human exposures to benzene, toluene and xylene (BTX) from service station emissions. The authors present six exposure scenarios, and concluded that the greatest risks, both for cancer and non-cancer endpoints, result from benzene exposure in the scenario involving service station attendants and mechanics repairing petrol dispensing pumps.

Scenario #5 in Edokpolo et al. (2014) assessed the risk to customers during car refuelling and concluded that the overall risk probability of cancer due to exposure to benzene during refuelling was 28 per million using a cancer risk approach; similar to that employed here, compared with our range of results of 8–60 per million. Extending upon this result of 28 per million, Edokpolo et al also report a cancer risk of 90 per million using an overall risk probability method.

The Edokpolo report has many strengths, including its recent date of publication, its relevance to a country comparable to the New Zealand fuel use patterns, and the wide range of exposure scenarios discussed. Furthermore, the benzene exposure estimate used in scenario #5 (risk to customers during car refuelling), 1.77 mg/m^3, is similar to the value used in this risk assessment and based on one of the same publications (Egeghy et al 2000). However, in this risk assessment, our methods differed from Edokpolo et al (2014) in three important ways. First, Edokpolo et al used a 30-year timeframe for exposure to chemicals via car refuelling. We believe that a 50 or even 60 year time frame is more appropriate, as people in New Zealand may begin driving at age 16 and may continue driving well into their 70s or beyond. Second, the Edokpolo et al study used the inhalation cancer slope factor of 0.0273 per mg/kg-day, apparently citing a US EPA value that is no longer shown in the US EPA IRIS database (IRIS 2003), and may have been removed (see http://www.epa.gov/iris/subst/0276.htm#revhis). We used both the US EPA value and the California EPA (OEHHA) cancer slope factor value of 0.1 per mg/kg-day to provide a range of potential risks (OEHHA 2003). Finally, Edokpolo et al. used an overall risk probability method which was developed by the authors to express cancer risk based on the overall risk probability curve. We simply present our screening level cancer risk assessment results as a linearised cancer risk model based on US EPA (US EPA 2005) guidelines for health risk assessments of carcinogens.

Our consideration of the child exploration risk concludes that any oral exposure may lead to severe toxicity, and that risk management measures should be taken in the home to reduce the likelihood of this event from occurring. Poisoning statistics in New Zealand confirm that these events do occur with frequency, as petrol is the leading cause of chemical injury-induced hospitalisation among 0-4 year olds. Mouth siphoning of petrol leads to similar risks from aspiration pneumonia, and should be avoided in all circumstances.

Risk management/risk reduction

New Zealand government agencies have already issued recommendations to reduce the risks to the public that can result from petrol use (Ministry of Business Innovation and Employment 2014; New Zealand EPA 2014). For example, guidelines state that petrol should only be stored in approved containers, which have a maximum capacity of 25

litres. Petrol containers should not be filled completely, as petrol liquid turns to vapour in warm weather, which makes the container expand. Other containers should never be used for storing petrol, including glass and plastic soft drink bottles. The penalties for not using an approved fuel container can include fines or even imprisonment (New Zealand EPA 2014). Research has shown that such measures can reduce the risk of accidental poisonings among children. In Pakistan, storing petrol in soft drink bottles was strongly associated with increased risk of unintentional poisonings among children under age five (Ahmed et al 2011).

Because petrol is so flammable, the NZ Ministry of Business Innovation and Employment advises that one should never smoke around petrol, refuel a hot engine or an engine that is running, or use electronic equipment such as cell phones near petrol. The dangers of swallowing petrol or getting it in the eyes or skin are discussed, as well as the appropriate measures to take in such situations. There is a strong warning to never siphon petrol by mouth, which can be fatal (Ministry of Business Innovation and Employment 2014b).

These strong risk reduction messages should have substantial impacts in lowering potential petrol-related morbidity and mortality. Still, it may be possible to further reduce the amount of petrol vapour that a customer is exposed to during automobile refuelling in New Zealand. Various systems exist to reduce exposure to petrol vapours during refuelling. These include rubber "splash collars" around dispenser pistols, "stage I" vapour recovery systems, which collect vapours during petrol unloading, and "stage II" recovery systems, which collect vapours released from a vehicle's petrol tank during refuelling. Regulations requiring both stage I and II vapour recovery systems have been recently enacted in New South Wales, Australia (NSW EPA 2014). Enactment of similar regulations in New Zealand could reduce customer exposure to petrol during refuelling.

[Intentionally blank]

Uncertainties in this report

This assessment has explored the potential exposures and risks of using petrol in common everyday scenarios, employing conservative assumptions about exposure duration, air concentrations, and health effects. All screening level risk assessments intend to derive estimates of risk using conservative assumptions in order to determine if further investigation might be necessary. While it is not the purpose of any screening level risk assessment to explore quantitatively the extent to which individual variables impact conclusions, it is worth noting that some key variables are influential on our conclusions which may be in need of further exploration:

- **Time of exposure in relation to acute hazard value for benzene** – the typical exposure scenario for petrol involves several minutes per event. However, no authoritative hazard values match this short term exposure. Therefore the closest short term, peer-reviewed authoritative value of one hour was used, which itself is based on a six-hour developmental toxicity study in mice. The argument becomes rhetorical because it cannot be determined one way or another if the entire six-hour exposure to these mice was required for the toxicological effect to occur. We chose to accept on face value the one-hour acute REL for benzene, adopted by the State of California for acute risk assessments. Other jurisdictions may have alternative acute values for benzene, but we chose a 2014, well documented one-hour value. The variability around this assumption cannot be known with precision without additional scientific studies of short term duration. The same value is used by the ATSDR for a 24 hour exposure.

- **Breathing rate** during exposure events was assumed to be 0.023 m^3/min. A lower breathing rate of 0.013 m^3/min has been suggested by reviewers as more reflective of actual breathing rates when refuelling at petrol stations.

- **The benzene air concentrations in petrol stations in New Zealand** have not been well characterised. We used a published value from the US of 2.9 mg/m^3. Robust measures of benzene in New Zealand petrol stations could reduce uncertainty around this parameter.

- **Average daily doses** are the basis for assessing chronic risks. We averaged the single event modelled doses across a chronic, continuous exposure to provide equivalent chronic doses for cancer and non-cancer risks. It is not known to what degree the once/week, several minute exposure scenario accurately reflects a more continuous chronic daily exposure when averaged. We have assumed for the purposes of this screening level risk assessment, that averaging these exposures is valid and appropriate for comparison with the available chronic hazard values from the US EPA and the California EPA.

- **Suitability of using rodent models** for human health risk assessment is nearly always a question, and a source of variability and/or uncertainty in risk assessments. Often, effects in animals are of questionable relevance to humans at low doses. In the case of benzene, however, epidemiology provides clear evidence of toxicological effects (myeloid cancers and myelodysplastic

syndrome) that can be difficult to reproduce in laboratory animals. Therefore, the use of animal data for benzene may not be conservative, and ideally more human epidemiological data with appropriate exposure assessments will become available on which to base future risk assessments.

Conclusions

Petrol is a commonly used hydrocarbon chemical mixture in New Zealand, which contains benzene, a known human carcinogen. This key component of petrol continues to drive risk assessments of this material due to cancer risk. Exposures from activities including refuelling car tanks or home gardening equipment during routine use are typically low. However, using published benzene concentrations and potency factors, we estimate that typical weekly car refuelling scenarios, over a lifetime of driving, could carry an additional cancer risk of approximately 8–60 additional cancer cases out of 1,000,000 individuals. Lawn-mower petrol tank re-filling is estimated to potentially carry a slightly lower cancer risk (4–30 additional cases out of 1,000,000 individuals), depending on the average amount spilled on the skin. The absence of specific New Zealand monitoring data at petrol stations represents a significant data gap and source of uncertainty in these calculations. The cancer types are expected to be specific to those caused by benzene, notably leukaemias and lymphomas. Risk management measures are already in effect to mitigate some of these exposures at the pump, although technology for further reducing petrol exposures at petrol stations has advanced in recent years.

Acute intoxications from child exploratory play and petrol siphoning are known to occur, with injuries driven by an aspiration pneumonitis that can result from accidental inhalation of petrol vapours and liquid. Current risk management measures are in place to reduce these occurrences, but the fact that petrol related injuries are the number one chemical injury resulting in hospitalisations in New Zealand indicate that continued efforts by public health agencies to prevent these situations from occurring are justified.

Non-cancer acute and chronic risks to the nervous system and child development were not significant, considering exposures to toluene, benzene, xylenes and using whole mixture DNELs, or component-based hazard indices. Acute exposures in refuelling scenarios were found to exceed a hazard index of 1.0 indicating risks are not negligible for haematological parameters due to the presence of benzene. These assessments used health protective assumptions in the face of substantial uncertainties about exposures and hazards, so the true risks are likely to be lower than reported here.

[Intentionally Blank]

Appendix A. Calculations of hazard quotients and hazard indices

Acute Risk - Car refuelling scenario (inhalation only)

Component	REL/DNEL		endpoints
Petrol	640	mg/m^3	Local effects
Benzene	0.027	mg/m^3	systemic - haematology
Toluene	37	mg/m^3	CNS
C8	22	mg/m^3	Local effects
Endpoint	**HQ**		
Local	0.057		
CNS	0.055		
Haematology	**2.69**		

Chronic Risk - Car refuelling scenario

Combined dose (chronic) mg/kg BW/d		RfD mg/kg BW/d	HQ (5^{th} %-ile BW)	HQ (50^{th} %-ile BW)	CA risk OEHHA	CA risk USEPA
petrol	0.097	none				
benzene	0.00057	0.004	0.14	0.13	5.7×10^{-5}	3.1×10^{-5}
toluene	0.0077	0.08	0.10	0.09		
Xylene/EB	0.015	0.2	0.08	0.07	assuming 100% xylene	

EB = ethylbenzene

Acute Risk – Lawnmower refuelling scenario

Component	REL/DNEL		Endpoints
Petrol	640	mg/m^3	Local effects
Benzene	0.027	mg/m^3	systemic - haematology
Toluene	37	mg/m^3	CNS
C8	22	mg/m^3	Local effects
Endpoint	**HQ**		
Local	0.038		
CNS	0.037		
Haematology	**1.79**		

Chronic Risk - Lawnmower refuelling scenario

Combined dose (chronic) mg/kg BW/d		RfD mg/kg BW/d	HQ (5^{th} %-ile BW)	HQ (50^{th} %-ile BW)	CA risk OEHHA	CA risk USEPA
petrol	0.044		0.24			
benzene	0.0003	0.004	0.08	0.08	3.0×10^{-5}	1.6×10^{-5}
toluene	0.0041	0.08	0.05	0.05		

xylene/EB	0.0079	0.2	0.04	0.04

EB = ethylbenzene

Acknowledgements

The authors thank Mr Vladimir Koutsaenko of Trading Standards, Ministry of Business, Innovation and Employment, for collating and providing data on aromatic components of petrol in New Zealand. We also thank Professor Roger Drew of ToxConsult, and Dr Natalia Foronda from the Ministry of Health for peer review comments.

References

Agency for Toxic Substances and Disease Registry (ATSDR). June 1995. Toxicological Profile for Gasoline. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=468&tid=83 (Accessed 10/6/14).

Agency for Toxic Substances and Disease Registry (ATSDR). August 2007. Toxicological Profile for Benzene. http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14 (Accessed 10/6/14).

Agency for Toxic Substances and Disease Registry (ATSDR). November 2014. Medical Management Guidelines. http://www.atsdr.cdc.gov/MMG/MMG.asp?id=465&tid=83

Ahmed B, Fatmi, Z, Siddiqui AR et al. 2011. Predictors of Unintentional Poisoning Among Children Under 5 Years of Age in Karachi: a Matched Case-Control Study. *Injury prevention : journal of the International Society for Child and Adolescent Injury Prevention* 17(1): 27–32.

Arnold SM, Angerer J, Boogaard PJ, et al. 2013. The Use of Biomonitoring Data in Exposure and Human Health Risk Assessment: Benzene Case Study. *Critical reviews in toxicology* 43(2): 119–153.

Bahadar H, Mostafalou S, Abdollahi M. 2014. Current Understandings and Perspectives on Non-Cancer Health Effects of Benzene: a Global Concern. *Toxicology and applied pharmacology* 276(2): 83–94.

Bailey HD, de Klerk NH, Fritschi L et al. 2011. Refuelling of Vehicles, the Use of Wood Burners and the Risk of Acute Lymphoblastic Leukaemia in Childhood. *Paediatric and perinatal epidemiology* 25(6): 528–539.

Barregard L, Holmberg E, Sallsten G. 2009. Leukaemia Incidence in People Living Close to an Oil Refinery. *Environmental research* 109(8): 985–990.

Batterman S, Su F-C, Li S et al. 2014. Personal Exposure to Mixtures of Volatile Organic Compounds: Modeling and Further Analysis of the RIOPA Data. *Research report (Health Effects Institute)* (181): 3–63.

Brady M. 1992. Heavy Metal: The Social Meaning of Petrol Sniffing in Australia. Aboriginal Studies Press, Canberra, Australia. http://www.books.google.com/books?isbn=0855752157 (Accessed 10/9/14).

Brender JD, Maantay JA, Chakraborty J. 2011. Residential Proximity to Environmental Hazards and Adverse Health Outcomes. *American journal of public health* 101 Suppl 1: S37–52.

Brosselin P, Rudant J, Orsi L et al. 2009. Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). *Occupational and Environmental Medicine* 66(9):598-606.

Burns CB, D'Abbs P, Currie B J. 1995. Patterns of Petrol Sniffing and Other Drug Use in Young Men From an Australian Aboriginal Community in Arnhem Land, Northern Territory. *Drug and alcohol review* 14(2): 159–169.

Cairney S, Dingwall K. 2010. The Mysterious Practice of Petrol Sniffing in Isolated Indigenous Groups. *Journal of paediatrics and child health* 46(9): 510–515.

Cairney S, Maruff P, Burns CB et al. 2005. Neurological and Cognitive Recovery Following Abstinence From Petrol Sniffing. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology* 30(5): 1019–1027.

Cairney S, O' Connor N, Dingwall, KM et al. 2013. A Prospective Study of Neurocognitive Changes 15 Years After Chronic Inhalant Abuse. *Addiction (Abingdon, England)* 108(6): 1107–1114.

Centers for Disease Control and Prevention. February 2013. Emergency Preparedness and Response: Facts about Benzene. http://www.bt.cdc.gov/agent/benzene/basics/facts.asp (Accessed 10/9/14).

CONCAWE (1987), *Survey of Exposures to Gasoline Vapour*. Report no. 4/87. The Hague.

CONCAWE (1994), *Review of European Oil Industry Benzene Exposure Data, 1986-1992*. Report no. 7/94. Brussels.

CONCAWE. 2012. Chemical Safety Report for low boiling point naphthas (gasolines). European Chemical Agency.

Cox R, Amundson T, Brackin B. 2008. Evaluation of the Patterns of Potentially Toxic Exposures in Mississippi Following Hurricane Katrina. *Clinical toxicology (Philadelphia, Pa.)* 46(8): 722–727.

Dingwall KM, Lewis MS, Maruff P et al. 2010. Assessing Cognition Following Petrol Sniffing for Indigenous Australians. *The Australian and New Zealand journal of psychiatry* 44(7): 631–639.

Dingwall KM, Maruff P, Fredrickson A et al. 2011. Cognitive Recovery During and After Treatment for Volatile Solvent Abuse. *Drug and alcohol dependence* 118(2-3): 180–185.

Divine BJ, Hartman CM. 2000. Update of a Study of Crude Oil Production Workers 1946-94. *Occupational and Environmental Medicine* 57(6): 411–417.

Duarte-Davidson R, Courage C, Rushton L et al. 2001. Benzene in the Environment: an Assessment of the Potential Risks to the Health of the Population. *Occupational and Environmental Medicine* 58(1):2–13.

Edokpolo B, Yu Q, Connell D. 2014. Health Risk Assessment of Ambient Air Concentrations of Benzene, Toluene and Xylene (BTX) in Service Station Environments. *International Journal of Environmental Research and Public Health* 11(6): 6354–6374.

Egeghy PP, Tornero-Velez R, Rappaport SM. 2000. Environmental and Biological Monitoring of Benzene During Self-Service Automobile Refueling. *Environmental health perspectives* 108(12): 1195–1202.

Eggertson L. 2014. Opal Fuel Reduces Gas-Sniffing and Suicides in Australia. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne* 186(8): E229–30.

Esteve-Turrillas, FA, Pastor A, de la Guardia M. 2007. Assessing Air Quality Inside Vehicles and at Filling Stations by Monitoring Benzene, Toluene, Ethylbenzene and Xylenes with the Use of Semipermeable Devices. *Analytica Chimica Acta* 593(1): 108–116.

European Chemical Agency (ECHA). 2010. REACH registration dossier IUCLID file for gasoline. http://echa.europa.eu

Forrester M (2009), Impact of Hurricane Ike on Texas Poison Center Calls. *Disaster medicine and public health preparedness* 3(3): 151–157.

Fustinoni S, Rossella F, Polledri E et al. 2012. Global DNA Methylation and Low-Level Exposure to Benzene. *La Medicina del lavoro* 103(2): 84–95.

Galbraith D, Gross SA, Paustenbach D. 2010. Benzene and Human Health: a Historical Review and Appraisal of Associations with Various Diseases. *Critical reviews in toxicology* 40 Suppl 2: 1–46.

Glass DC, Armstrong TW, Pearlman ED et al. 2010. Ensuring Comparability of Benzene Exposure Estimates Across Three Nested Case-Control Studies in the Petroleum Industry in Support of a Pooled Epidemiological Analysis. *Chemico-biological interactions* 184(1-2): 101–111.

Glass DC, Gray CN, Jolley DJ et al. 2003. Leukemia Risk Associated with Low-Level Benzene Exposure. *Epidemiology (Cambridge, Mass.)* 14(5): 569–577.

Hayes RB, Songnian Y, Dosemeci M et al. 2001. Benzene and Lymphohematopoietic Malignancies in Humans. *American journal of industrial medicine* 40(2): 117–126.

Hayes RB, Yin SN, Dosemeci M et al. 1997. Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China. Chinese Academy of Preventive Medicine--National Cancer Institute Benzene Study Group. *Journal of the National Cancer Institute* 89(14): 1065–1071.

Hayes RB, Yin S, Rothman N et al. 2000. Benzene and Lymphohematopoietic Malignancies in China. *Journal of toxicology and environmental health. Part A* 61(5-6): 419–432.

Hinwood A, Rodriguez C, Runnion T et al. 2007. Risk Factors for Increased BTEX Exposure in Four Australian Cities. *Chemosphere* 66(3): 533–541.

Infante PF. 2001. Benzene: an Historical Perspective on the American and European Occupational Setting. In: *Late lessons from early warnings: the precautionary*

principle 1896–2000. Ed. Harremoes, P. European Environment Agency, Copenhagen. (Chapter 4)

Infante PF. 1992. Benzene and Leukemia: the 0.1 Ppm ACGIH Proposed Threshold Limit Value for Benzene. *Applied Occupational and Environmental Hygiene* 7(4): 253–262.

International Agency for Research on Cancer (IARC). 2012. Monographs on the Evaluation on Carcinogenic Risks to Humans, Volume 100F, Benzene. http://monographs.iarc.fr/ENG/Monographs/vol100F/index.php (Accessed 10/6/14).

Irons RD, Kerzic PJ. 2014. Cytogenetics in Benzene-Associated Myelodysplastic Syndromes and Acute Myeloid Leukemia: New Insights Into a Disease Continuum. *Annals of the New York Academy of Sciences* 1310: 84–88.

Jamall IS, Willhite CC. 2008. Is Benzene Exposure From Gasoline Carcinogenic? *Journal of environmental monitoring : JEM* 10(2): 176–187.

Jamieson LM, Gunthorpe W, Cairney, SJ et al. .2010. Substance Use and Periodontal Disease Among Australian Aboriginal Young Adults. *Addiction (Abingdon, England* 105(4): 719–726.

Johnsrud EK, Koukouritaki SB, Divakaran K et al. 2003. Human hepatic CYP2E1 expression during development. *Journal of Pharmacology and Experimental Therapeutics* 307(1): 402-7.

Kane EV, Newton R. 2010. Benzene and the Risk of Non-Hodgkin Lymphoma: a Review and Meta-Analysis of the Literature. *Cancer epidemiology* 34(1): 7–12.

Keenan JJ, Gaffney S, Gross SA et al. 2013. An Evidence-Based Analysis of Epidemiologic Associations Between Lymphatic and Hematopoietic Cancers and Occupational Exposure to Gasoline. *Human & experimental toxicology* 32(10): 1007–1027.

Kim HK, Takematsu M, Biary R et al. 2013. Epidemic Gasoline Exposures Following Hurricane Sandy. *Prehospital and disaster medicine* 28(6): 586–591.

Lawton J, Malmquist E. 1961. Gasoline addiction in children. *Psychiatric Quarterly* 35(3):555-561.

Lv L, Lin GL, Gao X, et al. 2011. Case-Control Study of Risk Factors of Myelodysplastic Syndromes According to World Health Organization Classification in a Chinese Population. *American journal of hematology* 86(2): 163–169.

Lynge E, Andersen A, Nilsson R et al. 1997. Risk of Cancer and Exposure to Gasoline Vapors. *American journal of epidemiology* 145(5): 449–458.

MacFarland HN, Ulrich CE, Holdsworth CE (1984). A chronic inhalation study with unleaded gasoline vapour. *Journal of the American College of Toxicology* 3:231-248.

Maruff P, Burns CB, Tyler P et al. 1998. Neurological and Cognitive Abnormalities Associated with Chronic Petrol Sniffing. *Brain : a journal of neurology* 121 (Pt 10): 1903–1917.

McCarver DG ,Hines RN. 2002. The ontogeny of human drug metabolizing enzymes: Phase II conjugation enzymes and regulatory mechanisms. *Journal of Pharmacology and Experimental Therapeutics* 300: 361-366.

McKinney PA, Raji OY, van Tongeren M. et al. 2008. The UK Childhood Cancer Study: Maternal Occupational Exposures and Childhood Leukaemia and Lymphoma. *Radiation protection dosimetry* 132(2): 232–240.

Mehlman MA .1996. Dangerous and Cancer-Causing Properties of Products and Chemicals in the Oil-Refining and Petrochemical Industry--Part XXII: Health Hazards From Exposure to Gasoline Containing Methyl Tertiary Butyl Ether: Study of New Jersey Residents. *Toxicology and industrial health* 12(5): 613–627.

Midzenski MA, McDiarmid MA, Rothman N et al. 1992. Acute high dose exposure to .benzene in shipyard workers. *American Journal of Industrial Medicine* 22(4): 553-65.

Miligi L, Benvenuti A, Mattioli S et al. 2013. Risk of Childhood Leukaemia and Non-Hodgkin's Lymphoma After Parental Occupational Exposure to Solvents and Other Agents: the SETIL Study. *Occupational and Environmental Medicine* 70(9): 648–655.

Miller BG, Fransman W, Heederik D et al. 2010. A Review of the Data Quality and Comparability of Case-Control Studies of Low-Level Exposure to Benzene in the Petroleum Industry. *International archives of occupational and environmental health* 83(1): 69–76.

Ministry of Business Innovation and Employment. 2013. *Workplace exposure standards and biological exposure indices. 7th Edition.* http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/workplace-exposure-standards-and-biological-exposure-indices/workplace-exposure-standards-and-biological-indices-2013.pdf

Ministry of Business Innovation and Employment. 2014a. V. Koutsaenko, personal communication. Petrol aromatic content for NZ petrols 2012 - 2014.

Ministry of Business Innovation and Employment. 2014b. Petrol. http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/hsno/hsno-guidance-pages/petrol (Accessed 10/21/14)

Moro A, Bruckner N, Charao M, Sauer E, Freitas F, Durgante J, Bubols G, Campanharo S, Linden R, Souza A, Bonorino C, Moresco R, Pilger D, Gioda A, Farsky S, Duschi A, and Garcia S. 2015. Early hematological and immunological alterations in gasoline station attendants exposed to benzene. *Environmental Research* 137: 349-356.

Neasham D, Sifi A, Nielsen K et al. 2011. Occupation and Risk of Lymphoma: a Multicentre Prospective Cohort Study (EPIC). *Occupational and Environmental Medicine* 68(1): 77–81.

Northeast States for Coordinated Air Use Management (NESCAUM). 1989. Evaluation of the Health Effects from Exposure to Gasoline and Gasoline Vapors. Final Report. August 1989.

New South Wales Environmental Protection Agency (NSW EPA). 2014. Reducing service station emissions. http://www.epa.nsw.gov.au/air/petrolvapour.htm (Accessed 10/21/14).

New Zealand EPA. 2014. Petrol Containers. http://www.epa.govt.nz/hazardous-substances/at-home/petrol/Pages/Petrol-containers.aspx (Accessed 10/21/14).

Niazi GA, Fleming AF. 1997. Re: Benzene and the Dose-Related Incidence of Hematologic Neoplasms in China. *Journal of the National Cancer Institute* 89(22): 1728–1729.

Office of Environmental Health Hazard Assessment (OEHHA). 1997. Hazard Identification of the Developmental and Reproductive Toxic Effects of Benzene, Draft. http://oehha.ca.gov/prop65/hazard_ident/pdf_zip/benzene.pdf (Accessed 10/20/14)

Office of Environmental Health Hazard Assessment (OEHHA). 2003. Air Toxics Hot Spots Program Risk Assessment Guidelines: The Air Toxics Hot Spots Program Guidance Manual for Preparation of Health Risk Assessments. http://oehha.ca.gov/air/hot_spots/pdf/HRAguidefinal.pdf (Accessed 10/3/14).

Office of Environmental Health Hazard Assessment (OEHHA). 2009. Technical Support Document for Deriving Cancer Potency Factors. http://www.oehha.ca.gov/air/hot_spots/2009/TSDCancerPotency.pdf

Office of Environmental Health Hazard Assessment (OEHHA). 2013. Benzene reference exposure levels. http://www.oehha.ca.gov/air/chronic_rels/pdf/100413BenzeneREL_SRP.pdf

Patel AS, Talbott EO, Zborowski JV et al. 2004. Risk of Cancer as a Result of Community Exposure to Gasoline Vapors. *Archives of environmental health* 59(10): 497–503.

Raabe GK, Wong O. 1996. Leukemia Mortality by Cell Type in Petroleum Workers with Potential Exposure to Benzene. *Environmental health perspectives* 104 Suppl 6: 1381–1392.

Rekhadevi PV, Mahboob M, Rahman MF et al. 2011. Determination of Genetic Damage and Urinary Metabolites in Fuel Filling Station Attendants. *Environmental and molecular mutagenesis* 52(4): 310–318.

Rinsky RA, Smith AB, Hornung R et al. 1987. Benzene and Leukemia. an Epidemiologic Risk Assessment. *The New England journal of medicine* 316(17): 1044–1050.

Rushton L, Romaniuk, H. 1997. A Case-Control Study to Investigate the Risk of Leukaemia Associated with Exposure to Benzene in Petroleum Marketing and Distribution Workers in the United Kingdom. *Occupational and Environmental Medicine* 54(3): 152–166.

Rushton L, Schnatter AR, Tang G et al. 2014. Acute Myeloid and Chronic Lymphoid Leukaemias and Exposure to Low-Level Benzene Among Petroleum Workers. *British journal of cancer* 110(3): 783–787.

Schnatter AR, Armstrong TW, Nicolich MJ et al. 1996. Lymphohaematopoietic Malignancies and Quantitative Estimates of Exposure to Benzene in Canadian Petroleum Distribution Workers. *Occupational and Environmental Medicine* 53(11): 773–781.

Schnatter AR, Glass DC, Tang G et al. 2012. Myelodysplastic Syndrome and Benzene Exposure Among Petroleum Workers: an International Pooled Analysis. *Journal of the National Cancer Institute* 104(22): 1724–1737.

Schwartz E. 1987. Proportionate Mortality Ratio Analysis of Automobile Mechanics and Gasoline Service Station Workers in New Hampshire. *American journal of industrial medicine* 12(1): 91–99.

Shu XO, Gao YT, Brinton LA et al. 1988. A Population-Based Case-Control Study of Childhood Leukemia in Shanghai. *Cancer* 62(3): 635–644.

Silva-Néto RP, Peres MFP, Valença MM. 2014. Odorant Substances That Trigger Headaches in Migraine Patients. *Cephalalgia : an international journal of headache* 34(1): 14–21.

Singaraju M, Singaraju S, Parwani R et al. 2012. Cytogenetic Biomonitoring in Petrol Station Attendants: a Micronucleus Study. *Journal of cytology / Indian Academy of Cytologists* 29(1): 1–5.

Smith MT, Rothman N. 2000. Biomarkers in the Molecular Epidemiology of Benzene-Exposed Workers. *Journal of toxicology and environmental health. Part A* 61(5-6): 439–445.

Smith MT. 2010. Advances in Understanding Benzene Health Effects and Susceptibility. *Annual review of public health* 31: 133–48 2 p following 148.

Spiller H, Krenzelok E. 1997. Epidemiology of inhalant abuse reported to two regional poison centers. *Clinical Toxicology* 35(2):167-173.

Steinmaus C, Smith AH, Jones RM et al. 2008. Meta-Analysis of Benzene Exposure and Non-Hodgkin Lymphoma: Biases Could Mask an Important Association. *Occupational and Environmental Medicine* 65(6): 371–378.

Symanski E, Stock TH, Tee PG et al. 2009. Demographic, Residential, and Behavioral Determinants of Elevated Exposures to Benzene, Toluene, Ethylbenzene, and Xylenes Among the U.S. Population: Results From 1999-2000 NHANES. *Journal of toxicology and environmental health. Part A* 72(14): 915–924.

Talbott EO, Xu X, Youk AO et al. 2011. Risk of Leukemia as a Result of Community Exposure to Gasoline Vapors: a Follow-Up Study. *Environmental research* 111(4): 597–602.

Tefferi A, Vardiman JW. 2009. Myelodysplastic Syndromes. *The New England journal of medicine* 361(19): 1872–1885.

U.S. Environmental Protection Agency (U.S. EPA). 1999. Extrapolation of the benzene unit risk estimate to the oral exposure route. http://www.epa.gov/iris/supdocs/benzsup.pdf (Accessed 10/6/14).

U.S. Environmental Protection Agency (U.S. EPA). 2005. Guidelines for Carcinogen Risk Assessment. http://www.epa.gov/cancerguidelines (Accessed 10/6/14).

U.S. Environmental Protection Agency (U.S. EPA). Sept 2011 Exposure Factors Handbook: 2011 Edition. http://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252 (Accessed 10/6/14).

U.S. Environmental Protection Agency (U.S. EPA). 2003. Integrated Risk Information System (IRIS). Summary for Benzene. http://www.epa.gov/iris/subst/0276.htm.

Vainiotalo S, Peltonen Y, Ruonakangas A et al. 1999. Customer Exposure to MTBE, TAME, C6 Alkyl Methyl Ethers, and Benzene During Gasoline Refueling. *Environmental health perspectives* 107(2): 133–140.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver. Hypermethylation control of gene expression during the neonatal period. *European Journal of Biochemistry* 238(2): 476-83.

Vlaanderen J, Lan Q, Kromhout H et al. 2011. Occupational Benzene Exposure and the Risk of Lymphoma Subtypes: a Meta-Analysis of Cohort Studies Incorporating Three Study Quality Dimensions. *Environmental health perspectives* 119(2): 159–167.

Wallace L. 1996. Environmental Exposure to Benzene: an Update. *Environmental health perspectives* 104 Suppl 6: 1129–1136.

Welch F, Murray VS, Robins AG et al. 1999. Analysis of a Petrol Plume Over England: 18-19 January 1997. *Occupational and Environmental Medicine* 56(10): 649–656.

Wick R, Gilbert JD, Felgate P et al. 2007. Inhalant Deaths in South Australia: a 20-Year Retrospective Autopsy Study. *The American journal of forensic medicine and pathology* 28(4): 319–322.

Wilson N, Horrocks J. 2008. Lessons From the Removal of Lead From Gasoline for Controlling Other Environmental Pollutants: a Case Study From New Zealand. *Environmental health* 7: 1.

Wixtrom R, Brown S. 1992. Individual and population exposures to gasoline. *Journal of Exposure Analysis and Environmental Epidemiology* 2(1):23-78.

Wong O, Raabe GK. 1989. Critical Review of Cancer Epidemiology in Petroleum Industry Employees, with a Quantitative Meta-Analysis by Cancer Site. *American journal of industrial medicine* 15(3): 283–310.

Wong O, Raabe GK. 1997. Multiple Myeloma and Benzene Exposure in a Multinational Cohort of More Than 250,000 Petroleum Workers. *Regulatory toxicology and pharmacology: RTP* 26(2): 188–199.

Wong O, Trent L, Harris F. 1999. Nested Case-Control Study of Leukaemia, Multiple Myeloma, and Kidney Cancer in a Cohort of Petroleum Workers Exposed to Gasoline. *Occupational and Environmental Medicine* 56(4): 217–221.

WorkSafe New Zealand, Department of Labour, 2010. Workplace Exposure Standard Information sheet on benzene. http://www.business.govt.nz/worksafe/information-guidance/all-guidance-items/information-sheet-benzene-workplace-exposure-standard/benzene-wes.pdf

World Bank. 2014. World Road Statistics. http://data.worldbank.org/indicator/IS.ROD.SGAS.PC

World Health Organization 2000. WHO air quality guidelines for Europe, 2nd Edition. http://www.euro.who.int/en/health-topics/environment-and-health/air-quality/publications/pre2009/who-air-quality-guidelines-for-europe,-2nd-edition,-2000-cd-rom-version [site accessed 03/2015].

Zeise L, McDonald TA. 2000. California Perspective on the Assessment of Benzene Toxicological Risks. *Journal of toxicology and environmental health. Part A* 61(5-6): 479–483.