Korea
National Oil Corporation

Appendix J

Human Health Risk Assessment

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Appendix J1

Chemical Profiles

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ABBREVIATIONS

AHRE	Alberta Human Resources and Employment
FDA	Food and Drug Administration
FEV	Forced Expiratory Volume
HSDB	Hazardous Substances Data Bank
IPM	Individual PAH model
POI	Point of Impingement
RAIS	Risk Assessment Information System
TD Tolerable	Dose
TEEL-0	Temporary Emergency Exposure Limit
TNRCC	Texas Natural Resource Conservation Commission
µg/kg bw/d	microgram per kilogram body weight per day
µg/L	microgram per litre
µg/m³	microgram per metre squared
AAQC	Ambient Air Quality Criterion
AAQO	Ambient Air Quality Objective
ACGIH	American Conference of Governmental Hygienists Inc.
ADJ Adjusted	value
AENV Alberta	Environment
AQG	Air quality guideline
ATSDR	Agency for Toxic Substances and Disease Registry
BMC Benchmark	Concentration
BMCL ($_{01}$, $_{05}$, $_{10}$)	Benchmark Concentration 95% lower confidence interval
BMD Benchmark	Dose
CARB	California Air Resources Board
CCME	Canadian Council of Ministers of the Environment
CEPA	Canadian Environmental Protection Act
CEPA/FPAC	Canadian Environmental Protection Act/Federal–Provincial Advisory Committee
CNS	Central Nervous System
COHb	carboxyhemoglobin in blood
COPC	Chemical of Potential Concern
CR Carcinogenic	Risk
CR_{INHAL}	Carcinogenic Risk Inhalation
CWS Canada-Wide	Standard
ESL	Effects Screening Level
HEC	Human Equivalent Concentration
HHRA	Human Health Risk Assessment
IARC	International Agency for Research on Cancer
kg kilogram	
KNOC	Korea National Oil Corporation
L/d	litre per day
LOAEL Lowest-Observed-Adverse-Effect	level
MA DEP	Massachusetts Department of Environmental Protection
µg/m³	microgram per metre squared

µg/kg bw/d	microgram per kilogram of body weight per day
mg/m³	milligram per metre squared
mg/kg bw/d	millogram per kilogram of body weight per day
MRL	Minimal Risk Level
n	number (as in n = 8)
NAAQO	National Ambient Air Quality Objective
NAAQS	National Ambient Air Quality Standards
NOAEL	No-Observed-Adverse-Effect level
NTP	National Toxicology Program
OEHHA	California Office of Environmental Health Hazard Assessment
OMOE	Ontario Ministry of the Environment
PAH	Polycyclic Aromatic Hydrocarbon
PEF	Potency Equivalence Factor
$PM_{2.5}$	Particulate matter less than 2.5 micrograms
ppb	parts per billion
ppm	parts per million
REL	Reference Exposure Level
ReV	Reference Exposure Value
RfC	Reference Concentration
RfD	Reference Dose
RGDR	Regional Gas Dose Ratio
RIVM	Netherlands, National Institute of Public Health and the Environment, NIPHE).
RsC	Risk-specific Concentration
RsD	Risk-specific Dose
STEL	Short-Term Exposure Limit
TC	Tolerable Concentration
TCA	Tolerable Concentration in Air
TCEQ	Texas Commission on Environmental Quality
TDI	Tolerable Daily Intake
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalence
TLV	Threshold Limit Value
TLV-TWA	Threshold Limit Value – Time Weighted Average
TPHCWG	Total Petroleum Hydrocarbon Criteria Working Group
TRV	Toxicological Reference Value
US EPA	United States Environmental Protection Agency
US EPA IRIS	United States Environmental Protection Agency Integrated Risk Information System
WHO	World Health Organization

J1-1.0 Introduction

This appendix describes the scientific basis for the acute (short-term) and chronic (long-term) exposure limits used to assess potential human health risks associated with the COPCs for the KNOC Blackgold Expansion Project (the project).

Toxicity profiles are provided for each of the COPCs evaluated as part of the HHRA. These chemical-specific profiles summarize the basis of the acute inhalation, chronic inhalation and chronic multiple pathway exposure limits established by regulatory agencies. The rationale for the exposure limit selected for use in the HHRA is also described in each profile.

J1-1.1 Background

The dose of a chemical largely dictates the nature and severity of any health effects that might be observed. More specifically, it is the amount of the chemical that reaches the critical target site within the living system that determines whether an adverse response will be produced. The toxicity assessment ultimately requires understanding of the toxic effects that can be caused by the COPCs. Knowledge in this regard is typically obtained through review of the scientific literature describing the responses witnessed in laboratory animals or volunteer human subjects following administration of the chemical at various doses for varying periods of time under controlled conditions, or from observations gathered as part of community health studies (i.e., epidemiological investigations) examining the incidence of disease in relation to chemical exposures.

In general, chemicals may be categorized into two groups based on the nature of their toxic response – threshold and non-threshold chemicals. Threshold chemicals make up the largest category and consist of virtually all types of toxic responses and chemicals. For threshold chemicals, a minimum or 'threshold' dose must be exceeded for a toxic response to be observed, and the severity or magnitude of the toxic response is generally assumed to increase with increasing dose. Non-threshold chemicals are a select group of substances which potentially can produce cancer through mechanisms that do not involve a threshold response, and a dose-response relationship is not always apparent.

For non-carcinogens, exposure limits are often derived based on the identification of a NOAEL – the dose at which no adverse effects are observed. Alternatively, exposure limits may be based upon a LOAEL or a BMD/BMC. A NOAEL, LOAEL or BMD/BMC can then be used to derive an exposure limit or 'safe' level of exposure through the application of 'uncertainty' or safety factors that provide an added level of protection. The exposure limit refers to the dose of the chemical that is without effect on even the most sensitive subjects and is calculated as follows, using a NOAEL as an example:

$$\text{Exposure Limit} = \frac{\text{NOAEL}}{\text{Uncertainty Factor(s)}}$$

The uncertainty factor can vary from to 3 or √10 to over 1,000 in order to ensure adequate protection of any exposed population. The most common forms of uncertainty factors are listed in Table J1-1.

The need for these uncertainty factors is dictated largely by the practical constraints that apply to conventional toxicological research (i.e., the study of the harmful effects of chemicals). Most of the available information for some chemicals is limited to studies in laboratory rodents (e.g., rats, mice, guinea pigs, rabbits), owing largely to their availability in large numbers, their low cost, and the ease with which they can be housed and handled.

It is common practice to apply an uncertainty factor of 10 to account for possible differences in sensitivity between species (i.e., interspecies differences, such as those that might exist between rodents and humans) and an additional uncertainty factor of 10 to accommodate differences in sensitivity between individuals within the same species (i.e., intraspecies differences). Other uncertainty factors that are often applied include an uncertainty factor of 10 to adjust from subchronic to chronic exposure and a factor of 10 to account for the uncertainty associated with the use of a LOAEL instead of a NOAEL. Where the toxicity database is very limited, an additional uncertainty factor can be applied to account for uncertainties in the database.

In some instances, the uncertainty factors may be less than 10, based upon the chemical-specific information reviewed by an agency or organization in the derivation of the value. For example, values of 3 or √10 are used when the available information does not support the use of a factor of 10.

Table J1-1 Examples of Commonly Used Uncertainty Factors

Nature of Uncertainty	*Magnitude of Factor*	*Comments*
Differences in sensitivity between species	3 or √10, 10	Used to accommodate the uncertainty around the use of laboratory animal data to predict potential human responses.
Differences in sensitivity within a species	3 or √10, 10	Used to account for individuals within the human population that may be more sensitive to a chemical than the average person.
LOAEL to a NOAEL	3 or √10, 10	Used to account for the uncertainty surrounding the use of a LOAEL when a NOAEL is not available for the most sensitive test species.
Subchronic to chronic exposure duration	3 or √10, 10	Used to account for the uncertainty surrounding the use of data involving shorter exposure periods to predict the responses that might occur over longer periods of exposure. Subchronic data is used when exposures are expected to occur for long periods and defensible chronic toxicity data is not available.
Database uncertainty	3 or √10, 10	Used to account for a lack of toxicological information for one or more endpoints.

NOTE: Uncertainty factors are not applied in the derivation of non-threshold carcinogenic exposure limits.

Typically, exposure limits are differentiated on the basis of the duration of exposure in recognition of the variability in toxic responses that may be seen with the same chemical following an acute (short-term) vs. chronic (long-term) exposure. Differing terminology may be assigned to exposure limits depending on the source of exposure (e.g., air, water, food) and the regulatory jurisdiction involved. Often, generic terminology will apply, with the following terms and descriptions used:

- RfC - refers to the safe levels of air-borne threshold chemicals where the primary route of exposure is through inhalation. The RfC is expressed as a concentration of the chemical in air (i.e., micrograms per cubic metre - µg/m³).
- RfD - refers to the safe levels of threshold chemicals to which exposure occurs through multiple pathways, both primary and secondary (i.e., oral, dermal). It is most commonly expressed as the daily dose of the chemical per unit body weight of the receptor (i.e., micrograms per kilogram of body weight per day - µg/kg•bw/d).
- RsC – reserved for non-threshold carcinogens, the RsC refers to the concentration via inhalation that corresponds to a 'socially acceptable' incremental increase in the incidence of cancer, typically of one case in a population of 100,000 people. The RsC is expressed as a concentration in air (i.e., µg/m³).
- RsD – same as the RsC except that it refers to the dose from multiple pathways that corresponds to a 'socially acceptable' incremental increase in the incidence of cancer (one in 100,000), often expressed as the daily dose of the chemical per unit body weight of the receptor (e.g., µg/kg•bw/d).

In some instances, reliance must be placed on the guiding principle which states that the molecular structure of a chemical has a distinct bearing on its reactivity, biological activity and toxicity. This principle allows the toxicity of a chemical for which little or no toxicological information exists to be predicted on the basis of information available on another chemical of similar molecular structure. The second chemical is often termed a 'surrogate', and the term 'read across' has been coined to describe the principle. The principle is also often applied to groups of chemicals of similar structure in which toxicity data on many of the individual constituents of the group may be lacking. In such cases, all of the constituents are assumed to share the same toxic potency as the surrogate.

J1-1.2 Exposure Limit Selection

To ensure that the most defensible and appropriate exposure limit was selected for use in the HHRA, consideration was given to the following criteria:

- Established or recommended by reputable scientific authorities;
- Protective of the health of the general public based on the current scientific understanding of the health effects known to be associated with exposures to the COPC;
- Protective of sensitive individuals through the use of appropriate uncertainty factors; and
- Supported by adequate and available documentation.

In the case that the above criteria were supported by more than one standard, guideline or objective, the most scientifically defensible limit was selected and the rationale was provided.

Recognizing the fact that the toxic response can vary for the same chemical following an acute (short-term) vs. chronic (long-term) exposure, exposure limits can be differentiated based on the duration of exposure. For the purposes of this assessment, exposure limits selected to evaluate acute and chronic exposures were based on the following definitions:

- Acute – single or intermittent exposures lasting up to 24-hours; and
- Chronic – repeated, exposures over longer term periods that are conservatively assumed to take place over lifetime

J1-1.2.1 Acute Exposure Limits

A tiered approach was used to evaluate available exposure limits for the COPCs. In the first tier, the sources of acute exposure limits evaluated for this HHRA included:

- 1-Hour, 8-hour and 24-hour AAQOs developed by AENV;
- Acute MRLs developed by the ATSDR;
- Acute and 8-hour RELs developed by the California OEHHA;
- 1-Hour and 24-hour standards and guidelines developed by the OMOE;
- Acute ReVs developed by the TCEQ; and
- 10-Minute, 1-hour and 24-hour AQGs developed by the WHO.

If a suitable exposure limit could not be identified by one of the above regulatory agencies, then the search was expanded to the second tier of limits and agencies:

- Intermediate MRLs developed by the ATSDR; and,
- TLV - STELs developed by the ACGIH.

All supporting documents were critically evaluated to identify the most appropriate and defensible value for use in the HHRA.

J1-1.2.2 Chronic Exposure Limits

A tiered process was used in the review and selection of chronic exposure limits. The first tier of sources of exposure limits used in the HHRA for the chronic inhalation toxicity assessment included the following:

- Chronic MRLs developed by the ATSDR;
- TRVs developed by Health Canada;
- TCAs or CRs developed by the RIVM;
- Chronic RELs or cancer risk estimates developed by the OEHHA;
- RfCs or RsCs developed by the US EPA IRIS;

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J1-2.1.1.2 Chronic

Table J2-2 Chronic Inhalation Exposure Limits for Aliphatic C_5-C_8 Group

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
CCME RfC		18,400	CCME (2008)
MA DEP	RfC	200	MA DEP (2003)
RIVM T	CA	18,400	RIVM (2001)
TPHCWG RfC		18,400	TPHCWG (1997)

The CCME (2008) RfC and RIVM (2001) TCA of 18,400 µg/m³ for the C_5-C_8 aliphatic group was adopted from the TPHCWG (1997). The TPHCWG RfC is based on the neurotoxic endpoint of commercial hexane and was developed from a NOAEL of 10,307 mg/m³ for two (rat and mice) chronic bioassays involving lifetime exposure. The NOAEL was adjusted for continuous exposure (6/24 hours × 5/7 days) to a concentration of 1,840 mg/m³. The TPHCWG (1997) applied a cumulative uncertainty factor of 100 to the NOAEL to account for interspecies variability (10) and intraspecies variability (10). The TPHCWG (1997) recommends using the RfC derived for commercial hexane over an RfC specific to n-hexane (as is the case of the MA DEP RfC discussed below) as it is more representative of the aliphatic fraction. According to the TPHCWG (1997), using n-hexane alone results in an overestimation of the toxicity of the fraction because n-hexane is the most toxic of the group's constituents, it is uniquely toxic and its interaction with other petroleum compounds influences its toxicity. The RfC of **18,400 µg/m³** for commercial hexane was used to evaluate the risks associated with the aliphatic C_5-C_8 group. As the toxicological basis of this value is the neurotoxic endpoint of commercial hexane, the aliphatic C_5-C_8 group was included in the chronic inhalation *neurotoxicants* mixture.

The MA DEP (2003) RfC of 200 µg/m³ was derived from toxicity data specific to n-hexane, which, as mentioned above, is considered overly conservative when characterizing the toxicity of the aliphatic C_5-C_8 group as a whole. Thus, the MA DEP RfC was not selected for use in the chronic inhalation effects assessment.

J1-2.1.2 Oral Exposure Limits

J1-2.1.2.1 Chronic

Neither n-hexane nor n-pentane met the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required for the aliphatic C_5-C_8 group.

J1-2.1.3 References Aliphatic C_5-C_8 Group

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J1-2.2 Aromatic C_9-C_{16} Group

J1-2.2.1 Inhalation Exposure Limits

J1-2.2.1.1 Acute

Table J2-3 Acute Inhalation Exposure Limits for Aromatic C_9-C_{16} Group

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	– AENV	(2009)
ATSDR	–	– AT	SDR (2009)
OEHHA	–	– OEHHA	(2008)
OMOE	–	– OMOE	(2008)
TCEQ	–	– T	CEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	– W	HO (2000)

– = Not available

As no acute exposure limit was available for the aromatic C_9-C_{16} group, naphthalene was used as a surrogate for the group on an acute basis only. The adjusted ACGIH STEL for naphthalene (ACGIH 2009) of **2,000 µg/m³** was used as a 1-hour exposure limit for the aromatic C_9-C_{16} group. For the further details regarding the derivation of the adjusted STEL for naphthalene, refer to the toxicity profile for naphthalene.

As the toxicological basis of the ACGIH STEL is eye irritation, the aromatic C_9-C_{16} group was included in the acute *eye irritants* mixture.

J1-2.2.1.2 Chronic

Table J2-4 Chronic Inhalation Exposure Limits for Aromatic C_9-C_{16} Group

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
CCME RfC		200	CCME (2008)
MA DEP	RfC	50	MA DEP (2003)
RIVM T	CA	200	RIVM (2001)
TPHCWG RfC		200	TPHCWG (1997)

The MA DEP (2003) has developed an RfC of 50 µg/m³ based on a study by Clark et al. (1989). The MA DEP RfC is based on increased liver and kidney weights in male rats exposed to high flash aromatic naphtha, which is primarily composed of 9-carbon aromatic compounds. Rats were administered 0, 450, 900 or 1,800 mg/m³ of a mixture of C_9 aromatics for 6 hours/day, 5 days/week for 12 months (Clark et al. 1989). A NOAEL of 900 mg/m³ was identified for liver and kidney effects and converted to continuous exposure (6/24 hours x 5/7 days) resulting in a NOAEL of 160 mg/m³. The MA DEP (2003) applied a cumulative uncertainty factor of 3,000 to the NOAEL to account for the interspecies variability (10), intraspecies variability (10), use of a subchronic study (10), and database deficiencies (3). The partial uncertainty factor of 3 was

applied to account for the lack of toxicity information on non-PAH compounds in the C_9-C_{16} aromatic fraction (MA DEP 2003). This value of **50 µg/m³** was selected for use in the chronic effects assessment of the aromatic C_9-C_{16} group. As the toxicological basis of this value includes liver and kidney effects and no other COPCs in the chronic inhalation effects assessment have these endpoints, the aromatic C_9-C_{16} group was not part of a chronic inhalation mixture.

The CCME (2008) RfC and RIVM (2001) TCA of 200 µg/m³ were adopted from the TPHCWG (1997). The TPHCWG limit also was based on the 1989 study by Clark et al. The TPHCWG (1997) applied a cumulative uncertainty factor of 1,000 to the duration-adjusted NOAEL of 160 mg/m³ to account for the interspecies variability (10), intraspecies variability (10), and use of a subchronic study (10). This limit was not used in the chronic inhalation effects assessment, as the MA DEP (2003) RfC represents a more conservative limit.

J1-2.2.2 Oral Exposure Limits

J1-2.2.2.1 Chronic

Table J2-5 Chronic Oral Exposure Limits for Aromatic C_9-C_{16} Group

Regulatory Agency	*Type*	*Value (µg/kg bw/d)*	*Reference*
CCME RfD		40	CCME (2008)
MA DEP	RfD	30	MA DEP (2003)
RIVM T	DI	40	RIVM (2001)
TPHCWG RfD		40	TPHCWG (1997)

The CCME (2008) RfD and RIVM (2001) TDI of 40 µg/kg bw/d for the C_9-C_{16} aromatics are adopted from the TPHCWG (1997), which is based on the most commonly reported RfD value of eight individual compounds for which the US EPA has established oral RfDs (isopropylbenzene, acenaphthene, biphenyl, fluorene, anthracene, fluoranthene, naphthalene, pyrene). The TPHCWG (1997) examined the RfDs for liver and kidney effects together with toxicity data for naphthalenes and methylnaphthalenes to determine the RfD of 0.04 mg/kg bw/d. At the time of the TPHCWG (1997) assessment, four of the eight individual compounds (isopropylbenzene, naphthalene, fluorene and fluoranthene) had RfDs of 0.04 mg/kg bw/d, while the remaining compounds had RfDs ranging from 0.03 mg/kg bw/d to 0.3 mg/kg bw/d. Although the US EPA has revised the isopropylbenzene (0.1 mg/kg bw/d) and naphthalene (0.02 mg/kg bw/d) RfDs (US EPA 2010), the RfD of 0.04 mg/kg bw/d reflects the toxicity of the group as a whole and not a single compound within the group. The RfD of **40 µg/kg bw/d** was used in the chronic oral effects assessment of the C_9-C_{16} aromatics. As the toxicological basis of this value includes liver and kidney effects, the aromatic C_9-C_{16} group was included in the chronic oral *renal toxicants* mixtures.

The MA DEP (2003) selected the US EPA RfD for pyrene of 0.03 mg/kg bw/d to represent the RfD for the entire range of aromatic C_9-C_{16} compounds. The US EPA RfD for pyrene is based on kidney effects (renal tubular pathology, decreased kidney weights) observed in a subchronic

mouse oral bioassay. As this value is based upon only one substance, and the other values are based upon mixtures, the MA DEP RfD was not used in the chronic oral effects assessment.

J1-2.2.3 References Aromatic C_9-C_{16} Group

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J1-2.3 Aromatic C_{17}-C_{34} Group

J1-2.3.1 Inhalation Exposure Limits

J1-2.3.1.1 Acute

Table J2-6 Acute Inhalation Exposure Limits for Aromatic C_{17}-C_{34} Group

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
OEHHA	–	–	OEHHA (2008)
OMOE	–	–	OMOE (2008)
TCEQ	–	–	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

No acute exposure limit was available. Therefore, the aromatic C_{17}-C_{34} group was not evaluated on an acute basis.

J1-2.3.1.2 Chronic

Table J2-7 Chronic Inhalation Exposure Limits for Aromatic C_{17}-C_{34} Group

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
CCME	–	–	CCME (2008)
MA DEP	–	–	MA DEP (2003)
RIVM	–	–	RIVM (2001)
TPHCWG	–	–	TPHCWG (1997)

– = Not available

Inhalation toxicity data were not identified for the individual constituents or fractions in the C_{17}-C_{34} carbon range (CCME 2008). This could be the result of the hydrocarbons in this group not being volatile and inhalation being an unlikely exposure pathway. In addition, MA DEP (2003) does not provide a recommended value for inhalation exposure to C_{17}-C_{34} aromatics based on the limited volatility of the group.

As a result, the aromatic C_{17}-C_{34} group was not evaluated in the chronic inhalation effects assessment.

J1-2.3.2 Oral Exposure Limits

J1-2.3.2.1 Chronic

Table J2-8 Chronic Oral Exposure Limits for Aromatic C_{17}-C_{34} Group

Regulatory Agency	*Type*	*Value (µg/kg bw/d)*	*Reference*
CCME	RfD	30	CCME (2008)
MA DEP	–	–	MA DEP (2003)
RIVM	TDI	30	RIVM (2001)
TPHCWG	RfD	30	TPHCWG (1997)

– = Not available

The CCME (2008) RfD and RIVM (2001) TDI of 30 µg/kg bw/d for the aromatic C_{17}-C_{34} fraction were adopted from the TPHCWG (1997), which is based on the nephrotoxicity of pyrene. The RfD for pyrene was derived from a NOAEL of 75 mg/kg bw/d with a cumulative uncertainty factor of 1,000 applied to the NOAEL to account for interspecies variability (10), intraspecies variability (10), and use of a subchronic study (10). A modifying factor of 3 was also applied to the RfD because of the lack of adequate toxicity data. This RfD of **30 µg/kg bw/d** was used in the chronic oral effects assessment of the C_{17}-C_{34} aromatics. As the toxicological basis of this value includes kidney effects, the aromatic C_{17}-C_{34} group was included in the chronic oral *renal toxicants* mixture.

J1-2.3.3 References Aromatic C_{17}-C_{34} Group

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J1-2.4 Benzene

J1-2.4.1 Inhalation Exposure Limits

J1-2.4.1.1 Acute

Table J2-9 Acute Inhalation Exposure Limits for Benzene

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	1-hour AAQO	30	AENV (2009)
ATSDR	acute MRL	30	ATSDR (2009)
OEHHA	6-hour REL	1,300	OEHHA (2008)
OMOE	–	–	OMOE (2008)
TCEQ	acute ReV	580	TCEQ (2007)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The TCEQ (2007) has derived an acute ReV of 580 µg/m³ for benzene based on immunological effects. Male C57BL/6J mice (7 or 8 per concentration) were exposed to 0, 10.2, 31, 100, or 301 ppm (0, 32.6, 99, 320, or 960 mg/m³) benzene in whole-body dynamic inhalation chambers for 6 hours/day on 6 consecutive days. The control group was exposed to filtered, conditioned air only. Significant depression of femoral lipopolysaccharide induced B-colony-forming ability was observed at the 10.2 ppm exposure level in the absence of a significant depression of total number of B cells. Peripheral lymphocyte counts were depressed at all exposure levels. The TCEQ (2007) established a $LOAEL_{ADJ}$ of 18.5 ppm, using Haber's law and a default approach for converting exposures more than one hour to a 1-hour exposure level from TCEQ (2007). The $LOAEL_{ADJ}$ was converted to a $LOAEL_{HEC}$ using a RGDR. In the case that the animal

blood:gas partition coefficient is greater than the human blood:gas partition coefficient, a default value of 1 is used for the RGDR. Thus, the $LOAEL_{HEC}$ was calculated to be 18.5 ppm.

A cumulative uncertainty factor of 100 was applied to the $LOAEL_{HEC}$ to account for interspecies differences (3), intraspecies variability (10), and the use of a LOAEL (3). A factor of 3 was applied for extrapolation of animal data to humans since dosimetric adjustments were conducted to address toxicokinetic differences. In addition, studies indicate that benzene is metabolized along similar pathways in animals and humans and data suggests that mice are relatively sensitive in regards to hematotoxic effects of benzene (TCEQ 2007). A factor of 3 was applied for extrapolation from a LOAEL to a NOAEL on the basis that the LOAEL used to derive the acute ReV is lower than other LOAELs observed in animal and human studies, and the LOAEL is similar to NOAELs observed in mouse studies (TCEQ 2007). In addition, benchmark dose modelling of estimated lymphocyte count depression data produces a BMCL of 4 ppm, which supports a factor of 3 as being sufficiently conservative (TCEQ 2007). The TCEQ (2007) also states that lymphocyte count depression is a sensitive sentinel effect that is not a serious nature, and the reported decreased lymphocyte count at 10.2 ppm appears to be within the normal range. Finally, 10.2 ppm is below the levels at which more toxic to less toxic metabolites has been shown to occur in mice (TCEQ 2007). The resulting acute ReV of **580 µg/m³** was used as a 1-hour exposure limit in the acute inhalation effects assessment of benzene. As this value is based upon immunological effects and no other COPCs in the acute inhalation effects assessment have this endpoint, benzene was not included in an acute inhalation mixture.

Alberta Environment (2009) provides a 1-hour AAQO of 30 µg/m³ for benzene; however, the AAQO was adopted from the TCEQ and the specific basis was not provided. As a result, it was not used in the acute inhalation effects assessment.

The ATSDR (2007, 2009) has derived an acute MRL of 0.009 ppm (0.03 mg/m³) using the same key study (Rozen et al. 1984) as the TCEQ. As well, the ATSDR identified the same LOAEL value of 10.2 ppm (32.6 mg/m³). The difference between the ATSDR and TCEQ values originates from the adjustment of the LOAEL for continuous exposure and the uncertainty factors applied. The ATSDR (2007) adjusted the LOAEL from intermittent to continuous exposure (6 hours/24 hours) to a concentration of 2.55 ppm (8.16 mg/m³). The $LOAEL_{ADJ}$ was converted to a $LOAEL_{HEC}$ for a category 3 gas causing respiratory effects. The average ratio of the animal blood:air partition coefficient would be greater than 1; thus, a default value of 1 was used in calculating the HEC (ATSDR 2007). As a result, a $LOAEL_{HEC}$ of 2.55 ppm (8.16 mg/m³) was identified. The ATSDR (2007) applied a cumulative uncertainty factor of 300 to the $LOAEL_{HEC}$ to account for interspecies variability (3), intraspecies variability (10), and use of a LOAEL (10). A factor of 3 was applied for the extrapolation of laboratory animal data to humans since the calculation of a HEC addressed the pharmacokinetic aspects of the interspecies uncertainty factor. This value was not selected, as the time-adjustment process applied by TCEQ (2007) was more defensible given the dose-response and duration-related effects observed for benzene.

The OEHHA (2008) has derived a 6-hour acute REL of 1,300 µg/m³ based upon reproductive effects. The key study (Coate et al. 1984) involved the exposure of pregnant female rats (40 per group) to 0, 1, 10, 40 or 100 ppm (equivalent to 0, 3,240, 32,400, 129,600 or 324,000 µg/m³) for 6 hours/day on days 6 to 15 of gestation. Significantly decreased mean fetal weights were observed at the highest (100 ppm) exposure level. No fetotoxic, teratogenic or maternal toxicity was observed in the 40 ppm group. The study NOAEL was identified as 40 ppm for reduced fetal weight. A cumulative uncertainty factor of 100 was applied to account for interspecies differences (10) and intraspecies variability (10). The OEHHA (2008) notes that the NOAEL was not adjusted to a 1-hour exposure due to the uncertainty associated with extrapolating data from repeated exposures to a 1-hour concentration. As a result of this uncertainty, the 6-hour REL of 1,300 µg/m³ may be considered equivalent to a 1-hour REL. This value was not selected, as reproductive effects do not appear to the most sensitive endpoint in association with acute benzene exposure.

J1-2.4.1.2 Chronic

Table J2-10 Chronic Inhalation Exposure Limits for Benzene

Regulatory Agency	*Type* [(a)]	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
HEALTH CANADA	RsC	3	Health Canada (2004)
OEHHA	chronic REL	60	OEHHA (2008)
	RsC	0.3	OEHHA (2009)
RIVM	CR_{inhal}	2	RIVM (2001)
TCEQ	TCA	280	TCEQ (2007)
US EPA	RfC	30	US EPA (2010)
	RsC	1.3 to 4.5	US EPA (2010)
WHO	RsC	1.7	WHO (2000)

(a) The IARC (1998) has determined that there is *limited evidence* that benzene is carcinogenic in experimental animals and *sufficient evidence* that benzene is carcinogenic to man. As a result, only RsCs are listed in the above table.

– = Not available

The US EPA (2010) presents a range of potential carcinogenic risks from inhalation of benzene. The key data sets employed in the US EPA cancer assessment were those by Rinsky et al. (1981, 1987), which were also critically analyzed by Paustenbach et al. (1993), Crump and Allen (1984), Crump (1992, 1994), and US EPA (1998). The Rinsky et al. (1981, 1987) studies examined the incidence of leukemia in exposed white male workers in the rubber hydrochloride department of a pliofilm plant. The more comprehensive follow up study (Rinsky et al. 1987) involved the evaluation of 1,165 workers who were exposed for at least one day between 1965 and 1981. Individual assessments of cumulative exposure were calculated by Rinsky et al. for each worker based upon air sampling data. Inhalation unit risks of 2.2E-06 to 7.8E-06 per µg/m³ were extrapolated based on a low-dose linear model using maximum likelihood estimates for leukemia in humans (US EPA 2010). The inhalation unit risks equate to an RsC of 1.3 to 4.5 µg/m³ associated with a risk level of one in 100,000 (US EPA 2010). The RsC of

1.3 µg/m³ was selected as the chronic inhalation limit for benzene as it is the most conservative of the values presented within this range. As the toxicological basis of this value is leukemia and no other COPCs in the chronic inhalation effects assessment have this endpoint, benzene was not included in a chronic inhalation mixture.

In addition, the US EPA has derived an RfC of 20 µg/m³ based upon a cross-sectional occupational study where decreased lymphocyte counts were observed in exposed workers. Although a detailed rationale document is provided, this limit was not used in the assessment due to the existence of cancer-based limits that are more conservative. The US EPA RfC was not used in the chronic inhalation effects assessment, as the US EPA RsC represents a more conservative limit.

The OEHHA (2009) has derived a unit risk estimate of 2.9E-05 per µg/m³ (equivalent to an RsC of 0.34 µg/m³) based upon epidemiological studies of Chinese workers. Although it is not very clear, Yin et al. (1994, 1996) studies appear to be the basis of the OEHHA value. The Chinese cohort studies were determined by the US EPA to have methodological issues (poor exposure characterization, co-exposure to other agents, data quality) to the point where the study was not adequate for quantitative assessment. The US EPA RsC value, in contrast, is based upon Rinsky et al. (1981, 1987) studies that have been critically analyzed in several other studies.

An RsC of 3 µg/m³ is reported by Health Canada (2004) based on an inhalation unit risk of 0.0033 per mg/m³. This value was derived from the Rinsky et al. (1987) data discussed above in the US EPA summary, and was calculated through the identification of a dose associated with a 5% increase in mortality from acute myelogenous leukemia. However, this RsC was not used in the chronic inhalation effects assessment, as the US EPA RsC represents a more conservative limit.

The WHO (2000) provides an RsC of 1.7 µg/m³, which is associated with an increased cancer risk of one in 100,000. Using multiplicative risk estimates and a cumulative exposure model, a unit risk for lifetime exposure of 1.4 to 1.5E-05 per ppb was derived with the Paustenbach exposure matrix and 2.4E-05 per ppb with the Crump and Allen exposure matrix (WHO 2000). These values equate to unit risks that range from 4.4 to 7.5E-06 per µg/m³. From this, the WHO (2000) selected a representative unit risk of 6E-06 per µg/m³. The RIVM (2001) used the WHO unit risk of 6E-06 for an excess lifetime risk for leukemia as the basis of the CR_{inhal} of 2 µg/m³. Neither the WHO RsC nor the RIVM CR_{inhal} was used in the chronic inhalation effects assessment for benzene, as the US EPA RsC represents a more conservative limit.
The TCEQ (2007) has derived a chronic ReV of 280 µg/m³ based upon decreased lymphocyte counts in 44 benzene-exposed workers. This limit was not used in the chronic inhalation effects assessment, as the US EPA RsC is a more conservative limit.

The OEHHA (2000, 2008) has also derived a non-cancer based value of 60 µg/m³ based upon haematological effects in 303 male refinery workers. Occupational exposures ranged from 0ne to 21 years. This limit was not used in the chronic inhalation effects assessment, as the US EPA RsC represents a more conservative limit.

The TCEQ (2007) has derived a chronic ReV of 280 µg/m³ based upon immunological effects in exposed workers. However, this limit was not used in the chronic inhalation effects assessment, as the US EPA RsC represents a more conservative limit.

J1-2.4.2 Oral Exposure Limits

Benzene did not meet the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required.

J1-2.4.3 References Benzene

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J1-2.5 Benzo(a)pyrene (and Equivalents)

J1-2.5.1 Inhalation Exposure Limits

J1-2.5.1.1 Acute

Table J2-11 Acute Inhalation Exposure Limits for Benzo(a)pyrene

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
OEHHA	–	–	OEHHA (2008)
OMOE	24-hour standard	0.0011	OMOE (2008a)
TCEQ	–	–	TCEQ (2009)
USEPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The OMOE (2008a) has developed a 24-hour standard of 0.0011 µg/m³ based on the carcinogenic potential for benzo(a)pyrene. The limit was derived from an annual exposure limit of 0.00022 µg/m³ for protection against carcinogenic effects using a simple extrapolation factor generally considered to be overly conservative. This limit was not used in the acute effects assessment for benzo(a)pyrene because it did not account for the influence of duration of exposure on the carcinogenic action of a chemical.

After reviewing available information and determining that there are no available criteria for benzo(a)pyrene with adequate supporting documentation, benzo(a)pyrene was not assessed on an acute basis.

J1-2.5.1.2 Chronic

Benzo(a)pyrene and other carcinogenic PAHs were evaluated using two different approaches in the chronic inhalation assessment:

Approach 1: The evaluation of benzo(a)pyrene as an indicator of the potency of the mixture is based upon the approach used by the WHO in their review of air quality guidelines for PAHs (WHO 2000). Benzo(a)pyrene was chosen as the indicator PAH as it is the best characterized out of all the carcinogenic PAH compounds.

Approach 2: The toxic equivalency quotient (TEQ) approach is described by the US EPA (2002), where the carcinogenic potencies of PAHs are scaled to an index compound (benzo(a)pyrene) using toxic equivalency factors (TEFs) and then added together to calculate the total cancer risk for the mixture. This approach permits the evaluation of the mixture when limited data are available for most of the mixture components.

Health Canada (2006) equivalency factors are based upon work completed by Equilibrium and URS (2006), in which PEFs (analogous to TEFs) were evaluated from multiple sources, for all routes of exposure. In addition, information regarding the carcinogenicity and genotoxicity of each PAH evaluated by Equilibrium and URS was reviewed. PAHs that did not have evidence of being directly carcinogenic or genotoxic were not assigned PEF values (e.g., anthracene).

The PEFs used in the current assessment of carcinogenic PAHs via the TEQ approach were adopted from Health Canada. These values are shown in Table J2-12. Non-carcinogenic PAHs (i.e., PAHs without PEFs) were evaluated on their own or as part of an aromatic hydrocarbon group, as appropriate.

Table J2-12 Relative Potency of Individual PAHs Compared with Benzo(a)pyrene

Compound	*Potency Equivalency Factor*
7,12-Dimethylbenz(a)anthracene	10
Benz(a)anthracene	0.1
Benzo(a)pyrene	1
Benzo(b)fluoranthene	0.1
Benzo(g,h,i)perylene	0.01
Benzo(k)fluoranthene	0.1
Chrysene	0.01
Dibenz(a,h)anthracene	1
Fluoranthene	0.001
Indeno(1,2,3-cd)pyrene	0.1
Phenanthrene	0.001

Table J2-13 Chronic Inhalation Exposure Limits for Benzo(a)pyrene

Regulatory Agency	*Type* [(a)]	*Value (µg/m³)*	*Reference*
AENV	annual AAQO	0.0003	AENV (2009)
ATSDR	–	–	ATSDR (2009)
HEALTH CANADA	RsC	0.32	Health Canada (2004b)
OEHHA	RsC	0.009	OEHHA (2009)
RIVM	–	–	RIVM (2001)
TCEQ	–	–	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	RsC	0.00012	WHO (2000)

– = Not available

The WHO (2000) recommends an inhalation unit risk of 0.087 per µg/m³ based on epidemiological data from studies involving coke-oven workers. The WHO (2000) identified an upper-bound individual lifetime unit risk estimate associated with continuous exposure to 1 µg/m³ of benzene-soluble compounds of coke-oven emissions in ambient air of 0.00062 per µg/m³ based on a linearized multistage model. Benzo(a)pyrene was selected as an indicator of

general PAH mixtures from emissions of coke-ovens and similar combustion processes in urban air. In the benzene-soluble fraction of coke oven emissions, 0.71% is reported to be benzo(a)pyrene. On this basis, the lifetime risk of lung cancer of 0.087 per µg/m³ was calculated (WHO 2000). This lifetime unit risk equates to an RsC of 0.00012 µg/m³ that is associated with an acceptable incremental lifetime cancer risk of one in 100,000. This RsC of **0.00012 µg/m³** was selected for the chronic inhalation assessment of benzo(a)pyrene alone (Approach 1).

Health Canada (2004b) provides an inhalation unit risk of 3.10E-02 per mg/m³, which equates to an RsC of 0.32 µg/m³. This RsC is associated with an acceptable incremental lifetime cancer risk of developing respiratory tumours of one in 100,000. The RsC was developed based on exposure to benzo(a)pyrene via multi-stage modelling of respiratory tract tumours in Syrian golden hamsters (Thyssen et al. 1981; CEPA 1994). In the key study, groups of 24 male Syrian golden hamsters were exposed by inhalation (nose only) to 0, 2.2, 9.5, or 45.6 mg/m³ benzo(a)pyrene for 4.5 hours/day, 7 days/week for the first 10 weeks, and for 3 hours/day for the rest of the exposure period (up to 96 weeks). A decrease in body weight gain was observed in exposed animals during the first 10 weeks of the study; however, from the 10th to the 60th week, the body weights of all surviving exposed animals (with the exception of the highest exposure group) were similar to those of the controls. Mean survival also decreased in the highest exposure group. The incidences of unspecified tumours of the respiratory tract (nasal cavity, larynx, and trachea) were:

- 0/27 for controls;
- 0/27 for the low-dose group;
- 9/26 (35%) for the mid-dose group; and
- 13/25 (52%) for the high-dose group (Thyssen et al. 1981).

Exposure related neoplasms (unspecified) were present in the pharynx (0, 0, 23, and 56% for control, low-, mid-, and high-dose, respectively), esophagus (0, 0, 0, and 8% for control, low-, mid-, and high-dose, respectively), and forestomach (0, 0, 4, and 4% for control, low-, mid-, and high-dose, respectively). Lung tumours were not observed (Thyssen et al. 1981). The Health Canada RsC of **0.32 µg/m³** was selected for the chronic inhalation assessment of benzo(a)pyrene (TEQ). As the toxicological basis of this value is the incidence of respiratory tumours and no other COPCs have this endpoint, benzo(a)pyrene was not included in a chronic oral mixture.

The OEHHA (2009) presents an inhalation unit risk estimate of 1.1E-03 per µg/m³, which is equivalent to an RsC of about 0.009 µg/m³. This value was derived from the Thyssen et al. 1981 study (discussed above as the basis of the Health Canada value). Linearized multistage modelling was used to evaluate the respiratory tumour incidence data. The OEHHA applied adjustments to account for differences in body surface area and body weight – it is not clear if such adjustments were made in the Health Canada approach. However, the rationale for completing such adjustments is not well described.

Supporting documentation for the AENV (2009) value of 0.003 µg/m³ was not available, although it is noted that the value is adopted from the OMOE. The OMOE value of 0.003 µg/m³ represents a half-hour standard, and the current benzo(a)pyrene air standards in Ontario are under review (OMOE 2008b). As a result, the AENV value was not used in the assessment.

J1-2.5.2 Oral Exposure Limits

J1-2.5.2.1 Chronic

Table J2-14 Chronic Oral Exposure Limits for Benzo(a)pyrene

Regulatory Agency	*Type*	*Value (µg/kg bw/d)*	*Reference*
ATSDR	–	–	ATSDR (2009)
HEALTH CANADA	RsD	0.0043	Health Canada (2004b)
OEHHA	RsC	0.001	OEHHA (2009)
RIVM	RsD	0.05	RIVM (2001)
US EPA	RsD	0.0014	US EPA (2010)
WHO	–	–	WHO (2008)

– = Not available

The US EPA (2010) provides an oral slope factor of 7.3 per mg/kg bw/d based on the geometric mean of four slope factors obtained by different modelling procedures and multiple datasets from two different studies. The US EPA (2010) considered each dataset to be acceptable for the derivation of an oral slope factor for benzo(a)pyrene, but the use of a geometric mean of all four slope factors was preferred because it made use of more of the available data. The four slope factors were calculated as follows:

1. Data from Neal and Rigdon (1967) was fit to a two-stage dose response model that included a term to permit the modelling of benzo(a)pyrene as its own promoter (modification of Moolgavkar-Venson-Knudson, generalized forms of two-stage model). In this model, the transition rates and the growth rate of preneoplastic cells were both considered to be exposure-dependent. In addition to the Neal and Rigdon (1967) control group, historical control stomach tumour data from a related, but not identical, mouse strain (SWR/J Swill) was used in the modelling (Rabstein et al. 1973). In the historical control data, the forestomach tumour incidence rate was 2/268 and 1/402 for males and females, respectively. The lifetime unit risk for humans was calculated based on the following standard assumptions: mouse food consumption was 13% of its body weight per day, human body weight was assumed to be 70 kg, and the assumed body weight of the mouse 0.034 kg (US EPA 2010). The standard assumption of surface area equivalence between mice and humans was the cube root of 70 kg/0.034 kg. A conditional upper-bound estimate was calculated to be 5.9 per mg/kg bw/day (US EPA 2010).
2. The Neal and Rigdon (1967) dataset was also used to generate an upper-bound estimate extrapolated linearly from the 10% response point to the background of an empirically fitted dose-response curve (modification of Moolgavkar-Venson-Knudson,

generalized forms of two-stage model). An upper-bound was calculated to be 9.0 per mg/kg bw/day (US EPA 2010).

3. In order to reflect the partial lifetime exposure pattern over different parts of the animals' lifetimes, a generalized Weibull-type dose-response model was selected to assess the Neal and Rigdon (1967) data alone (i.e., excluding the two additional control groups from Rabstein et al. 1973). An upper-bound was calculated to be 4.5 per mg/kg bw/d (US EPA 2010).
4. A linearized multistage procedure was used to calculate an upper bound estimate for humans from a rat dataset (Brune et al. 1981). Sprague-Dawley (rats/sex/group) were fed 0.15 mg/kg benzo(a)pyrene (reported to be 'highly pure') in the diet either every 9 days or 5 days/week. These treatments resulted in annual average doses of 6 or 39 mg/kg, respectively. The control group contained 32 rats per sex. Treatment continued until the rats were moribund or dead; survival was similar in all groups. The combined incidence of tumours of the forestomach, esophagus and larynx was 3/64, 3/64 and 10/64 in the control group, the group fed benzo(a)pyrene every 9 days, and the group fed benzo(a)pyrene 5 days/week, respectively. A trend analysis showed a statistically significant tendency for the proportion of animals with tumours of the forestomach, esophagus or larynx to increase steadily with dose. An oral slope factor of 11.7 per mg/kg bw/d was calculated (US EPA 2010).

Because the US EPA considered in its development of an oral slope factor (i) different modelling procedures, (ii) multiple datasets from two different studies, and (iii) both sexes of more than one strain of mice and species of out bred rodents, the US EPA RsD of **0.0014 µg/kg bw/d** was selected as the chronic oral limit for benzo(a)pyrene (TEQ). As the toxicological basis of this value is gastrointestinal tumours and no other COPCs have this endpoint, the benzo(a)pyrene group was not included in a chronic oral mixture.

Health Canada (2004b) presents an oral slope factor of 2.3 per mg/kg bw/day, which is equivalent to an RsD of 0.004 µg/kg bw/day. This RsD is based on the Canadian guidelines for drinking water (Health Canada 1988). The Canadian drinking water quality guideline for benzo(a)pyrene took into consideration the increased incidence of stomach tumours (squamous cell papillomas and some carcinomas) (Health Canada 1988; Neal and Rigdon 1967). In the key study, male and female CFW-Swiss mice were fed concentrations of 0 ppm, 1 ppm, 10 ppm, 20 ppm, 40 ppm, 45 ppm, 50 ppm, 100 ppm or 250 ppm benzo(a)pyrene in the diet (purity was not reported). The control group contained 289 mice (number of mice/sex was not specified). No forestomach tumours were reported in the 0 ppm, 1 ppm, or 10 ppm dose groups. The incidence of forestomach tumours in the 20 ppm, 40 ppm, 45 ppm, 50 ppm, 100 ppm or 250 ppm dose groups were 1/23, 0/37, 1/40, 4/40, 23/40, 19/23 and 66/73, respectively. Incorporating a surface area correction and using the robust linear extrapolation model, the unit lifetime risk associated with the ingestion of 1 µg/L benzo(a)pyrene in drinking water was estimated as 5E-05. Using an adult body weight of 70.7 kg and an adult water ingestion rate of 1.5 L/d (Health Canada 2004a), an oral slope factor of 2.3 per mg/kg bw/d was calculated. The US EPA value was selected over this value as it took more studies into consideration than just the Neal and Rigdon dataset.

The OEHHA (2009) has derived an oral slope factor of 11.5 per mg/kg bw/d, which is equivalent to an RsD of about 0.001 µg/kg bw/d, based upon the Neal and Rigdon (1967) data, however the approaches used are not clear in the supporting document. As a result, this value was not used in the assessment.

The RIVM (2001) presents an oral RsD of 0.5 µg/kg bw/d associated with a one in 10,000 risk level (or 0.05 µg/kg bw/d for a one in 100,000 risk level). This value was derived from an unpublished study, where rats were administered 0, 3, 10 or 30 mg/kg bw/d of benzo(a)pyrene via oral gavage, 5 days/week for a duration of 2 years. Tumours in the forestomach, liver, kidney, skin, intestine and auditory canal and sarcomas of the esophagus, skin, and mammary glands were observed. However, the incidence relative to controls is not clear. Given that the study cited by the RIVM is a draft and thus not peer reviewed, the RIVM value was not used in the assessment.

J1-2.5.3 References Benzo(a)pyrene

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J1-2.6 Carbon Monoxide

J1-2.6.1 Inhalation Exposure Limits

Chemicals of potential concern that are regulated at the federal government level in the form of either a NAAQOs or as a CWS were not subjected to the typical screening process for exposure limits. Instead, the AAQOs adopted by AENV (2009) from Health Canada were given priority. Carbon monoxide is one of these chemicals.

J1-2.6.1.1 Acute Inhalation Exposure Limits

Alberta Environment (AENV 2009) provides a 1-hour AAQO of **15,000 µg/m³** and an 8-hour AAQO of **6,000 µg/m³** for carbon monoxide. These AAQOs were adopted from the Canadian Environmental Protection Act and Federal Provincial Advisory Committee (CEPA/FPAC) Working Group on Air Quality Objectives and Guidelines, who recommends maximum desirable, acceptable and tolerable objectives for carbon monoxide. These objectives are based on the maximum desirable levels (i.e., the lowest objective), and were developed to protect the subpopulation sensitive to cardio-respiratory effects (CEPA/FPAC 1994).

As there are no 24-hour guidelines available, the acute assessment was completed on a 1-hour and 8-hour basis only.

J1-2.6.1.2 Chronic Inhalation Exposure Limits

The critical effect of carbon monoxide exposure is the formation of carboxyhemoglobin (COHb) in blood. Given that COHb concentrations reach a steady-state after 6 to 8 hours of exposure, carbon monoxide exposure for longer periods of time (i.e., chronic exposure), is not expected to cause accumulation of COHb in the blood (WHO 2000). For this reason, regulatory exposure limits are not available for chronic exposure to carbon monoxide, and carbon monoxide was not included in the chronic inhalation assessment.

Epidemiological studies have identified associations between ambient low-level carbon monoxide concentrations and various health effects (Burnett et al. 2000; Moolgavkar 2000). However, the study results are inconsistent and it has been suggested that carbon monoxide might represent only a surrogate compound for particulate emissions from mobile sources (Sarnat et al. 2001; Schwartz 1999).

J1-2.6.2 Oral Exposure Limits

Carbon monoxide is a gaseous criteria air contaminant. As such, it was not evaluated in the multiple pathway assessment.

J1-2.6.3 References for Carbon Monoxide

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J1-2.7 Dichlorobenzene

1,4-Dichlorobenzene was used as the surrogate for dichlorobenzene as it represents the most toxic isomer.

J1-2.7.1 Inhalation Exposure Limits

J1-2.7.1.1 Acute

Table J2-15 Acute Inhalation Exposure Limits for Dichlorobenzene

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	8-hour MRL	12,000	ATSDR (2009)
OEHHA	–	–	OEHHA (2008)
OMOE	24-hour standard	95	OMOE (2008)
TCEQ	acute ReV	3,000	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The TCEQ (2009) has derived an acute ReV of 0.50 ppm (3,000 µg/m³) based on eye and nasal irritation in exposed workers. The TCEQ (2009) used an occupational study conducted by Hollingsworth et al. (1956) as the key study in the derivation of the acute ReV. Fifty-eight male workers involved in the handling of 1,4-dichlorobenzene were generally exposed for 8 hours/day, 5 days/week, continually or intermittently for periods of 8 months to 25 years (mean of 4.75 years). The TCEQ (2009) selected the NOAEL of 15 ppm (90 mg/m³) as the point-of-departure for derivation of the acute ReV. The TCEQ (2009) did not extrapolate the NOAEL from an 8-hour workday to a 1-hour exposure because acute irritant effects of 1,4-dichlorobenzene appear to be primarily concentration dependent rather than duration-dependent. An uncertainty factor of 10 was applied to the NOAEL to account for intraspecies variability and a factor of 3 was applied to account for limitations in the acute toxicological database for 1,4-dichlorobenzene (TCEQ 2009). An additional uncertainty factor of 3 for database uncertainty resulting in an acute ReV of **3,000 µg/m³**. This value was used as a

1-hour exposure limit in the acute effects assessment of dichlorobenzene. As the toxicological basis of this value is eye and nasal irritation, dichlorobenzene was included in the acute *eye irritants* and *nasal irritants* mixtures.

The ATSDR (2006, 2009) has developed an acute inhalation MRL for 1,4-dichlorobenzene of 2 ppm (12,000 µg/m³) based on the same study NOAEL of 15 ppm (90 mg/m³) for eye and nose irritation in occupationally exposed workers used by the TCEQ to derive the acute ReV. An uncertainty factor of 10 was applied to the NOAEL to account for intraspecies variability (ATSDR 2006). No adjustment was made for an occupational exposure of 8 hours/day to 1-hour or 24-hour exposure durations. Given that the TCEQ acute ReV is more conservative than the ATSDR value as a result of the incorporation of an additional uncertainty factor, the ATSDR MRL was not used in the acute effects assessment.

The OMOE (2008) provides a 24-hour standard for 1,4-dichlorobenzene protective of health; however, the scientific basis is not provided. As a result, the study team is unable to comment on the scientific merit of this standard and did not use it in the acute effects assessment.

J1-2.7.1.2 Chronic

Table J2-16 Chronic Inhalation Exposure Limits for Dichlorobenzene

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	chronic MRL	60	ATSDR (2009)
HEALTH CANADA	TC	95	Health Canada (2004a)
OEHHA	chronic REL RsC	800 0.9	OEHHA (2008) OEHHA (2009)
RIVM	TCA	670	RIVM (2001)
TCEQ	chronic ReV	110	TCEQ (2009)
US EPA	RfC	800	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The ATSDR (2006, 2009) has developed a chronic MRL of 0.01 ppm (60 µg/m³) for the increased incidence of nasal lesions in female rats based upon Aiso et al. (2005). Male and female F344/DuCrj rats and male and female Crj: BDF1 mice were exposed to 0, 20, 75 or 300 ppm 1,4-dichlorobenzene via inhalation for 6 hours/day, 5 days/week for a duration of 104 weeks. Absolute and relative liver and kidney weights were increased in the 300 ppm group in both sexes, in both species. Histopathological changes in the nasal epithelia were observed in female rats at 75 ppm and 300 ppm, and in male rats at 300 ppm. Lesions included increased incidences of eosinophilic changes in the olfactory and respiratory epithelium. Renal lesions were observed only in male rats at the highest dose level. In mice, nasal lesions in respiratory and olfactory epithelium were observed in males at 75 ppm but not at 300 ppm, and in females only at 300 ppm. Centrilobular hepatocellular hypertrophy was significantly increased in male mice exposed to 300 ppm. Lesions of the olfactory epithelium in female rats were determined by the ATSDR to be the most sensitive effect, and benchmark dose modelling was completed

on this data set. A $BMCL_{10}$ of 9.51 ppm was determined from the dose-response modelling, and was adjusted for intermittent exposure (6/24 hours × 5/7 days) to a $BMCL_{10\ (ADJ)}$ of 1.7 ppm. A human equivalent concentration was determined using the US EPA (1994) approach for deriving a RGDR:

$$RGDR = \frac{VE\ (rat) / SA\ (rat)}{VE\ (human) / SA\ (human)}$$

$$RGDR = \frac{0.24 / 15}{20 / 200}$$

$$RGDR = 0.16$$

Where:

VE (rat) = calculated ventilation rate for a rat, 0.24 L/min

SA (rat) = extrathoracic region surface area of rat, 15 cm^2

VE (human) = calculated ventilation rate for a human, 20 L/min

SA (human) = extrathoracic region surface area of 200 cm^2

Multiplying the $BMCL_{10\ (ADJ)}$ of 1.7 ppm by the RGDR of 0.16 results in a $BMCL_{10\ (HEC)}$ of 0.27 ppm, to which a cumulative uncertainty factor of 30 was applied to account for interspecies differences (3) and intraspecies variability (10). The resulting chronic MRL of 0.01 ppm (**60 µg/m³**) was chosen as the exposure limit for dichlorobenzene in the chronic inhalation assessment. As the toxicological basis of this value is nasal irritation, dichlorobenzene was included in the chronic *nasal irritants* mixture.

Health Canada (2004) has developed a TC of 95 µg/m³ for 1,4-dichlorobenzene. Although this TC is based on health considerations, the specific basis of its derivation is unknown. As a result, this value was not considered for use in the chronic effects assessment.

The RIVM (2001) presents a TCA of 670 µg/m³ for 1,4-dichlorobenzene, based upon a NOAEL of 450 mg/m³. The NOAEL was adjusted for intermittent exposure to a value of 67 mg/m³. A cumulative uncertainty factor of 100 was applied (presumably for interspecies and intraspecies differences). As limited information regarding this value was provided in the supporting documentation, it was not used in the assessment.

The OEHHA (2000, 2008) has derived a chronic REL of 800 µg/m³ based upon nasal and eye irritation, and increased liver and kidney weights in rats (CPA 1986). Male and female Sprague-Dawley rats were exposed via inhalation to 0, 50, 150 or 450 ppm 1,4-dichlorobenzene for 6 hours/day, 7 days/week for a duration of 10 weeks and were mated for 3 weeks. It was not clear if the animals were exposed during mating. The F_1 generation were exposed to the same concentrations of 1,4-dichlorobenzene as the F_0 generation, and also were mated. No developmental abnormalities were observed. At 450 ppm, significant decreases in live births,

pup weights and survival were observed. At 150 ppm, nasal and eye irritation, and increased liver and kidney weights were observed in the animals following the 10-week exposure period. The study NOAEL was identified as being 50 ppm (301 mg/m³). This NOAEL was adjusted to account for intermittent exposure (6/24 hours), resulting in a $NOAEL_{ADJ}$ of 13 ppm. The RGDR between rats and humans for these endpoints was determined by the OEHHA to be 1, thus the HEC is the same as the $NOAEL_{ADJ}$ of 13 ppm. A cumulative uncertainty factor of 100 was applied to account for the use of a subchronic study (3), interspecies differences (3), and intraspecies variability (10).

In addition, the OEHHA (2009) has derived a unit risk estimate of 1.1E-05 per µg/m³ for 1,4-dichlorobenzene, which is equivalent to an RsC of 0.9 µg/m³. However, this value is based upon a chronic oral bioassay and was not selected for use in the assessment due to uncertainty associated with route-to-route extrapolation.

The US EPA (2010) has derived an RfC of 800 µg/m³ using the same study and NOAEL as the OEHHA (2000). A $NOAEL_{HEC}$ of 75 mg/m³ was derived and a cumulative uncertainty factor of 90 was applied to account for interspecies differences, (3) intraspecies differences (10), and the extrapolation of a subchronic study (3).

The TCEQ (2009) has established a chronic ReV of 110 µg/m³ based upon the incidence of nasal lesions in rats, and considers the same toxicological studies as the OEHHA, US EPA and ATSDR chronic limits. The study NOAEL was interpreted by the TCEQ as being 66 ppm in rats. In addition, benchmark dose modelling was conducted on the incidence rates of nasal lesions in female rats from the Aiso et al. (2005) study (relied upon by the ATSDR 2006, described above), and increased liver weights in male rats from the CPA (1986) study (relied upon by the US EPA and OEHHA in the derivation of their limits, which are discussed above). Following adjustments for continuous exposure (6/24 hours, 5/7 days) the $BMCL_{10}$ value for the Aiso et al. (2005) study was calculated to be 2.7 ppm and for the CPA (1986) study, 32.77 ppm. As the ReV derived from the Aiso et al. (2005) study was selected by the TCEQ, the discussion of the calculation of the HEC and the application of uncertainty factors below is limited to the Aiso et al. (2005) $BMCL_{10}$. A HEC was calculated by multiplying the $BMCL_{10}$ by a RGDR of 0.2, calculated following the approach of the US EPA (1994). A cumulative uncertainty factor of 30 was applied to the HEC of 0.535 ppm to account for interspecies differences in pharmacokinetics (3), and intraspecies variability (10). The result is a chronic ReV of 100 µg/m³. Although the ReV is based upon the same key study as the ATSDR MRL, it is not used in the chronic effects assessment as the ATSDR MRL is slightly more conservative.

J1-2.7.2 Oral Exposure Limits

Dichlorobenzene did not meet the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required.

J1-2.7.3 References for Dichlorobenzene

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J1-2.8 Formaldehyde

J1-2.8.1 Inhalation Exposure Limits

J1-2.8.1.1 Acute

Table J2-17 Acute Inhalation Exposure Limits for Formaldehyde

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	1-hour AAQO	65	AENV (2009)
ATSDR	acute MRL	50	ATSDR (2009)
OEHHA	acute REL 8-hour REL	55 9	OEHHA (2008a)
OMOE	24-hour standard	65	OMOE (2008)
TCEQ	acute ReV	50	TCEQ (2008)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The ATSDR (1999, 2009) has developed an acute inhalation MRL for formaldehyde of 0.04 ppm (50 µg/m³) based on a LOAEL of 0.4 ppm for nasal and eye irritation. Occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed (control) patients, all of whom were non-smokers, were separated into two groups. Group 1 included seven male and three female volunteers with skin hypersensitivity to formaldehyde and Group 2 included 11 healthy males with no history of allergic diseases. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 (placebo) or 0.4 ppm (0.5 mg/m³) formaldehyde and again 4 and 18 hours after the exposure period. In both groups, the placebo did not result in any effects on nasal wash cellular contents or symptom score. Exposure to 0.4 ppm formaldehyde showed statistically significant increased average symptom scores compared with average placebo scores, in both groups. As well, eosinophil counts and albumin

levels were elevated in both groups. After 18 hours, symptom scores, eosinophil counts and albumin levels were no longer elevated. A cumulative uncertainty factor of 10 was incorporated by the ATSDR (1999) to account for intraspecies variability (3) and to account for the use of a minimal LOAEL (3). An uncertainty factor of 3 was considered adequately protective of human variability as the symptoms of irritation were observed in a potentially sensitive group of subjects. This acute (2-hour) MRL of **50 µg/m³** was conservatively used as the 1-hour exposure limit in the acute effects assessment for formaldehyde as it represents the most conservative value that is supported by adequate documentation. As the toxicological basis of this limit was eye and nasal irritation, formaldehyde was included in the acute *eye irritants* and *nasal irritants* mixtures.

The OEHHA (2008a,b) has derived 1-hour and 8-hour RELs for formaldehyde. The acute 1-hour REL is based upon a study involving 19 healthy non-smokers. People were exposed to 0.5 to 3 ppm formaldehyde for a 3-hour period. A NOAEL of 0.5 ppm and a LOAEL of 1 ppm were determined from the study results for mild-moderate eye irritation. Benchmark dose modeling was conducted, and the $BMCL_{05}$ was determined to be about 0.44 ppm (530 µg/m³). The OEHHA (2008b) applied an uncertainty factor of 10 to this value to account for intraspecies differences, resulting in the 1-hour REL of 55 µg/m³. This value was not used as the ATSDR value is slightly lower and is well supported by scientific rationale. The 8-hour REL derived by the OEHHA was based upon long-term occupational studies with exposures ranging from 1 to 36 years. As the value is not based upon acute exposures, it was not considered further.

The OMOE (2008) provides a 24-hour standard of 65 µg/m³ based on a health effects. As the OMOE does not provide supporting documentation for the derivation of this standard, it was not considered further.

The TCEQ (2008) has developed an acute ReV of 50 µg/m³ for formaldehyde based on eye and nose irritation in human volunteers. The TCEQ (2008) derived the acute ReV based on the same study used by the ATSDR (Pazdrak et al. 1993) in addition to another study by Krakowiak et al. (1998), which also identified a LOAEL of 0.4 ppm. Similar to the ATSDR, the TCEQ (2008) applied a cumulative uncertainty factor of 10 to account for use of a minimal LOAEL (3) and intraspecies variability (3). A factor of 3 for intraspecies variability was considered sufficient given that the studies included potentially sensitive subpopulations (TCEQ 2008). This value is the same as the ATSDR MRL.

J1-2.8.1.2 Chronic

Table J2-18 Chronic Inhalation Exposure Limits for Formaldehyde

Regulatory Agency	*Type*[(a)]	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	chronic MRL	10	ATSDR (2009)
HEALTH CANADA	RsC	1.9	Health Canada (2004)
OEHHA	chronic REL	9	OEHHA (2008a)
	RsC	2	OEHHA (2009)
RIVM	–	–	RIVM (2001)
TCEQ	chronic ReV	11	TCEQ (2008)
	RsC	18	TCEQ (2008)
US EPA	RsC	0.8	US EPA (2010)
WHO	–	–	WHO (2000)

(a) The IARC (2006) has determined that formaldehyde *is carcinogenic to humans (Group 1)* based on *sufficient evidence* in humans and experimental animals.
– = Not available

The TCEQ (2008) has derived a non-carcinogenic chronic ReV of 11 µg/m³ based upon the incidence of eye, nasal and respiratory irritation in exposed workers. In the occupational study by Wilhelmsson and Holmstrom (1992), workers were exposed to a mean formaldehyde concentration of 0.21 ppm (0.26 mg/m³) for an average duration of 10 years. Exposure workers were compared with a control group of non-occupationally exposed workers who on average, were exposed to 0.07 ppm (0.09 mg/m³). Both groups of workers included atopic individuals with Type I hypersensitivity who were responsive to formaldehyde in cutaneous tests. Eye irritation and immune-mediated discomfort and irritation of the nasal passages and respiratory tract were observed in the exposed group but not in the reference group. The study LOAEL was identified as 0.26 mg/m³ and the NOAEL as 0.09 mg/m³. Three other human studies were examined as supporting evidence for the Wilhelmsson and Holmstrom (1992) study, with similar LOAEL and NOAEL values reported. The TCEQ adjusted the NOAEL Of 0.09 mg/m³ for continuous exposure (10/20 m³-day × 5/7 days) to a $NOAEL_{HEC}$ of 0.032 mg/m³. An uncertainty factor of 3 was applied to account for intraspecies variability, given that the study included some sensitive individuals. The TCEQ non-carcinogenic ReV of **11 µg/m³** was selected for the chronic effects assessment of formaldehyde. From this, formaldehyde was included in *nasal irritants* and *respiratory irritants* mixtures in the chronic inhalation assessment.

The TCEQ (2008) also has derived a cancer-based exposure limit for formaldehyde of 18 µg/m³ derived from a comprehensive analysis of three rodent tumourigenicity data sets by Schlosser et al. (2003). One of the three data sets was the Kerns et al. (1983) study upon which the US EPA RsC is based. The pooled data modelled included 482 rats exposed to 0.7, 2.0, 6.0, 10.0 or 15.0 ppm and 122 controls. $BMCL_{01}$ values were calculated for the various modelling approaches and endpoints (tumours, cell proliferation). Schlosser et al. (2003) conducted benchmark dose analysis of the data, and also applied computational flux modelling to account for differences in nasal dosimetry and a pharmacokinetic model to predict DNA cross-link

formation. The dose-response relationship in the data for tumour incidence and cell proliferation were both highly non-linear. The TCEQ selected the 95% $BMCL_{01}$ of 0.44 ppm based on cell proliferation as the point of departure for the derivation of a cancer-based ReV, as it represented the most conservative value derived from biologically-based modelling approaches. A cumulative uncertainty factor of 30 was applied to the $BMCL_{01}$ to account for intraspecies variability (10) and interspecies differences (3) due to the use of a pharmacokinetic-based biological model in the derivation of the $BMCL_{01}$. Based on the weight of evidence, eye, nasal and respiratory irritation in humans are more sensitive endpoints than cell proliferation in rats. As such, the TCEQ non-carcinogenic ReV was selected for the assessment.

The ATSDR (1999, 2009) has derived a chronic MRL of 10 µg/m³. This value is based upon histological changes in nasal mucosa in occupationally exposed workers (n = 70) in a formaldehyde and formaldehyde resins producing chemical plant; furniture factory workers (n = 100) who were exposed to particle boards and glue components; and a control group of non-exposed office workers (n = 36) (Holmstrom et al. 1989). Average employment duration time for the two groups were 10.4 years (range 1 to 36 years) for the chemical workers, and 9.0 years (range 1 to 30 years) for furniture workers. Air concentration estimates of workers' breathing zones were determined to be 0.04 to 0.4 ppm formaldehyde (median 0.24 ± 0.13 ppm) for the chemical workers, and from 0.16 to 0.4 ppm (median 0.20 ± 0.04 ppm) for the furniture workers. Nasal mucosal specimens were taken from the workers from the middle turbinate. A significant difference in the mean histological scores for the chemical workers but not for the furniture workers was observed relative to controls. Histological abnormalities observed in samples from exposed workers included: epithelial dysplasia, cilia loss, goblet cell hyperplasia, cuboidal and squamous cell metaplasia. In addition, exposed workers reported mild eye irritation in the 0.04 to 0.4 ppm (mean 0.24 ppm) range of exposures. The study LOAEL was determined by the ATSDR to be 0.24 ppm. Although the workers were only exposed 8 hours/day, 5 days a week, adjustments for continuous exposure were not made by the ATSDR based on the rationale that the effects of formaldehyde exposure are more related to concentration than to duration. A total uncertainty factor of 30 was applied for use of a LOAEL (3) and for intraspecies variation (10). This value is similar to the TCEQ value (described above) in both magnitude and toxicological basis.

The OEHHA (2008a, b) chronic REL of 9 µg/m³ is based upon the same study as the TCEQ chronic ReV (Wilhelmsson and Holmstrom 1992). The same NOAEL (0.09 mg/m³) was identified by the OEHHA as the TCEQ. However, no adjustment was made for continuous exposure, although the rationale for not doing this is not clear. An uncertainty factor of 10 was applied to the NOAEL to account for intraspecies variability, resulting in the chronic REL of 9 µg/m³.

The US EPA (2010) has derived an inhalation RsC of 0.8 µg/m³ based on an inhalation study by Kerns et al. (1983) that examined the incidence of squamous cell carcinomas in rats exposed to formaldehyde. In the Kerns et al. (1983) study, Fischer 344 rats and B6C3F1 mice were exposed to 0, 2, 5.6 or 14.3 ppm (equivalent to 0, 2.5, 7 or 17.6 mg/m³) for 6 hours/day, 5 days/week for a duration of 24 months. Five animals were sacrificed in each exposure group at 6 and 12 months, while 20 were sacrificed in each exposure group at 18 months (Kerns et al.

1983). Squamous cell carcinomas and polyploidy adenomas were seen in the nasal cavities male and female rats exposed to 14.3 ppm, and in male animals (polyploidy adenoma only) at 5.6 ppm. In the 5.6 ppm group, only one rat of each sex presented nasal carcinomas. In exposed mice, squamous cell carcinomas were seen in two males at 14.3 ppm. No significant lesions were observed. Using the linearized multistage procedure with additional risk the US EPA (2010) developed an inhalation unit risk of 1.3E-05 per µg/m³, which equates to an RsC of 0.8 µg/m³ that is associated with a one in 100,000 excess cancer risk. This value was not used in the chronic effects assessment, as the TCEQ takes into account mechanistic data and the overall scientific weight of evidence. The Kerns study also focused on higher exposure concentrations of formaldehyde, with tumours being most prevalent at the higher doses.

The OEHHA (2009) presents an inhalation unit risk estimate of 6.0E-06 per µg/m³, which is equivalent to an RsC of 2 µg/m³. This value was derived based upon the Kerns et al. (1983) study and the US EPA RsC described above.

Health Canada (2004) presents a tumorigenic concentration (TC_{05}) for formaldehyde of 9.5 mg/m³ (CEPA 2001). This TC_{05} represents the total intake associated with a 5% increase in incidence of nasal squamous tumours in rats exposed to formaldehyde for up to 24 months (Monticello et al. 1996). The TC_{05} corresponds to an RsC of 1.9 µg/m³ that is associated with an increased cancer risk of one in 100,000. This value was not used in the chronic inhalation assessment, as the TCEQ specifically accounts for mechanistic data and considers the overall weight of evidence in the derivation of its chronic limit for formaldehyde.

J1-2.8.2 Oral Exposure Limits

J1-2.8.2.1 Chronic

Table J2-19 Chronic Oral Exposure Limits for Formaldehyde

Regulatory Agency	*Type*	*Value (µg/kg bw/d)*	*Reference*
ATSDR	MRL	200	ATSDR (2009)
HEALTH CANADA	TDI	150	Health Canada (2003)
RIVM	–	–	RIVM (2001)
US EPA	RfD	200	US EPA (2010)
WHO	–	–	WHO (2009)[(a)]

[(a)] There is a historic WHO drinking water quality guideline of 0.9 mg/L, but documentation supporting its basis is not available, and a TDI or equivalent is not presented in the existing WHO documentation. In addition, the WHO is re-evaluating formaldehyde in relation to drinking water.
– = Not available

The ATSDR (1999, 2009) and the US EPA (2010) have both derived chronic oral exposure limits of 200 µg/kg bw/day for formaldehyde based on the same study by Til et al. (1989). Male and female Wistar rats were administered formaldehyde in drinking water at mean doses of 0, 1.1, 15 or 82 mg/kg day (males) and 0, 1.8, 21 or 109 mg/kg bw/day (females). About 10 rats/sex/dose were sacrificed and evaluated after 12 to 18 months of exposure, and the remaining rats were evaluated at 24 months. Reduced body weights were observed in males at week 1, and in females from week 24 through the rest of the exposure period. In male and

female high-dose rats, significant histopathological changes in the gastrointestinal tract were observed after 12 to 24 months of exposure. Necrotic changes in the kidneys of high-dose males and females also were observed. A NOAEL of 15 mg/kg bw/day was identified by both the ATSDR and US EPA based upon reduced body weights, and histopathological changes of the gastrointestinal tract and kidneys. Both agencies applied a cumulative uncertainty factor of 100 to account for interspecies differences (10) and intraspecies variability (10). The chronic oral limit of **200 µg/kg bw/d** was selected for use in the multiple pathway assessment of formaldehyde. Formaldehyde was added to the *renal toxicants* mixture, as the basis of the limit was kidney effects. Although the limit was also based on changes in the gastrointestinal tract, no other COPC in the chronic oral effects assessment had this endpoint, therefore a gastrointestinal tract toxicant mixture was not required.

The Health Canada Drinking Water Quality Bureau (Health Canada 2003) has derived an oral TDI of 150 µg/kg bw/d, also based upon the Til et al. (1989) study (described above for the ATSDR and US EPA values). A NOAEL of 15 mg/kg bw/d was identified for pathological changes in the stomach and renal papillary necrosis in male rats. A cumulative uncertainty factor of 100 was applied to the NOAEL account for interspecies differences (10) and intraspecies variability (10). The Health Canada TDI is essentially the same as the ATSDR value – numerical rounding appears to be the only difference.

J1-2.8.3 References Formaldehyde

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J1-2.9 Hexane

J1-2.9.1 Inhalation Exposure Limits

J1-2.9.1.1 Acute

Table J2-20 Acute Inhalation Exposure Limits for Hexane

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV 1-hour	AAQO 24-hour AAQO	21,000 7,000	AENV (2009)
ATSDR –		–	ATSDR (2009)
OEHHA –		–	OEHHA (2008)
OMOE	24-hour standard	7,500	OMOE (2008)
TCEQ			TCEQ (2007)
WHO –		–	WHO (2000)

– = Not available

The OMOE (2005, 2008) provides a 24-hour standard of 7,500 µg/m³ for n-hexane and n-hexane isomers. This standard was developed from a NOAEL of 58 ppm (204 mg/m³) for polyneuropathy in humans (Sanagi et al. 1980). Workers were exposed to a low concentration of n-hexane and acetone in a tungsten carbide alloys facility for an average of 6.2 years. Significant decreases in mean motor nerve conduction velocities and slowed residual latency of motor conduction of lower extremities were observed. This value was not given further consideration, as it is based upon a chronic exposure duration, which is not relevant to the acute effects assessment.

Alberta Environment (2009) provides a 24-hour AAQO of 7,000 µg/m³ for n-hexane based on the California OEHHA value. The 1-hour AAQO of 21,000 µg/m³ was derived from the 24-hour objective (AENV 2009). The California OEHHA developed a chronic REL of 7,000 µg/m³ based on a NOAEL of 100 ppm for nervous system effects in mice (AENV 2009). As this value is based upon chronic exposure data, it was not used in the acute assessment.

Due to the lack of a defensible acute exposure limit, n-hexane was not evaluated on an acute basis.

J1-2.9.1.2 Chronic

Table J2-21 Chronic Inhalation Exposure Limits for Hexane

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	chronic MRL	2,100	ATSDR (2009)
HEALTH CANADA	–	–	Health Canada (2004a,b)
OEHHA	chronic REL	7,000	OEHHA (2008)
RIVM	–	–	RIVM (2001)
TCEQ	chronic ReV	670	TCEQ (2007)
US EPA	RfC	700	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The TCEQ (2007) has derived a chronic ReV of 670 µg/m³ based upon human occupational data. In the key study by Chang et al. (1993), a group of workers in a printing factory were evaluated for potential neurological effects. Workers were exposed to hexane concentrations ranging from 80 to 210 ppm, with an average exposure concentration of 132 ppm. Workers were exposed for 12 hours/day, 6 days/week for a mean duration of 2.6 years. Approximately 40% of the workers evaluated demonstrated subclinical neuropathy. In addition, reduced sensory and action potentials, motor nerve conduction velocity and increased distal latency were reported for exposed workers. The average concentration of 132 ppm was identified as a LOAEL by the TCEQ. This LOAEL was adjusted by the TCEQ to account for continuous exposure (10/20 m³-day × 6/7 days), resulting in a $LOAEL_{HEC}$ of 57 ppm. A cumulative uncertainty factor of 300 was applied to account for the use of a LOAEL (10), intraspecies variability (10), and database uncertainties (3). The resulting ReV of **670 µg/m³** was selected for use in the chronic effects assessment. As the toxicological endpoint involved neurological effects, n-hexane was included in the chronic inhalation *neurotoxicants* mixture.

The US EPA (2010) developed a chronic RfC of 700 µg/m³ for neurotoxicity. This RfC is based on a benchmark concentration level (BMCL) of 430 mg/m³ for peripheral neuropathy (decreased mean conduction velocity at 12 weeks) in a rat subchronic inhalation study. Male Wistar rats were exposed to 0, 500, 1,200, or 3,000 ppm (equivalent to 0, 1,762, 4,230 or 10,574 mg/m³) of n-hexane for 12 hours/day, 7 days/week for a duration of 16 weeks. Statistically significant decreases in weight gain, and mean conduction velocity accompanied by neural demyelination and remyelination were observed in the middle and high dose groups. A study NOAEL of 50 ppm (1,762 mg/m³) was identified by the US EPA. The incidence of decreased mean conduction velocity was selected as the endpoint of interest, and benchmark dose modeling was conducted. From the modeling, a BMC of 550 mg/m³ and a BMCL of 430 mg/m³ were identified. The BMCL was adjusted from intermittent to continuous exposure (12/24 hours) to a concentration of 215 mg/m³. The blood:gas (air) partition coefficient ($H_{b/g}$) value for n-hexane in humans is 0.8, whereas a value of 2.29 has been reported in rats (US EPA 2010). The $BMCL_{HEC}$ is equal to 215 mg/m³. The US EPA (2010) applied a cumulative uncertainty factor of 300 to the $BMCL_{HEC}$ to account for interspecies variability (3), intraspecies variability (10),

extrapolation to chronic exposure from data in a less-than lifetime study (3), and database deficiencies (3, due to the limited reproductive and developmental information available for n-hexane). The US EPA RfC of 700 µg/m³ was not selected as a human-based value that is similar in magnitude is available.

The ATSDR (1999, 2009) has derived a chronic MRL of 2,100 µg/m³ (0.6 ppm) based upon the incidence of neurological effects in exposed workers. A group of 14 exposed workers were compared with age-matched unexposed workers. The 8-hour time-weighted average exposure concentration of n-hexane was determined to be about 58 ppm (204,000 µg/m³). Workers also were co-exposed to acetone. Exposure durations were found to range from 1 to 12 years, with the average duration being about 6.2 years. A significant trend in decreased muscle strength was observed in exposed workers. Significantly decreased nerve conduction velocities and increased residual latency of motor nerve conduction were observed in exposed workers. The LOAEL was determined to be 58 ppm. No adjustment for continuous exposure was made, as the ATSDR states that steady-state concentrations of n-hexane in blood are reached after 100 minutes of exposure. A cumulative uncertainty factor of 100 was applied to the LOAEL to account for the use of a LOAEL instead of a NOAEL (10) and intraspecies variability (10). This value was not selected, as the influence that acetone co-exposure may have had on the exposed workers is not clear.

The OEHHA (2000, 2008) has established a chronic REL of 7,000 µg/m³ based upon peripheral neuropathy in mice. In the key study, male SM-A mice were exposed to 0, 100, 250, 500, 1,000 or 2,000 ppm commercial hexane (approximately 67.5% n-hexane) continuously, 6 days/week for a duration of 1 year. A significant, dose-related increase in muscle neurophysiology and dose-related abnormalities in posture and muscle atrophy were observed at concentrations 250 ppm and above. The study NOAEL was identified as 100 ppm for commercial hexane, and 68 ppm for n-hexane (based upon the mixture containing about 67.5% n-hexane, and the exposure frequency of 6 days/week). A cumulative uncertainty factor of 30 was applied to this value to account for interspecies differences (3) and intraspecies variability (10). This value was not used in the chronic effects assessment, as the evaluation conducted by the US EPA is more robust due to the use of a BMCL.

J1-2.9.2 Oral Exposure Limits

Hexane did not meet the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required.

J1-2.9.3 References Hexane

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J1-2.10 Naphthalene

J1-2.10.1 Inhalation Exposure Limits

J1-2.10.1.1 Acute

Table J2-22 Acute Inhalation Exposure Limits for Naphthalene

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
OEHHA	–	–	OEHHA (2008)
OMOE	24-hour standard	22.5	OMOE (2008)
TCEQ	–	–	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The OMOE (2008) presents air quality standard for naphthalene, although no supporting documentation is available. Acute exposure limits were not available from the other agencies.

The ACGIH (2009) recommends a STEL of 15 ppm (79 mg/m³) based on eye irritation as a result of occupational exposure to naphthalene. The STEL equates to a 15-minute air concentration that should not be exceeded at any time during a workday. The 15-minute STEL can be adjusted to an equivalent 1-hour concentration using a modified Haber's Law.

$$C_{ADJ}^{n} \times T_{ADJ} = C^{n} \times T$$

$$C^{1} \times 60 \text{ minutes} = (79\ \mu g/m^3)^{1} \times 15 \text{ minutes}$$

Where:

C_{ADJ} = duration-adjusted concentration

T_{ADJ} = desired time of exposure (60-minutes)

C = concentration of exposure (79 µg/m³)

T = time of exposure (15-minutes)

n = chemical-specific modification factor designed to account for the toxicity of a chemical being concentration and/or duration dependent. The OEHHA recommends using a default n value of 1 in the adjustment for less than 1-hour exposure.

Based on the above conversion factor, the STEL was adjusted to a concentration of 20 mg/m³. An uncertainty factor of 10 was applied to the duration adjusted STEL to account for intraspecies variability. The adjusted STEL of **2,000 µg/m³** was used as a 1-hour exposure limit in the acute effects assessment for the aromatic C_9-C_{16} group, which used naphthalene as the

surrogate for the group. As the toxicological basis of this value is eye irritation, the aromatic C_9-C_{16} group was included in the acute *eye irritants* mixture.

The OMOE (2008) has developed an AAQC for naphthalene of 22.5 µg/m³ based on a 24-hour averaging period. Although the 24-hour criterion is based on health considerations, the specific basis of its derivation remains unknown as no supporting documentation is available.

J1-2.10.1.2 Chronic

Table J2-23 Chronic Inhalation Exposure Limits for Naphthalene

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	chronic MRL	3.7	ATSDR (2009)
HEALTH CANADA	–	–	Health Canada (2004a,b)
OEHHA	chronic REL	9	OEHHA (2008)
	RsC	0.3	OEHHA (2009)
RIVM	–	–	RIVM (2001)
TCEQ	–	–	TCEQ (2009)
US EPA	RfC	3	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The US EPA (2009) has derived a chronic inhalation RfC for naphthalene of 3 µg/m³. This RfC was estimated from a chronic inhalation mouse study that reported a duration-adjusted $LOAEL_{HEC}$ of 9.3 mg/m³ based on hyperplasia and metaplasia in respiratory and olfactory epithelium (NTP 1992 – described below under OEHHA). The US EPA (2009) incorporated a cumulative uncertainty factor of 3,000 to account for interspecies variability (10), sensitive human individuals in the population (10), extrapolation from a NOAEL to a LOAEL (10), and for database uncertainties (3). Database uncertainties included the lack of a two generation reproductive toxicity study and chronic inhalation data for other animal species. The US EPA RfC of **3 µg/m³** was selected as the chronic inhalation limit for naphthalene over the OEHHA value, primarily as it is the more conservative value. This is of importance in light of the high incidence of adverse effects at the lowest dose level in the NTP (1992) study (see below). As the toxicological basis of this value includes nasal and respiratory lesions, naphthalene was included in the chronic inhalation *nasal irritants* and *respiratory irritants* mixtures.

The OEHHA (2000, 2008) has derived a chronic REL of 9 µg/m³ [1] (0.002 ppm) based upon a 2-year NTP (1992) bioassay. Male and female B6C3F1 mice were exposed to 0, 10, or 30 ppm for 6 hours/day, 5 days/week for a duration of 104 weeks. No significant increase in tumour incidence was observed in males, but the incidence of pulmonary alveolar/bronchiolar adenomas was increased in females exposed to 30 ppm relative to controls. Non-neoplastic lesions were observed in the nasal passages and lungs of both male and female mice, namely lesions indicative of an inflammatory response. Both males and females in the 10 and 30 ppm groups had exposure-related increases in alveolar histiocyte and lymphocyte infiltration, alveolar hyperplasia, interstitial fibrosis, and in more advanced lesions – granulomatous inflammation.

Bronchial submucousal glands were also observed to be distended when the above lesions were present. Mild lesions in the nasal passages of exposed mice were also observed. The OEHHA (2000) determined that the study LOAEL was 10 ppm, but note that almost all animals (>96%) exposed to this concentration exhibited some type of an adverse effect, which limits the reliance of this study with respect to being the basis of a health-protective value. The LOAEL of 10 ppm was adjusted for continuous exposure to 1.8 ppm (6/24 hours, 5/7 days). To account for uncertainties, a cumulative uncertainty factor of 1,000 was applied to the adjusted LOAEL. This factor took into account: the use of a LOAEL (10), interspecies differences (10), and intraspecies variability (10).

The ATSDR (2005, 2009) chronic MRL of 3.7 µg/m³ (0.0007 ppm) is based on the same NTP study used in the derivation of the US EPA and OEHHA values, as well as a more recent study in rats (NTP 2000) where male and female F344 rats were exposed to 0, 10, 30 or 60 ppm for 6 hours/day, 5 days/week for a duration of 105 weeks. A LOAEL of 10 ppm was identified for the incidence of non-cancerous lesions in olfactory epithelium in both rats and mice (from NTP 2000 and NTP 1992, respectively). This LOAEL was adjusted for continuous exposure (6/24 hours/day × 5/7 days/week) to 1.8 ppm (or 9,400 µg/m³). This value was further adjusted to a $LOAEL_{HEC}$ of 0.2 ppm (1,000 µg/m³) by multiplying the $LOAEL_{ADJ}$ by an RGDR of 0.132 (calculated by the ATSDR). The $LOAEL_{HEC}$ was divided by a cumulative uncertainty factor of 300 to account for the use of a LOAEL (10), interspecies differences (3, due to the calculation of a HEC), and intraspecies variability (10).

In addition, the OEHHA (2009) presents a cancer unit risk value of 3.4E-05 per µg/m³, which is equivalent to an RsC of 0.3 µg/m³. This value is based upon two bioassays by the NTP (1992, 2000). The details of the NTP (1992) study are provided above in the summary for the OEHHA value). In the NTP (2000) study, male and female F344 rats were exposed to 0, 10, 30 or 60 ppm for 6 hours/day, 5 days/week for 105 weeks. Increased incidences of respiratory epithelial adenoma and olfactory epithelial blastoma were observed in male and female rats. A positive dose-response relationship was observed in male rats only for the respiratory epithelial adenomas, and the incidence of these tumours was statistically significant at all exposure concentrations in males. The incidence of these tumours was not statistically significant or was of marginal significance in females. The olfactory epithelial neuroblastomas were significantly increased in all exposure levels in females, and in the 30 and 60 ppm groups for males. The exposure concentrations were adjusted for continuous exposure (6/24 hours × 5/7 days). Dose scaling based on body weight and breathing rates was conducted. In addition, pharmacokinetic modeling was conducted for both rats and mice and all modeling runs confirmed that the dose-response relationship was linear. A linearized multistage model and a benchmark dose model were both applied to the data set, and similar ranges of unit risk values were calculated. The OEHHA (2009) notes that no naphthalene related tumours have been observed in humans. Given that the US EPA and other agencies have not derived cancer-based values, it suggests that the weight of evidence at the current time in support of human carcinogenicity in association with naphthalene exposure is limited.

J1-2.10.2 Oral Exposure Limits

Naphthalene did not meet the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required.

Although naphthalene was not included in the multiple pathway assessment as an individual COPC, it was included as part of the aromatic C_9-C_{16} group.

J1-2.10.3 References Naphthalene

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J1-2.11 Nitrogen Dioxide

Chemicals of potential concern that are regulated at the federal government level in the form of either a NAAQOs or as a CWS were not subjected to the typical screening process for exposure limits. Instead, the AAQOs adopted by AENV (2009) from Health Canada were given priority. Nitrogen dioxide is one of these chemicals.

J1-2.11.1 Inhalation Exposure Limits

J1-2.11.1.1 Acute

The exposure limits used for the acute effects assessment of nitrogen dioxide were based on AENV's AAQOs (AENV 2009). These include a 1-hour objective of 400 µg/m³ and a 24-hour objective of 200 µg/m³. These AAQOs were adopted from Health Canada's National Ambient Air Quality Objectives for nitrogen dioxide. The NAAQOs are developed in three tiers: maximum desirable, acceptable and tolerable objectives. The Alberta AAQOs are based on the maximum acceptable levels, as maximum desirable NAAQOs (i.e., the lowest objectives) have not been developed for nitrogen dioxide on an acute-basis. These NAAQOs are health based and rely on controlled studies of the most sensitive population (i.e., asthmatics) to nitrogen dioxide. Given that the NAAQOs are federally regulated, precedence was given to the AENV/NAAQO guidelines for nitrogen dioxide over other available values. Nitrogen dioxide was included in the acute inhalation *respiratory irritants* mixture.

Using the above objectives and guidelines, the acute assessment for nitrogen dioxide was completed on both a 1-hour and 24-hour basis.

J1-2.11.1.2 Chronic

The chronic exposure limit used for the assessment of nitrogen dioxide concentrations in air was the AENV AAQO of 60 µg/m³ (AENV 2009). This guideline was adopted from Health Canada's NAAQO for nitrogen dioxide based on an annual averaging time. The NAAQOs are developed in three tiers: maximum desirable, acceptable and tolerable objectives. The maximum desirable level (i.e., the lowest objective) was adopted as the annual objective in Alberta. This objective is health-based and relies on controlled studies of the most sensitive population (i.e., asthmatics) to nitrogen dioxide. Nitrogen dioxide was included in the chronic inhalation *respiratory irritants* mixture.

J1-2.11.2 Oral Exposure Limits

J1-2.11.2.1 Chronic

Nitrogen dioxide is a gaseous criteria air contaminant and acts at the point of contact (i.e., respiratory system). As such, it was not evaluated in the multiple pathway assessment.

J1-2.11.3 References for Nitrogen dioxide

AENV (Alberta Environment). 2009. Alberta Ambient Air Quality Objectives. Facts at your Fingertips. April 2009. Available at: http://environment.gov.ab.ca/info/library/5726.pdf Accessed May 2009.

J1-2.12 Particulate Matter ($PM_{2.5}$)

Chemicals of potential concern that are regulated at the federal government level in the form of either a NAAQOs or as a CWS were not subjected to the typical screening process for exposure limits. Instead, the AAQOs adopted by AENV (2009) from Health Canada were given priority. Particulate matter is one of these chemicals.

J1-2.12.1 Inhalation Exposure Limits

J1-2.12.1.1 Acute

The Scientific Assessment Document (Part 1) of The National Ambient Air Quality Objectives for Particulate Matter prepared by the CEPA/FPAC Working Group on Air Quality Objectives and Guidelines concluded that both the mortality and hospitalization studies support the identification of 15 µg/m³ averaged over 24 hours as the reference level for $PM_{2.5}$ (CEPA/FPAC 1999). The reference level was considered an estimate of the lowest ambient particulate matter level at which statistically significant increases in health responses can be detected based on data available up to 1996. It was derived based on the average 24-hour concentrations measured in the cities where these effects were found. The CEPA/FPAC (1999) Working Group states that reference levels should not be interpreted as thresholds of effects, or levels at which impacts do not occur. They are defined under Canada's National Ambient Air Quality Objectives as levels above which there are demonstrated effects on human health and/or the environment (CEPA/FPAC 1999).

A Canada-Wide Standard (CWS) of 30 µg/m³ $PM_{2.5}$ averaged over 24 hours was developed by the CCME under the Canadian Environmental Protection Act (CEPA) (CCME 2000). Under this CWS, the government is committed to reduce levels of $PM_{2.5}$ significantly by 2010. Achievement of this standard is based on the 24-hour 98th percentile of the ambient measurement annually, measured over three consecutive years. The CWS is considered to be an important step towards the long-term goal of reducing the health risks of $PM_{2.5}$. It represents a balance between achieving the best health and environmental protection possible and the feasibility and costs of reducing pollutant emissions that contribute to $PM_{2.5}$ in ambient air. The CWS of **30 µg/m³** was used in the acute assessment of $PM_{2.5}$.

J1-2.12.1.2 Chronic

The California Air Resources Board (CARB) has identified an air quality annual average standard for $PM_{2.5}$ of **12 µg/m³** (CARB 2002a,b). This recommended arithmetic mean value was "based on a growing body of epidemiological and toxicological studies showing significant toxicity (resulting in mortality and morbidity) related to exposure to fine particles". Similar to the CEPA/FPAC reference level, the value was derived mainly based on the average 24-hour concentrations in cities where statistically significant increases in health responses were detected. The CARB Staff report recommendation was adopted by the State of California as an ambient air quality standard in June of 2002. This value was selected, as it falls within the range of annual criteria recommended by the WHO and US EPA.

In 1997, the US EPA first set National Ambient Air Quality Standards (NAAQS) for fine particles. Two primary $PM_{2.5}$ standards were set: an annual standard of 15 µg/m³ to protect against health effects caused by exposures ranging from days to years and a 24-hour standard of 65 µg/m³ to provide additional protection on days with high peak $PM_{2.5}$ concentrations. In September 2006, the US EPA issued a new suite of standards to better protect public health from particle pollution. The revised NAAQS for $PM_{2.5}$ reduced the 24-hour standard from 65 to 35 µg/m³ and retained the annual standard of 15 µg/m³ (US EPA 2006). The 24-hour standard is based on the 98th percentile annual measurement, averaged over 3 years, while the annual standard is met when the 3-year average of the annual average $PM_{2.5}$ concentration is less than or equal to 15 µg/m³. The US EPA (2006) also retained the existing 24-hour NAAQS for PM_{10} of 150 µg/m³ and revoked the annual PM_{10} standard of 50 µg/m³.

The WHO recommends an annual average of 10 µg/m³ and a daily 99th percentile of 25 µg/m³ for the protection of public health. The WHO (2005) suggests the annual average should take precedence over the daily guideline because at low levels there is less concern for episodic excursions. The annual average guideline is based on long-term exposure studies using the American Cancer Society data (Pope et al. 2002) and Harvard Six-Cities data (Dockery et al. 1993). The studies reported a robust association between PM exposure and mortality. Historical mean $PM_{2.5}$ concentrations across cities in these two studies were 18 and 20 µg/m³, respectively but average concentrations in individual cities were as low 11 µg/m³ over the period of study. An annual mean guideline concentration of 10 µg/m³ was therefore noted to be below the mean for most likely effects (WHO 2005). However, both the WHO (2005) and the US EPA (2005) note that statistical uncertainties in the risk estimates become apparent at concentrations of about 13 µg/m³, below which confidence bounds significantly widen, indicating the possibility

of an effects threshold. In their staff paper, the US EPA (2005) noted that an annual standard of 12 µg/m³ would be precautionary, but a standard set below the range of 12 to 15 µg/m³ would be highly precautionary, "giving little weight to the remaining uncertainties in the broader body of evidence, including other long-term exposure studies that provide far more inconsistent results".

J1-2.12.2 Oral Exposure Limits

J1-2.12.2.1 Chronic

Particulate matter was not evaluated in the multiple pathway assessment.

J1-2.12.3 References for Particulate Matter

CARB (California Air Resources Board). 2002a. California Ambient Air Quality Standards (CAAQS). Particulate Matter (PM_{10} and $PM_{2.5}$). Available at: http://www.arb.ca.gov/research/aaqs/caaqs/caaqs.htm. Accessed May 2009.

CARB (California Air Resources Board). 2002b. Staff Report: Public Hearing to Consider Amendments to the Ambient Air Quality Standards for Particulate Matter and Sulfates. California Environmental Protection Agency, Air Resources Board. May, 2002.

CCME (Canadian Council of Ministers of the Environment). 2000. Canada-Wide Standards for Particulate Matter (PM) and Ozone. Accepted November 29, 1999, for endorsement in May 2000.

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J1-2.13 Pyrene

J1-2.13.1 Inhalation Exposure Limits

J1-2.13.1.1 Acute

Table J2-24 Acute Inhalation Exposure Limits for Pyrene

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
OEHHA	–	–	OEHHA (2008)
OMOE	–	–	OMOE (2008)
TCEQ	–	–	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

No acute inhalation exposure limits were available for pyrene. As a result, pyrene was not evaluated on an acute basis.

J1-2.13.1.2 Chronic

Table J2-25 Chronic Inhalation Exposure Limits for Pyrene

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	–	–	ATSDR (2009)
HEALTH CANADA	–	–	Health Canada (2004a,b)
OEHHA	–	–	OEHHA (2008)
RIVM	–	–	RIVM (2001)
TCEQ	–	–	TCEQ (2009)
US EPA	–	–	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

No chronic inhalation exposure limits were available for pyrene. As a result, pyrene was not evaluated on a chronic inhalation basis.

J1-2.13.2 Oral Exposure Limits

J1-2.13.2.1 Chronic

Table J2-26 Chronic Oral Exposure Limits for Pyrene

Regulatory Agency	*Type*	*Value (µg/kg bw/d)*	*Reference*
ATSDR	–	–	ATSDR (2009)
HEALTH CANADA	–	–	Health Canada (2004a,b)
OEHHA	–	–	OEHHA (2008)
RIVM	CR_{oral}	50	RIVM (2001)
US EPA	RfD	30	US EPA (2010)

– = Not available

The US EPA (2010) has derived a chronic RfD of 30 µg/kg bw/d for pyrene based on kidney effects in mice. Male and female CD-1 mice (20 per sex per dose) were exposed to 0, 75, 125, or 250 mg/kg bw/d pyrene in corn oil via oral gavage for 13 weeks. Mild kidney lesions were observed in all dose groups in both sexes, primarily renal tubular degeneration sometimes appearing with interstitial lymphocytic infiltrates or fibrosis. Relative and absolute kidney weights were reduced in the 125 and 250 mg/kg bw/d dose groups. The lowest dose group (75 mg/kg bw/d) was determined to be the NOAEL, while the 125 mg/kg bw/d was considered the LOAEL. A cumulative uncertainty factor of 3,000 was applied to the NOAEL to account for interspecies differences (10), intraspecies variability (10), the use of a subchronic study (10), and lack of data in another species and reproductive and developmental studies (3). The resulting oral RfD of **30 µg/kg bw/d** was used in this assessment. As the toxicological basis of this value is kidney effects, pyrene was included in the chronic oral *renal toxicants* mixture.

The RIVM presents a CR_{oral} of 500 µg/kg bw/d for pyrene, which is associated with a lifetime excess cancer risk of one in 10,000. Converted to a risk level of one in 100,000, this value is 50 µg/kg bw/d. As limited information regarding this value was provided in the supporting documentation, it was not used in the assessment.

J1-2.13.3 References Pyrene

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ATSDR (Agency for Toxic Substances and Disease Registry). 2009. Minimal Risk Levels (MRLs) for Hazardous Substances. December 2008. Atlanta, GA: US Department of Health and Human Services, Public Health Service. Available at: http://www.atsdr.cdc.gov/mrls Accessed March 2010.

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OEHHA (California Office of Environmental Health Hazard Assessment). 2008. Acute, 8-hour and Chronic Reference Exposure Level (REL) Summary. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Sacramento, CA. Available at: http://www.oehha.ca.gov/air/allrels.html. Accessed August 2009.

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J1-2.14 Sulphur Dioxide

Chemicals of potential concern that are regulated at the federal government level in the form of either a NAAQO or as a CWS were not subjected to the typical screening process for exposure limits. Instead, the AAQOs adopted by AENV (2009) from Health Canada were given priority. Sulphur dioxide is one of these chemicals.

J1-2.14.1 Inhalation Exposure Limits

J1-2.14.1.1 Acute

The acute exposure limit used for the assessment of sulphur dioxide concentrations in air was Alberta's 1-hour ambient air quality objective (AAQO) of **450 µg/m³**. This AAQO was adopted from Health Canada's NAAQOs, which recommends maximum desirable, acceptable and tolerable objectives for sulphur dioxide. This guideline is health-based and is based on controlled studies in sensitive populations (i.e., asthmatics). As the AAQO is based on a federal NAAQO, this value was given precedence over other available limits. As the assumed toxicological basis of this value is respiratory irritation, sulphur dioxide was included in the acute inhalation respiratory irritants mixture.

Sulphur dioxide also was assessed using a 10-minute air quality guideline of 500 µg/m³ developed by the World Health Organization (WHO 2000). This guideline is based on changes in lung function in asthmatics (WHO 2000). The 10-minute exposure period is relevant, given

that the effects of sulphur dioxide exposure in humans primarily involved irritation at the point of contact (irritation) and 'peak' in severity within the first moments of exposure (WHO 2000).

Alberta Environment (2009) also provides a 24-hour AAQO of **150 µg/m³** for sulphur dioxide based on vegetation effects. This objective was not used in the HHRA as it is not health-based and it is without supporting documentation.

The chronic exposure limit used for the assessment of sulphur dioxide concentrations in air was based on Alberta's annual AAQO of **30 µg/m³** (AENV 2009). This AAQO was adopted from the Health Canada annual NAAQO, which includes maximum desirable, acceptable and tolerable objectives for sulphur dioxide. As this value is based on a federal objective, it was given precedence over all other sources. Sulphur dioxide was included in the chronic inhalation *respiratory irritants* mixture.

J1-2.14.2 Oral Exposure Limits

J1-2.14.2.1 Chronic

Sulphur dioxide is a gaseous criteria air contaminant which acts on the point of contact (i.e., respiratory system). As such, it was not evaluated in the multiple pathway assessment.

J1-2.14.3 References for Sulphur Dioxide

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J1-2.15 Toluene

J1-2.15.1 Inhalation Exposure Limits

J1-2.15.1.1 Acute

Table J2-27 Acute Inhalation Exposure Limits for Toluene

Regulatory Agency	*Averaging Time*	*Value (µg/m³)*	*Reference*
AENV	1-hour AAQO	1,880	AENV (2009)
	24-hour AAQO	400	AENV (2009)
ATSDR	acute MRL	3,800	ATSDR (2009)
OEHHA	1-hour REL	37,000	OEHHA (2008)
OMOE	–	–	OMOE (2008)
TCEQ	acute ReV	15,000	TCEQ (2008)
US EPA	–	–	US EPA (2010)
WHO	1-week AQG	260	WHO (2000)

− = Not available

The ATSDR (2000, 2009) has derived an acute MRL of 1 ppm (3,800 µg/m³) based on neurological effects. A NOAEL of 40 ppm (150 mg/m³) was reported based on a study by Andersen et al. (1983), where 16 healthy subjects with no previous exposure to organic solvents were exposed to toluene for 6 hours/day over 4 consecutive days. The ATSDR (2000) adjusted the NOAEL for intermittent exposure (6/24 hours × 4/7 days), and applied an uncertainty factor of 10 to account for intraspecies variability (ATSDR 2000).

The same key study was selected in the TCEQ (2008) and OEHHA (1999) assessments. The variation between the ATSDR, TCEQ and OEHHA exposure limits arises from the different duration adjustment applied. The TCEQ (2008) elected not to adjust the exposure duration based upon a weight of evidence that suggests that concentration rather than duration is the primary determinant of the effects of toluene. The TCEQ (2008) applied the same uncertainty factor of 10 for intraspecies variability as was applied by the ATSDR to the NOAEL of 40 ppm (150 mg/m³). The result is an acute ReV of 15,000 µg/m³.

The OEHHA (1999, 2008) converted the 6-hour exposure duration to a 1-hour REL of 98 ppm (370 mg/m³) based on a modified Haber's Law, and applied an uncertainty factor of 10 for intraspecies variability, resulting in a 1-hour REL of 37,000 µg/m³.

The ATSDR, TCEQ and OEHHA share the opinion that a NOAEL of 150 mg/m³ is appropriate for short-term inhalation of toluene and that an uncertainty factor of 10 is sufficiently protective of the general population. The TCEQ acute ReV of **15,000 µg/m³** was used as a 1-hour exposure limit in the acute effects assessment of toluene, as it represents a conservative value that takes into account the short-term, concentration-related effects of toluene. As the toxicological basis of this value includes neurological effects, toluene was included in the acute inhalation *neurotoxicants* mixture.

Alberta Environment (2009) has established a 1-hour AAQO of 1,880 µg/m³, which was adopted from the TCEQ. In turn, the TCEQ ESL was based on the ACGIH TLV-TWA of 50 ppm (188 mg/m³) for altered CNS performance (TCEQ 2008; ACGIH 1991, 2009). Alberta Environment adjusted the TLV-TWA by applying a cumulative uncertainty factor of 100, although the rationale behind the uncertainty factor is not clear. As well, TLV-TWAs are developed to be protective of a worker repeatedly exposed during an 8-hour workday and a 40-hour workweek. Given that the TLV-TWA is intended to be protective of longer-term exposures, the 1-hour AAQO was not used in this assessment. The 24-hour AAQO of 400 µg/m³ was adopted from the Michigan Department of Environmental Quality and the Washington Department of Ecology (AENV 2004, 2009). These regulatory agencies based their 24-hour guidelines on the US EPA chronic inhalation RfC of 400 µg/m³ (AENV 2004). The US EPA (2010) RfC has since been revised to an inhalation RfC of 5,000 µg/m³ for neurological effects. As these values are based on longer-term exposure data, they were not considered further in this assessment.

The WHO (2000) provides an AQG of 260 µg/m³ based on a 1-week averaging time. A LOAEL of 332 mg/m³ (88 ppm) was identified for CNS effects from occupational studies. The LOAEL

was adjusted for continuous exposure (8/24 hours × 5/7 days) to a concentration of 79 mg/m³. The WHO (2000) applied a cumulative uncertainty factor of 300 to the duration-adjusted LOAEL to account for intraspecies variability (10), use of a LOAEL (10), and for potential effects on the developing CNS (3). This guideline was not used in the short-term assessment of toluene as the ATSDR (2008), TCEQ (2008), and OEHHA (2008) each provide acute exposure limits based on more recent reviews that identified a NOAEL for toluene.

J1-2.15.1.2 Chronic

Table J2-28 Chronic Inhalation Exposure Limits for Toluene

Regulatory Agency	*Type*	*Value (µg/m³)*	*Reference*
AENV	–	–	AENV (2009)
ATSDR	chronic MRL	300	ATSDR (2009)
HEALTH CANADA	TC	3,800	Health Canada (2004)
OEHHA	chronic REL	300	OEHHA (2008)
RIVM	TCA	400	RIVM (2001)
TCEQ	chronic ReV	4,100	TCEQ (2008)
US EPA	RfC	5,000	US EPA (2010)
WHO	–	–	WHO (2000)

– = Not available

The US EPA (2010) has derived an inhalation RfC based upon the findings of 10 human studies, each of which examined the neurological effects in occupationally exposed workers. These studies were all more recent than the studies used by Health Canada and the ATSDR. An average NOAEL of 34 ppm (128 mg/m³) was identified from the meta-analysis. This NOAEL was adjusted for the differences in breathing rates between workers and members of the public and the reduced weekly exposure time (US EPA 2010):

$$NOAEL_{ADJ} = NOAEL \times \frac{MV_{ho}}{MV_h} \times \frac{Exp_{ho}}{Exp_h}$$

Where:

$NOAEL_{ADJ}$ = no-observable-adverse-effects level in the human population from continuous exposure to toluene (mg/m³)

NOAEL = no-observable-adverse-effects level for discontinuous exposure in an occupational setting (128 mg/m³)

MV_{ho} = amount of air used by a worker during an 8-hour work period (10 m³-d)

MV_h = amount of air used by an individual in the general population during a day (20 m³-d)

Exp_{ho} = days per week a worker is exposed (5 days)

Exp_h = days per week an individual in the general population is exposed (7 days)

The US EPA (2010) also applied an uncertainty factor of 10 to the $NOAEL_{ADJ}$ to account for human variability. The US EPA RfC of **5,000 µg/m³** represents the most recent analysis of the available scientific literature and therefore was used in the current assessment. As the toxicological basis of this value includes neurological effects, toluene was included in the chronic inhalation *neurotoxicants* mixture.

The ATSDR (2000, 2009) has derived a chronic inhalation MRL of 0.08 ppm (300 µg/m³) based on colour vision impairment in workers exposed to toluene. Three groups of Croatian workers were examined through interviews, medical examinations and colour vision testing (Zavalic et al. 1998). A LOAEL of 35 ppm (130 mg/m³) was determined for alcohol- and age-adjusted colour vision impairment. The LOAEL was adjusted for intermittent exposure (8/24 hours × 5/7 days) to a concentration of 8 ppm (30 mg/m³). The ATSDR (2000) applied a cumulative uncertainty factor of 100 to the duration-adjusted LOAEL to account for intraspecies variability (10) and the use of a LOAEL (10). This MRL was not used as the chronic exposure limit for toluene as it was developed from a LOAEL, as opposed to the NOAEL used in the US EPA derivation.

Health Canada (2004) established its chronic TC of 3,800 µg/m³ on the same lowest reported NOAEL of 150 mg/m³ (40 ppm) for neurological effects and respiratory irritation in human volunteers as was used by the ATSDR to derive the acute MRL (Andersen et al. 1983; CEPA 1992). The study NOAEL was adjusted from 6-hour daily dosing to continuous exposure and an uncertainty factor of 10 was applied to account for intraspecies variability.

The OEHHA (2000, 2008) has derived a chronic REL of 300 µg/m³ based on a rat study and supported by human data. In the key animal study, male rats were exposed to 0, 40, 80, 160 or 320 ppm for 6 hours/day, 5 days/week for 4 weeks. Significantly decreased brain weights (specifically the caudate-putamen and subcortical limbic areas), and altered dopaminergic nerve receptor activity were observed at concentrations of 80 ppm and above. A human occupational study of female workers in an electronics assembly plant exposed on average to toluene vapours for about 5.7 years also suggested a LOAEL of about 88 ppm. The OEHHA selected 40 ppm as a LOAEL. This value was adjusted for continuous exposure (6/24 hours, 5/7 days) to a $LOAEL_{ADJ}$ of 7 ppm. The OEHHA (2000) applied a cumulative uncertainty factor of 100 to account for the use of a LOAEL (10) and human variability (10). This value was not used in the chronic effects assessment, as although it is verified by some human data, its basis is primarily derived from an animal study. Further, the REL is derived from a LOAEL, rather than a NOAEL (as in the US EPA RfC derivation process).

The TCEQ (2008) describes the process used to derive the chronic ReV of 4,100 µg/m³. This value is based upon a human occupational study where workers were exposed to 0, 32 or 132 ppm for over 10 years. A significant increase in colour confusion was observed at 132 ppm. A NOAEL of 32 ppm for the incidence of neurological effects was identified. This NOAEL was determined by the TCEQ to be supported by the results of three other studies, where average LOAELs ranging from 50 to 140 ppm were reported. The NOAEL of 32 ppm was adjusted to account for differences in the air volume inhaled by workers versus the general public, and to adjust for continuous exposure (10/20 m³-day × 5/7 days). The $NOAEL_{ADJ}$ was determined to be

about 11.4 ppm. The TCEQ applied an uncertainty factor of 10 to this value to account for human variability. Preference was given to the US EPA RfC because its NOAEL was derived from the analysis of 10 different studies and is based upon a greater scientific weight of evidence.

The RIVM (2001) has developed a TCA of 400 µg/m³ for toluene. This TCA was adopted from a previous US EPA RfC, which has since been revised. As a result, this TCA was not used in the chronic inhalation effects assessment for toluene.

J1-2.15.2 Oral Exposure Limits

Toluene did not meet the physical-chemical criteria for inclusion in the multiple pathway assessment. Thus, a chronic oral exposure limit was not required.

J1-2.15.3 References Toluene

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