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SUMMARY DOCUMENT

Indoor Air Reference Levels for Chronic Exposure to Volatile Organic Compounds

Canada

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SUMMARY DOCUMENT

Indoor Air Reference Levels for Chronic Exposure to Volatile Organic Compounds

Water and Air Quality Bureau
Healthy Environments and Consumer Safety Branch

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LIST OF ACRONYMS

AEL	Adverse Effect Level
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration (lower limit of a one-sided 95% confidence interval on the BMC)
BMD	benchmark dose
BMDL	benchmark dose (lower limit of a one-sided 95% confidence interval on the BMD)
CalEPA	California Environmental Protection Agency
COHb	carboxyhemoglobin
DAF	dosimetric adjustment factor
HEC	human equivalent concentration
IARL	indoor air reference level
LEC	lowest effective concentration
LOAEL	lowest observed adverse effect level
NOAEL	no observed adverse effect level
PBPK	physiologically based pharmacokinetic
PoD	point of departure
RfC	reference concentration
RGDR	regional gas dose ratio
RIAQG	Residential Indoor Air Quality Guideline
RIVM	National Institute for Public Health and the Environment
TC	tolerable concentration
TC_{01}, TC_{05}	tumorigenic concentration (concentration of a contaminant in air generally associated with a 1% or 5% increase in incidence or mortality due to tumours, respectively)
TRV	toxicological reference value
UF	uncertainty factor
UF_A	uncertainty factor for interspecies variability
UF_{DB}	uncertainty factor for database deficiency
UF_H	uncertainty factor for intraspecies variability
UF_L	uncertainty factor for use of a LOAEL or effect level extrapolation factor
UFs	uncertainty factor for study duration
US EPA	United States Environmental Protection Agency
VCCEP	Voluntary Children's Chemical Evaluation Program
VOC	volatile organic compound
WHO	World Health Organization

1.0 INTRODUCTION

Volatile organic compounds (VOCs) are a diverse group of chemicals characterized by a high vapour pressure, as they are emitted in the form of a gas from solids or liquids at ordinary room temperatures.[1] They are ubiquitous since they are found in both ambient and indoor air.

Known or suspected human health effects of VOCs vary considerably from one compound to another and with respect to the level of exposure. Levels of different VOCs present in the home depend on indoor sources (e.g., smoking, cooking, combustion appliances, building materials, furniture, and a wide range of consumer products) as well as infiltration of VOCs from outdoors (Health Canada 2017) or from an attached garage (Mallach et al. 2017). Strength of emissions, changes in emissions over time, adsorption and desorption processes, secondary reactions with other chemicals, and amount of ventilation in different rooms and in the house as a whole, all influence the levels of VOCs that may be measured at any given time.

For a given VOC, the indoor air reference level (IARL) for chronic exposure is an estimate of a concentration limit for continuous long-term inhalation exposures (up to a lifetime) below which adverse health effects are not expected to occur. In the case of carcinogenic substances, the IARL is an estimate of the continuous lifetime exposure associated with a negligible cancer risk.[2] The IARL applies to the general population including vulnerable subgroups.

Indoor air reference levels are intended to supplement Health Canada's Residential Indoor Air Quality Guidelines (RIAQGs), which are based on comprehensive reviews of the literature, are externally peer-reviewed, and are submitted for public comment. In developing IARLs, the Health Canada review is limited to hazard assessments from internationally recognized health and environmental organizations[3] and the key studies identified in these assessments.

This overview document provides a summary of IARLs for chronic exposure to VOCs that are current as of December 2016. This document, along with the derived IARLs, will be updated periodically to reflect changes in the hazard assessments that form the basis of these values. Details on the methodology for selecting VOCs for evaluation and deriving IARLs can be found in the companion document *Derivation of Health Canada Indoor Air Reference Levels: Methodology for Volatile Organic Compounds* (Health Canada 2013). The methodology describes criteria for evaluating hazard assessments on the basis of the strength of the underlying science as well as consistency with Health Canada policies and practice.

[1] Definitions of VOCs are often tailored to a specific application or regulatory context, and therefore may diverge from a strict chemical definition based on vapour pressure. For all the VOCs referred to in this document, the predominant route of human exposure is through inhalation.

[2] An additional lifetime cancer risk less than or equal to 1 in 100 000 is considered to be negligible.

[3] The following are considered authoritative organizations: Health Canada, the World Health Organization (WHO), the US Environmental Protection Agency (US EPA), the Office of Environmental Health Hazard Assessment of the California Environmental Protection Agency (CalEPA), the Agency for Toxic Substances and Disease Registry (ATSDR), the Voluntary Children's Chemical Evaluation Program (VCCEP), and the National Institute for Public Health and the Environment (RIVM) of the Netherlands. Assessments by other governmental and recognized public health organizations may be considered if the organization conducts independent assessments of the scientific literature, its hazard assessment methodologies are consistent with those of Health Canada, and the supporting document for the assessment is peer-reviewed, published, and available.

2.0 CONSIDERATIONS IN THE DETERMINATION OF INDOOR AIR REFERENCE LEVELS

Authoritative agencies and organizations follow similar procedures for conducting hazard assessments for cancer and non-cancer endpoints. Generally, hazard assessments lead to the derivation of toxicological reference values (TRVs). The TRV nomenclature varies among the different organizations and includes chronic reference exposure level, reference concentration (RfC), tolerable concentration (TC), and minimal risk level. These all provide a quantitative value below which adverse non-cancer health effects are not expected to be observed for durations of up to a lifetime exposure, including consideration of vulnerable and susceptible subpopulations. For non-threshold carcinogenic effects, the TRVs are often referred to as cancer potency factors, slope factors or inhalation unit risks. For these TRVs, it is necessary to define the level of potential excess lifetime cancer risk that would be considered negligible or acceptable. For the purpose of IARLs, a risk level of 1 in 100 000 is retained.

For some VOCs, both cancer and non-cancer TRVs have been derived. Assessments for cancer and non-cancer health endpoints are considered independently, and the most appropriate TRV for each effect is identified. The IARL is typically based on the most conservative value of the selected cancer and non-cancer TRVs, but might vary depending on the mode of action of carcinogenesis.

No IARL was determined in cases where the available assessments were considered inadequate. The specific reasons for such a conclusion are included in the rationale of the individual substance report.

3.0 APPLICATION OF INDOOR AIR REFERENCE LEVELS

The primary use of IARLs is to evaluate the health impacts of indoor VOC emissions from building materials and consumer products. On the basis of the measured emission factors and assumptions about typical product use and building characteristics, indoor air concentrations of different VOCs can be estimated. The associated potential health risks may then be evaluated by comparing estimated concentrations with IARLs.

In addition to working to promote the development of Canadian standards, Health Canada may collaborate with other international organizations in developing new health-based emission standards or in promoting the use of an existing standard. The IARLs provide benchmarks for Health Canada to evaluate VOC product emission standards produced internationally and endorse such standards when appropriate.

In some cases, a VOC may be produced primarily by sources other than building materials or consumer products (e.g., certain VOCs produced by fuel combustion). In these cases, IARLs may also be used to identify VOCs in the indoor environment of greatest potential concern to health and in support of the development of appropriate risk management actions.

Derivation of an IARL is also the first step in determining if a full assessment leading to an RIAQG is required and if so, the level of priority for such an assessment. The framework for this prioritization process is included as well in the aforementioned Health Canada document published in 2013. If an RIAQG is subsequently developed, this guideline value would supersede the IARL in risk management and communication actions.

4.0 UNCERTAINTIES AND ASSUMPTIONS IN HAZARD AND EXPOSURE ASSESSMENTS

All hazard assessments must consider the uncertainties in the underlying toxicological and epidemiological data. Assumptions with respect to intraspecies variability, interspecies extrapolation, and/or extrapolation from high to low levels of exposure as well as adjustments related to exposure patterns and duration of toxicological studies are inherent in the hazard assessment process. The completeness of the scientific literature with respect to the range of potential health effects on different subpopulations also varies considerably from one compound to another. In deriving a TRV, these uncertainties are addressed through the use of uncertainty factors applied in a precautionary manner. Variability and uncertainty can also be addressed using chemical-specific data (e.g., with the application of physiologically-based pharmacokinetic models or chemical-specific adjustment factors). This approach allows health organizations to determine a level of exposure that would not be expected to result in adverse effects, based on the information available at the time of the assessment.

There are also major uncertainties in estimating indoor air concentrations over long periods of time in Canadian homes. In particular, if the indoor air concentration is modelled on the basis of VOC emissions from products, as measured in chamber tests, the estimated long-term indoor air concentration may be quite different from the actual measured concentration over time. Factors influencing this estimate include the number and type of source materials, patterns of use, age of the material, and rate of decay of the emissions over time as well as home environmental conditions (e.g., temperature, humidity, ventilation rate, presence of reactive compounds). If the indoor air concentration is based on measured concentrations in Canadian homes, the type, location, and number of homes as well as the demographics of the study participants may limit the representativeness of the measured concentrations.

Given these uncertainties, any comparison of an estimated indoor air concentration with an IARL should be interpreted as providing an indication of potential risk and not a measure of actual risk. The level of uncertainty in risk estimates may be reduced through additional health or exposure data. For example, population-based epidemiological studies may provide more information for evaluating health effects at low concentrations typically encountered in the home. Furthermore, emission testing under more realistic conditions, or modelling with inputs that are more specific to the material or environment under consideration, may also reduce the overall uncertainty in risk estimates.

5.0 INDOOR AIR REFERENCE LEVELS

The methodology for selecting IARLs has been previously presented (Health Canada 2013). Table 1 summarizes the IARLs identified for selected VOCs as well as the critical effect on which the IARL is based and the source of the underlying TRV. Summary tables of the TRVs are presented in Section 6.

The derivation of each IARL is documented in a separate report. These individual substance reports are available upon request (air@hc-sc.gc.ca).

Indoor air reference levels were not reported for acetaldehyde as Health Canada is currently undertaking a full risk assessment. Should new data become available for the remaining VOCs, a reevaluation of the IARLs will be completed on a cyclical basis.

Table 1. Indoor Air Reference Levels

VOC[1]	IARL ($\mu g/m^3$)	Critical Effect		Reference
		Cancer	Non-Cancer	
1,3-Butadiene	1.7	leukemia		EC/HC (2000a)
1,4-Dichlorobenzene	60		nasal lesions	ATSDR (2006)
2-Butoxyethanol	11 000		hematological effects	EC/HC (2002)
2-Ethoxyethanol	70		testicular degeneration and hematological changes	CalEPA (2000)
3-Chloropropene	1		peripheral nerve damage	US EPA (1991)
Acetaldehyde[2]				
Acetone	70 000		developmental effects	VCCEP (2003)
Acrolein	0.35		respiratory epithelial lesions	CalEPA (2008)
Aniline	1		effects on spleen	US EPA (1990a)
Carbon tetrachloride	1.7	adrenal gland tumours		US EPA (2010)
Chloroform	300		kidney and liver toxicity	CalEPA (2000)
Cyclohexane	6000		reduced pup weight	US EPA (2003a)
Dichloromethane	600		effects on liver	US EPA (2011)
Epichlorohydrin	1		histological changes in the nose	US EPA (1994)
Ethylbenzene	2000		effects on, pituitary gland and liver	CalEPA (2000)
Ethylene oxide	0.002	lymphoid and breast cancer		US EPA (2016)

VOC[1]	IARL (µg/m^3)	Critical Effect		Reference
		Cancer	Non-Cancer	
Isopropyl alcohol	7000		kidney lesions	CalEPA (2000)
Isopropylbenzene[3]	400		effects on kidney	US EPA (1997)
Methyl ethyl ketone	5000		developmental effects	US EPA (2003b)
Methyl isobutyl ketone[3]	3000		developmental effects	US EPA (2003c)
Propionaldehyde	8		olfactory epithelium atrophy	US EPA (2008)
Propylene oxide	2.7	nasal cavity tumours		US EPA (1990b)
Styrene	850		neurotoxicity	ATSDR (2010)
Tetrachloroethylene	40		neurotoxicity, visual impairment, and neurobehavioural effects	US EPA (2012), ATSDR (2014)
Toluene diisocyanate	0.008		decreased lung function	CalEPA (2016)
Xylenes, mixture	100		increased sensitivity to pain	US EPA (2003d)

[1]Data for four additional VOCs (1,1,2,2-tetrachloroethane; 1,2-dichloroethane; 4,4-methylenedianiline; phenol) were reviewed, but were not included in this table because no IARL was recommended. These VOCs may be revisited in the future if data to select an IARL become available.
[2]Health Canada is currently undertaking a full risk assessment of acetaldehyde in indoor air.
[3]Isopropylbenzene and methyl isobutyl ketone are currently being assessed by Health Canada's Chemicals Management Plan, which may warrant revisiting their respective IARL.

6.0 TABLES OF TRVs FOR INDIVIDUAL VOCs

TOXICOLOGICAL REFERENCE VALUES FOR 1,3-BUTADIENE (CAS No. 106-99-0)

	NEOPLASTIC			NON-NEOPLASTIC	
Organization[1]	CalEPA	Health Canada[2]	US EPA	CalEPA	US EPA
Year of publication	1992[3]	**2000**	2002	2013[3]	2002
Species	Mice	**Humans**	Humans	Mice	Mice
Endpoint	Lung tumours	**Leukemia**	Leukemia	Ovarian atrophy	Ovarian atrophy
Unit risk $(\mu g/m^3)^{-1}$	1.7×10^{-4}	**5.9×10^{-6}**	3×10^{-5}		
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	17	**1.7**	0.3		
Point of departure				$BMCL_{05\ HEC}$ = 0.664 mg/m^3	$BMCL_{10\ HEC}$ = 2 mg/m^3
Uncertainty factors[4]				300 (UF_H = 10, UF_A = 3)	1000 (UF_H = 10, UF_A = 3, UF_L = 10, UF_{DB} = 3)
Concentration ($\mu g/m^3$)				2.2	2
Critical study[5]	1	**2**	2	3	3
Comments		**TC_{01} = 1.7 mg/m³** **Unit risk = (0.01)/TC_{01}**	LEC_{01} = 300 µg/m³ with adjustments from Health Canada and further adjustment for cancer incidence not mortality. Factor of 2 applied to adjust for potential for females to be more susceptible.	$BMCL_{05\ HEC}$: Benchmark concentration adjusted for continuous exposure and dosimetric differences between rats and humans (using PBPK model data): $BMCL_{05}$ x 5/7 days x 6/24 hours x 1.68 DAF	US EPA expressed medium confidence in the study selected, but low confidence in the dataset and resulting reference concentration. [Suggested by application of UF_L to a BMCL.] $BMCL_{10\ HEC}$ based on 2 lower doses, adjusted for continuous exposure and time to response (5/7 days x 6/24 hours). ppm equivalence across species assumed (equal to use RGDR = 1) UF_{DB} mainly for lack of 2-generational reproductive and neurodevelopmental studies.

[1] The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2000a).
[2] The TRV in the bolded column was retained as the IARL.
[3] Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[4] UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL or effect level extrapolation factor, UF_{DB} = database deficiency
[5] 1. Melnick et al. (1990): 2-year inhalation study; 2. Delzell, Sathiakumar and Macaluso (1995): retrospective cohort; 3. NTP (1993): 2-year inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR 1,4-DICHLOROBENZENE (CAS No. 106-46-7)

	NEOPLASTIC	NON-NEOPLASTIC				
Organization[1]	CalEPA	ATSDR[2]	CalEPA	Health Canada	RIVM	US EPA
Year of publication	1999[3]	**2006**	2001[3]	1993c; 1996	2001	1994
Species	Mice	**Rats**	Rats	Rats	Rats	Rats
Endpoint	Liver tumours	**Nasal lesions**	Reduced body weight and food consumption; tremors; nasal and ocular discharge; increased liver and kidney weights	Increased liver and kidney weights; increased urinary protein/coproporphyrin	Increased liver and kidney weights; increased urinary protein/coproporphyrin	Increased liver weight
Unit risk ($\mu g/m^3$)$^{-1}$	1.1×10^{-5}					
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.9					
Point of departure		**LOAEL = 450 mg/m^3 NOAEL = 120 mg/m^3 $BMCL_{10}$ = 57 mg/m^3 $BMCL_{10\ ADJ}$ = 10 mg/m^3 $BMCL_{10\ HE}$ = 1.6 mg/m^3**	LOAEL = 900 mg/m^3 NOAEL = 300 mg/m^3 $NOAEL_{ADJ}$ = 78mg/m^3 $NOAEL_{HE}$ = 78 mg/m^3	LOAEL = 3000 mg/m^3 NOAEL = 450 mg/m^3 $NOAEL_{ADJ}$ = 67 mg/m^3 $NOAEL_{HEC}$ = 48 mg/m^3	LOAEL = 3000 mg/m^3 NOAEL = 450 mg/m^3 $NOAEL_{ADJ}$ = 67 mg/m^3	LOAEL = 900 mg/m^3 NOAEL = 300 mg/m^3 $NOAEL_{ADJ}$ = 75 mg/m^3 $NOAEL_{HEC}$ = 75 mg/m^3
Uncertainty factors[4]		**30 (UF_H = 10, UF_A = 3)**	100 (UF_H = 10, UF_A = 3, UF_S = 3)	500 (UF_H = 10, UF_A = 10, UF_S = 5)	100 (UF_H = 10, UF_A = 10)	100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration ($\mu g/m^3$)		**60**	800	95	670	800
Critical study[5]	1	**2, 3**	4	5	6	4
Comments		**$BMCL_{10\ HE}$ = NOAEL x 5/7 days x 6/24 hours x 0.16 (RGDR)**	$NOAEL_{HEC}$ = NOAEL x 7/7 days x 6/24 hours x 1.0 (RGDR)	$NOAEL_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 0.71 (breathing rate adjustment)	$NOAEL_{ADJ}$ = NOAEL x 5/7 days x 5/24 hours x 0.71 (breathing rate adjustment). Appears to be same critical study as Loeser and Litchfield (1983).	$NOAEL_{HEC}$ = NOAEL x 7/7 days x 6/24 hours

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993c) and Health Canada (1996). The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[5]1. NTP (1987): 2-year gavage study; 2. Aiso et al. (2005): 2-year inhalation study; 3. Japan Bioassay Research Center (1995): 2-year inhalation study; 4. Chlorobenzene Producers Association (1986): 2-generation reproductive inhalation study; 5. Loeser and Litchfield (1983): 2-year inhalation study; 6. Riley et al. (1980): 2-year inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR 2-BUTOXYETHANOL (CAS No. 111-76-2)

	NON-NEOPLASTIC		
Organization[1]	**ATSDR**	**Health Canada[2]**	**US EPA**
Year of publication	1998	**2002**	2010
Species	Humans	**Rats**	Rats
Endpoint	Hematological effects	**Hematological effects**	Hemosiderin deposition
Point of departure	NOAEL = 2.9 mg/m^3	**BMC_{05} = 5.3 mg/m^3**	$BMCL_{10,HEC}$ = 16 mg/m^3
Uncertainty factors[3]	3 (UF_H = 3)	**0.5** **(UF_H = 10, UF_A = 0.05)**	10 (UF_H = 10, UF_A = 1, UF_{DB} = 1)
Concentration (µg/m^3)	970	**11 000**	1600
Critical study[4]	1	**2**	2
Comments	The small significant effects on hematological parameters reported in humans were within the range of normal clinical values (hence the concentration was designated a NOAEL).	**UF_A includes adjustment factors of 0.5 (toxicokinetics) and 0.1 (toxicodynamics) to account for lower sensitivity of humans compared to rats.**	The $BMCL_{10,HEC}$ was back-calculated from the $BMCL_{10}$ for 2-butoxyacetic acid (area under the curve in blood = 133 µmol-hour/L) using a PBPK model. US EPA has high confidence in the study, and a medium-to-high confidence in the RfC and database.

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2002)
[2]The TRV in the bolded column was retained as the IARL.
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_{DB} = database deficiency
[4]1. Haufroid et al. (1997): occupational study; 2. NTP (1998, 2000): 2-year inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR 2-ETHOXYETHANOL (CAS No. 110-80-5)

Organization	NON-NEOPLASTIC		
	CalEPA [1]	**US EPA**	**WHO**
Year of publication	**2000[2]**	1991	2010
Species	**Rabbits**	Rabbits	Rats
Endpoint	**Testicular degeneration and hematological changes**	Testicular degeneration and hematological changes	Developmental toxicity
Unit risk ($\mu g/m^3)^{-1}$			
Concentration at 1 x 10^{-5} risk level ($\mu g/m^3$)			
Point of departure	**NOAEL = 380 mg/m^3** **$NOAEL_{ADJ}$ = 68 mg/m^3** **$NOAEL_{HEC}$ = 68 mg/m^3**	NOAEL = 380 mg/m^3 $NOAEL_{ADJ}$ = 68 mg/m^3 $NOAEL_{HEC}$ = 68 mg/m^3	NOAEL = 40 mg/m^3 $NOAEL_{ADJ}$ = 10 mg/m^3
Uncertainty factors[3]	**1000** **(UF_H = 10, UF_A = 10, UF_S = 10)**	300 (UF_H = 10, UF_A = 3, UF_S = 10)	100 (UF_H = 10, UF_A = 10)
Concentration ($\mu g/m^3$)	**70**	200	100
Critical study[4]	**1**	1	2, 3
Comments	**LOAEL = 1485 mg/m^3** **$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 5 days/7 days** **$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x 1 (RGDR)**	LOAEL = 1485 mg/m^3 $NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 5 days/7 days $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x 1 (RGDR) US EPA has medium confidence in the study, database and RfC.	$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours

[1] The TRV in the bolded column was retained as the IARL.
[2] Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b).
[3] UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[4] 1. Barbe et al. (1984): 13-week inhalation study; 2/3. Tinston et al. (1983); Doe (1984): gestation day 6–15 developmental inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR 3-CHLOROPROPENE (CAS No. 107-05-1)

	NEOPLASTIC	NON-NEOPLASTIC
Organization	**CalEPA**	**US EPA** [1]
Year of publication	1999[2]	**1991**
Species	Mice	**Rabbits and rats**
Endpoint	Squamous cell papillomas and carcinomas of the forestomach	**Peripheral nerve damage**
Unit risk $(\mu g/m^3)^{-1}$	6.0×10^{-6}	
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.67	
Point of departure		**NOAEL = 17 mg/m^3** **$NOAEL_{ADJ}$ = 3.6 mg/m^3** **$NOAEL_{HEC}$ = 3.6 mg/m^3**
Uncertainty factors[3]		**3000** **(UF_H = 10, UF_A = 3, UF_S = 10, UF_{DB} = 10)**
Concentration ($\mu g/m^3$)		**1**
Critical study[4]	1	**2**
Comments	Inhalation unit risk derived from an oral cancer potency factor in female mice exposed by gavage	**$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 6 days/7 days** **$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x 1 (RGDR)** **US EPA has low confidence in the study, database and RfC.**

[1]The TRV in the bolded column was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2011).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[4]1. NCI (1977): 78-week ingestion study (gavage); 2. Lu et al. (1982): 3-month inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR ACETONE (CAS No. 67-64-1)

	NON-NEOPLASTIC	
Organization[1]	**ATSDR**	**VCCEP**[2]
Year of publication	1994	2003
Species	Humans	**Rats**
Endpoint	Neurological effects	**Developmental effects**
Point of departure	LOAEL = 3000 mg/m^3	**NOAEL = 5300 mg/m^3** **NOAEL$_{HEC}$ = 2100 mg/m^3**
Uncertainty factors[3]	100 (UF_H = 10, UF_L = 10)	**30** **(UF_H = 10, UF_A = 3)**
Concentration (µg/m^3)	31 000	**70 000**
Critical study[4]	1	**2**
Comments		**NOAEL$_{HEC}$ calculated using PBPK modelling**

[1]The VCCEP assessment was published under the authorship of American Chemistry Council Acetone Panel (2003).
[2]The TRV in the bolded column was retained as the IARL.
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL
[4]1. Stewart et al. (1975): 6-week controlled human exposure study; 2. Mast et al. (1988): 2-generation reproductive inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR ACROLEIN (CAS No. 107-02-8)

Organization[1]	NON-NEOPLASTIC		
	CalEPA[2]	Health Canada	US EPA
Year of publication	**2008**[3]	2000	2003
Species	**Rats**	Rats	Rats
Endpoint	**Respiratory epithelial lesions**	Respiratory epithelial lesions	Respiratory epithelial lesions
Point of departure	**LOAEL = 1400 µg/m^3** **NOAEL = 460 µg/m^3** **NOAEL$_{ADJ}$ = 82 µg/m^3** **NOAEL$_{HEC}$ = 70 µg/m^3**	BMC$_{05}$ = 141 µg/m^3 BMC$_{05\ ADJ}$ = 35 µg/m^3	LOAEL = 900 µg/m^3 LOAEL$_{ADJ}$ = 160 µg/m^3 LOAEL$_{HEC}$ = 20 µg/m^3
Uncertainty factors[4]	**200** **(UF$_H$ = 10, UF$_A$ = 2 (toxicokinetics) x 3 (toxicodynamics), UF$_S$ = 3)**	100 (UF$_H$ = 10, UF$_A$ = 10)	1000 (UF$_H$ = 10, UF$_A$ = 3, UF$_L$ = 3, UF$_S$ = 10)
Concentration (µg/m^3)	**0.35**	0.4	0.02
Critical study[5]	**1**	2	3
Comments	**NOAEL$_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 0.85 (DAF)** **UF$_A$ of 2 (toxicokinetics) was due to uncertainty in use of a DAF from a chemical analogue.**	BMC$_{05\ ADJ}$ = BMC$_{05}$ x 6/24 hours Based on a 3-day rat inhalation study with only 5 to 6 males for each of 2 treated doses; LOAEL approach also considered.	NOAEL$_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 0.14 (RGDR) The UF$_L$ was for use of a minimal LOAEL. Dose-related effects were observed, although only in 1 out of 12 animals at this dose. Similar effects were observed at a lower dose in another study.

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2000b).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b).
[4]UF$_H$ = intraspecies variability, UF$_A$ = interspecies variability, UF$_L$ = use of a LOAEL, UF$_S$ = extrapolation for study duration
[5]1. Dorman et al. (2008): 13-week inhalation study; 2. Cassee, Groten and Feron (1996): 3-day inhalation study; 3. Feron et al. (1978): 13-week inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR ANILINE (CAS No. 62-53-3)

	NEOPLASTIC	NON-NEOPLASTIC
Organization	**CalEPA**	**US EPA[1]**
Year of publication	1999[2]	**1990**
Species	Rats	**Rats**
Endpoint	Spleen tumours	**Effects on spleen**
Unit risk ($\mu g/m^3)^{-1}$	1.6×10^{-6}	
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	6.25	
Point of departure		**NOAEL = 19 mg/m^3** **$NOAEL_{ADJ}$ = 3.4 mg/m^3** **$NOAEL_{HEC}$ = 3.4 mg/m^3**
Uncertainty factors[3]		**3000** **(UF_H = 10, UF_A = 10, UF_S = 10, UF_{DB} = 3)**
Concentration ($\mu g/m^3$)		**1**
Critical study[4]	1	**2, 3**
Comments	Based on a US EPA oral slope factor. US EPA (1994) did not derive an inhalation unit risk.	**$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 5 days/7 days** **$NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x 1 (RGDR)** **US EPA has low confidence in the study, database and RfC.**

[1]The TRV in the bolded column was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2011).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[4]1. CIIT (1982): 2-year ingestion study; 2.Oberst et al. (1956): 20- to 26-week inhalation study; 3. E.I. duPont deNemours and Company Inc. (1982): 2-week inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR CARBON TETRACHLORIDE (CAS No. 56-23-5)

	NEOPLASTIC		NON-NEOPLASTIC				
Organization[1]	CalEPA	US EPA[2]	ATSDR	CalEPA	RIVM	US EPA	WHO
Year of publication	1987[3]	**2010**	2005	2001[3]	2001	2010	1999
Species	Mice	**Mice**	Rats	Guinea pigs	Rats	Rats	Rats
Endpoint	Hepatomas	**Adrenal gland tumours**	Liver toxicity	Liver toxicity	Liver toxicity	Liver toxicity	Liver and kidney toxicity
Unit risk ($\mu g/m^3)^{-1}$	4.2×10^{-5}	**6×10^{-6}**					
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.24	**1.7**					
Point of departure			NOAEL = 32 mg/m^3 $NOAEL_{HEC}$ = 5.7 mg/m^3	LOAEL = 32 mg/m^3 $LOAEL_{HEC}$ = 11 mg/m^3	NOAEL = 32 mg/m^3 $NOAEL_{HEC}$ = 6.3 mg/m^3	$BMCL_{10\ HEC}$ = 14.3 mg/m^3	(1) NOAEL = 6.1 mg/m^3 (2) NOAEL = 32 mg/m^3; $NOAEL_{HEC}$ = 6.7 mg/m^3 (3) NOAEL = 32 mg/m^3; $NOAEL_{HEC}$ = 5.7 mg/m^3
Uncertainty factors[4]			30 (UF_H = 10, UF_A = 3)	300 (UF_H = 10, UF_A = 3, UF_L = 3, UF_S = 3)	100 (UF_H = 10, UF_A = 10)	100 (UF_H = 10; UF_A = 3; UF_{DB} = 3)	(1) 1000 (UF_H = 10, UF_A = 10, UF_S = 10) (2) 1000 (UF_H = 10, UF_A = 10, UF_S = 10) (3) 500 (UF_H = 10, UF_A = 10, UF_L = 5)
Concentration ($\mu g/m^3$)			190	40	60	100	(1) 6.1 (2) 6.7 (3) 11.4
Critical study[5]	1	**2, 3**	3	4	5	2, 3	(1) 6 (2) 4 (3) 3
Comments	Linear multistage procedure Single treated dose	**BMD modelling with PBPK to get LEC_{10} from which unit risk was calculated.**	$NOAEL_{HEC}$ = NOAEL 5/7 days x 6/24 hr x 1 (RGDR)	$LOAEL_{HEC}$ = LOAEL 5/7 days x 7/24 hr x 1.7 (RGDR)	$NOAEL_{HEC}$ = NOAEL 5/7 days x 7/24 hr	BMD with PBPK to estimate $BMDL_{10}$, converted to human equivalent. UF_{DB} for lack of a reproductive study	Three TCs were derived based on three different studies. (3) UF_L of 5 used for marginal effect instead of NOAEL.

[1]The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[5]1. Edwards and Dalton (1942): 8-month gavage study (only 4-month exposure); 2. Nagano et al. (2007): 2-year inhalation study; 3. Japan Bioassay Research Center (1998): 2-year inhalation study; 4. Adams et al. (1952): 7-month inhalation study; 5. Vermeire et al. (1991): summary report; 6. Prendegast (1967): 90-day inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR CHLOROFORM (CAS No. 67-66-3)

	NEOPLASTIC			NON-NEOPLASTIC		
Organization[1]	**CalEPA**	**Health Canada**	**US EPA**	**ATSDR**	**CalEPA^**	**RIVM**
Year of publication	1990[5]	2001	2001	1997	**2000[3]**	2001
Species	Rats	Rats	Mice	Humans	**Rats**	Rats
Endpoint	Kidney tumours	Kidney tumours	Hepatocellular carcinoma	Liver toxicity	**Kidney and liver toxicity**	None
Unit risk $(\mu g/m^3)^{-1}$	5.3×10^{-6}		2.3×10^{-5}			
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.9		0.4			
Point of departure				LOAEL = 10 mg/m^3	**LOAEL = 120 mg/m^3** **$LOAEL_{HEC}$ = 75 mg/m^3**	NOAEL = 110 mg/m^3
Uncertainty factors[4]				100 (UF_H = 10, UF_L = 10)	**300** **(UF_H = 10, UF_A = 3, UF_L = 10)**	1000 (UF_H = 10, UF_A = 10, UF_S = 10)
Concentration ($\mu g/m^3$)		147 000		100	**300**	100
Critical study[5]	1, 2, 3, 4	1	2	5	**6**	6
Comments	Linear multistage procedure with PBPK Based on a 1990 California Department of Health Services analysis.	PBPK used to determine 3.9 mg/L per hour, the rate of metabolism associated with a 5% increase in tumour risk (TC_{05}). Adjusted for lifetime to TC_{05} = 147 mg/m^3	Linearized multistage procedure, extra risk		**$LOAEL_{HEC}$ = LOAEL x 5/7 days x 7/24 hours x 3 (RGDR)** **CalEPA used a different part of the same study as RIVM.**	UF_S for 4 hour/day, 5 days/week, 6-month exposure. RIVM used a different part of the same study as CalEPA.

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2001a). The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2011, 2014a, 2014b).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL, UF_S = extrapolation for study duration
[5]1. Jorgenson et al. (1985): 2-year drinking water study; 2. NCI (1976): 78-week gavage study; 3. Roe, Palmer and Worden (1979): 80-week study in toothpaste; 4. Tumasonis, McMartin and Bush (1985): 2-year drinking water study; 5. Bomski, Sobolewska and Strakowaki (1967): 1- to 4-year occupational case-control study; 6. Torkelson, Oyen and Rowe (1976): 6-month inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR CYCLOHEXANE (CAS No. 110-82-7)

Organization	NON-NEOPLASTIC US EPA [1]
Year of publication	**2003**
Species	**Rats**
Endpoint	**Reduced pup weight (F1 and F2 generations)**
Point of departure	**NOAEL = 6886 mg/m^3** **NOAEL$_{ADJ}$ = 1700 mg/m^3** **BMCL$_{1sd}$[2] = 1822 mg/m^3**
Uncertainty factors[3]	**300** **(UF$_H$ = 10, UF$_A$ = 3, UF$_{DB}$ = 10)**
Concentration (µg/m^3)	**6000**
Critical study[4]	**1, 2**
Comments	**NOAEL$_{ADJ}$ = NOAEL x 6/24 hours x 1 (RGDR)** **UF$_{DB}$ for lack of data for chronic and developmental neurotoxicity studies**

[1]The TRV in the bolded column was retained as the IARL.
[2]BMCL$_{1sd(HEC)}$: benchmark concentration lower limit of a 1-sided 95% confidence interval for 1 standard deviation; human equivalent concentration.
[3]UF$_H$ = intraspecies variability, UF$_A$ = interspecies variability, UF$_{DB}$ = database deficiency
[4]1/2. DuPont HLR (1997); Kreckmann et al. (2000): 2-generation reproductive inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR DICHLOROMETHANE (CAS No. 75-09-2)

	NEOPLASTIC			NON-NEOPLASTIC			
Organization[1]	CalEPA	Health Canada	US EPA	ATSDR	CalEPA	RIVM	US EPA^
Year of publication	1989[3]	1993	2011	2000	2000[3]	2001	**2011**
Species	Mice	Mice	Mice	Rats	Humans	Humans	**Rats**
Endpoint	Lung tumours	Lung tumours	Lung and liver tumours	Effects on liver	Increased carboxyhemoglobin	Increased carboxyhemoglobin	**Effects on liver**
Unit risk ($\mu g/m^3)^{-1}$	1.0×10^{-6}	2.3×10^{-8}	1.0×10^{-8}				
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	10	435	1000				
Point of departure				NOAEL = 170 mg/m^3 $NOAEL_{ADJ}$ = 31 mg/m^3	LOAEL = 139 000 mg/m^3 $LOAEL_{ADJ}$ = 48 700 mg/m^3	LOAEL = 90 mg/m^3 $LOAEL_{ADJ}$ = 3 mg/m^3	**$BMDL_{10}$ = 532 mg dichloromethane metabolized via CYP pathway/Liver tissue/day** **$HEC_{1\%}$ = 17.2 mg/m^3**
Uncertainty factors[4]				30 (UF_H = 10, UF_A = 3)	100 (UF_H = 10, UF_L = 10)	0	**30** **(UF_H = 3, UF_A = 3, UF_{DB} = 3)**
Concentration ($\mu g/m^3$)				1000	400	3000	**600**
Critical study°	1, 2	1, 2	1, 2	3	4	4	**3**
Comments		Based on the lowest PBPK modified $TD_{0.05}$ value.	Application of age-dependent adjustment factors results in a 70-year risk of 1.7×10^{-8}.	$NOAEL_{ADJ}$ = NOAEL 5/7 days x 6/24 hours UF_A = 3 because of consideration of RGDR (value of 1 used). COHb levels also increased >10% at 700 mg/m^3.	$LOAEL_{ADJ}$ = LOAEL x 5/7 days x [(10 m^3/d)/(20 m^3/d)] Limited subjects and exposure information.	$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 7.5/24 hours x (0.1/1). The last factor was to adjust for an unacceptable 0.1% increase in COHb, relative to the observed 1% COHb increase. Limited subjects and exposure information.	**$HEC_{1\%}$ determined by PBPK modelling of calculated $BMDL_{10}$ value.** **Value of 600 $\mu g/m^3$ was rounded from 573 $\mu g/m^3$.**

[1]The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011)..
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL, UF_{DB} = database deficiency
[5]1. NTP (1986b): 2-year inhalation study; 2. Mennear et al. (1988): 2-year inhalation study; 3. Nitschke et al. (1988): 2-year inhalation study; 4. DiVincenzo and Kaplan (1981): 5-day occupational inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR EPICHLOROHYDRIN (CAS No. 106-89-8)

	NEOPLASTIC		NON-NEOPLASTIC	
Organization	**CalEPA**	**US EPA**	**CalEPA**	**US EPA[1]**
Year of publication	1999[2]	1988	2001	**1994**
Species	Rats	Rats	Rats and mice	**Rats and mice**
Endpoint	Papillomas and carcinomas of the forestomach	Nasal cavity tumours	Histological changes in the nose	**Histological changes in the nose**
Unit risk $(\mu g/m^3)^{-1}$	2.3×10^{-5}	1.2×10^{-6}		
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.43	8		
Point of departure			NOAEL = 19 mg/m^3 $NOAEL_{ADJ}$ = 3.4 mg/m^3 $NOAEL_{HEC}$ = 0.31 mg/m^3	**NOAEL = 19 mg/m^3** **$NOAEL_{ADJ}$ = 3.4 mg/m^3** **$NOAEL_{HEC}$ = 0.36 mg/m^3**
Uncertainty factors[3]			100 (UF_H =10, UF_A = 3, UF_S = 3)	**300** **(UF_H = 10, UF_A = 3, $UF_{S,\ DB}$ = 10)**
Concentration ($\mu g/m^3$)			3	**1**
Critical study[4]	1	2	3	**3**
Comments	Inhalation unit risk derived from oral cancer potency factor in male rats exposed via drinking water. Data from the Laskin et al. (1980) inhalation study were not retained due to the poor survival of the study animals (data considered to be less suitable for generating a cancer potency factor than the data from the study of Konishi et al. (1980)). Relevance of forestomach tumours in rodents to humans is unclear and not well addressed in this assessment.		$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 5 days/7 days $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ x 0.14 m^3/day / 20 m^3/day x 200 cm^2/15 cm^2 (based on rat data)	**$NOAEL_{ADJ}$ = NOAEL x 6 hours/24 hours x 5 days/7 days** **$NOAEL_{HEC}$= $NOAEL_{ADJ}$ x 0.14 m^3/day / 20 m^3/day x 177 cm^2/11.6 cm^2 (based on rat data)** **US EPA has medium confidence in the RfC, in the study and in the database.**

[1]The TRV in the bolded column was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[4]1. Konishi et al. (1980): 81-week ingestion study (drinking water); 2. Laskin et al. (1980): 30-day inhalation study; 3. Quast et al. (1979): 90-day inhalation study (whole body)

TOXICOLOGICAL REFERENCE VALUES FOR ETHYLBENZENE (CAS No. 100-41-4)

	NEOPLASTIC		NON-NEOPLASTIC					
Organization[1]	**CalEPA**	**VCCEP**	**ATSDR**	**CalEPA^**	**RIVM**	**US EPA**	**VCCEP**	**WHO**
Year of publication	2007[2]	2007	2010	**2000[3]**	2001	1991	2007	1996
Species	Rats	Mice	Rats	**Rats and mice**	Rats and mice	Rabbits	Rats	Rats and mice
Endpoint	Kidney tumours	Lung tumours	Effects on kidney	**Effects on pituitary gland and liver (mice)**	Effects on liver and kidney	Developmental effects	Auditory effects	Effects on liver and kidney
Unit risk $(\mu g/m^3)^{-1}$	2.5×10^{-6}							
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	4							
Point of departure		40 500 mg metabolised in lung/kg lung/wk	LOAEL = 330 mg/m^3	**LOAEL = 1100 mg/m^3 NOAEL = 330 mg/m^3 $NOAEL_{ADJ}$ = 57 mg/m^3**	NOAEL = 430 mg/m^3 $NOAEL_{ADJ}$ = 77 mg/m^3	LOAEL = 4340 mg/m^3	LOEL = 860 mg/m^3 LED_{0105}[4] = 272.8 mg-h ethylbenzene/L RPT[5]/wk	NOEL = 2150 mg/m^3
Uncertainty factors[6]		300 (UF_H = 10, UF_A = 3, $UF_{severity\ of\ lesion}$ = 10)	300 (UF_H = 10, UF_A = 3, UF_L = 10)	**30 (UF_H = 10, UF_A = 3)**	100 (UF_H = 10, UF_A = 3)	300 (UF_H = 10, UF_A = 3, UF_S = 10)	100 (UF_H = 10, UF_A = 3, UF_S = 3)	100 (UF_H = 5, UF_A = 10; UF_{DB} = 2)
Concentration ($\mu g/m^3$)		2100	260	**2000**	770	1000	1300	22 000
Critical study[7]	1	1	1	**1, 2**	3	4, 5	6	3
Comments	More recent evidence suggests ethylbenzene may be a threshold carcinogen.		More recent data suggest effects on kidney, particularly chronic progressive nephropathy (common in aging rats), are unlikely to be relevant to humans.	**$NOAEL_{ADJ}$ = NOAEL x 5/7 days x 6/24 hours**	$NOAEL_{ADJ}$ = NOAEL x 5/7 days x 6/24 hours Sub-chronic study	US EPA has low confidence in this derivation; published prior to NTP (1999).	Sub-chronic study supportive of chronic effects	Stated NOAEL would be higher than 4300 mg/m^3 because organ weight increases were not accompanied by cellular changes.

[1]The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[4]LED_{0105}: the 95% upper confidence limit on the lowest effective dose resulting in a loss of 1.05% percent of outer hair cells in the cochlea.
[5]RPT: richly perfused tissue.
[6]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[7]1. NTP (1999): 2-year inhalation study; 2. Chan et al. (1998): 2-year inhalation study; 3. NTP (1992): 13-week inhalation study; 4. Andrew et al. (1981): gestation days 1–19 and 1–24, developmental study; 5. Hardin , Bond and Sikov (1981): gestation days 1–19 and 1–24, developmental study; 6. Gagnaire et al. (2007): 13-week inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR ETHYLENE OXIDE (CAS No. 75-21-8)

	NEOPLASTIC			NON-NEOPLASTIC
Organization[1]	**CalEPA**	**Health Canada**	**US EPA^**	**CalEPA**
Year of publication	1987[3]	2001	**2016**	2001[3]
Species	Rats	Rats	**Humans**	Rats
Endpoint	Mononuclear leukemia	Mononuclear leukemia	**Lymphoid and breast cancer**	Neurological effects
Unit risk $(\mu g/m^3)^{-1}$	8.8×10^{-5}	2.3×10^{-5}	**5.0×10^{-3}**	
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.11	0.43	**0.002**	
Point of departure				NOAEL = 18 mg/m^3 $NOAEL_{ADJ}$ = 3.2 mg/m^3
Uncertainty factors[4]				100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration ($\mu g/m^3$)				30
Critical study[5]	1	2	**3**	2
Comments	Based on a 1985 US EPA analysis that considered human equivalent dose	Unit risk of 2.3×10^{-5} $(\mu g/m^3)^{-1}$ estimated from TC_{05} value of 2.2 mg/m^3	**Adult-based value was 3.0×10^{-3} per $\mu g/m^3$, to which age-dependent adjustment factors were applied to provide the lifetime exposure value presented above.**	$NOAEL_{ADJ}$ = PoD x 5/7 days x 6/24 hours

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2001b).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[4] UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[5]1. Snellings, Weil and Maronpot (1981): 2-year inhalation study; 2. Snellings, Weil and Maronpot (1984): 10- or 11-week inhalation study; 3. Steenland et al. (2003, 2004): retrospective cohort

TOXICOLOGICAL REFERENCE VALUES FOR ISOPROPYL ALCOHOL (CAS No. 67-63-0)

Organization	NON-NEOPLASTIC CalEPA [1]
Year of publication	**2000**[2]
Species	**Rats and mice**
Endpoint	**Kidney lesions**
Point of departure	**NOAEL = 1200 mg/m^3** **NOAEL$_{HEC}$ = 220 mg/m^3**
Uncertainty factors[3]	**30** **(UF_H = 10, UF_A = 3)**
Concentration (µg/m^3)	**7000**
Critical study[4]	**1**
Comments	**NOAEL$_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 1 (RGDR)**

[1]The TRV in the bolded column was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA report (2015, 2014a, 2014b).
[3]UF_H = intraspecies variability, UF_A = interspecies variability
[4]1.Burleigh-Flayer et al. (1997): 78-week (mice) or 2-year (rat) inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR ISOPROPYLBENZENE (CAS No. 98-82-8)

Organization	NON-NEOPLASTIC US EPA [1]
Year of publication	**1997**
Species	**Rats**
Endpoint	**Effects on kidney**
Point of departure	**NOAEL = 2438 mg/m^3** **NOAEL$_{HEC}$ = 435 mg/m^3**
Uncertainty factors[2]	**1000** **(UF_H = 10, UF_A = 10, UF_S = 10)**
Concentration (µg/m^3)	**400**
Critical study[3]	**1**
Comments	**NOAEL$_{HEC}$ = PoD x 5/7 days x 6/24 hours x 1 (RGDR)** **Since the publication of this assessment, a 2-year study has been published (NTP 2009).**

[1]The TRV in the bolded column was retained as the IARL.
[2]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[3]1. Cushman et al. (1995): 13-week inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR METHYL ETHYL KETONE (CAS No. 78-93-3)

Organization	NON-NEOPLASTIC US EPA [1]
Year of publication	**2003**
Species	**Rats**
Endpoint	**Developmental effects**
Point of departure	**LEC_{10} = 5202 mg/m^3** **$LEC_{10\ HEC}$ = 1517 mg/m^3**
Uncertainty factors[2]	**300** **(UF_H = 10, UF_A = 3, UF_{DB} = 10)**
Concentration (µg/m^3)	**5000**
Critical study[3]	**1, 2, 3**
Comments	**$LEC_{10\ HEC}$ = LEC_{10} x 7/24 hours** **UF_{DB} for lack of developmental neurotoxicity data, chronic inhalation toxicity study, and multigeneration reproductive toxicity study.**

[1]The TRV in the bolded column was retained as the IARL.
[2]UF_H = intraspecies variability, UF_A = interspecies variability, UF_{DB} = database deficiency
[3]1. Schwetz et al. (1991): gestation day 6-15 developmental inhalation study; 2. Mast et al. (1989): gestation day 6-15 developmental inhalation study; 3. NTP (1990): gestation day 6-15 developmental inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR METHYL ISOBUTYL KETONE (CAS No. 108-10-1)

Organization	NON-NEOPLASTIC US EPA [1]
Year of publication	**2003**
Species	**Rats and mice**
Endpoint	**Developmental effects**
Point of departure	**NOAEL = 4100 mg/m^3** **NOAEL$_{HEC}$ = 1026 mg/m^3**
Uncertainty factors[2]	**300** **(UF_H = 10, UF_A = 3, UF_{DB} = 10)**
Concentration (µg/m^3)	**3000**
Critical study[3]	**1**
Comments	**NOAEL$_{HEC}$ = PoD x 6/24 hours x 1 (RGDR)** **UF_{DB} for lack of developmental neurotoxicity, neurotoxicity, and chronic toxicity studies.** **US EPA has low to medium confidence in this RfC. Since the publication of this assessment, a 2-year study has been published by the NTP in 2007, which is under review.**

[1]The TRV in the bolded column was retained as the IARL.
[2]UF_H = intraspecies variability, UF_A = interspecies variability, UF_{DB} = database deficiency
[3]1. Tyl et al. (1987): gestation day 6-15 developmental inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR PROPIONALDEHYDE (CAS No. 123-38-6)

Organization	NON-NEOPLASTIC US EPA [1]
Year of publication	**2008**
Species	**Rats**
Endpoint	**Olfactory epithelium atrophy**
Point of departure	**LOAEL = 357 mg/m^3** **BMCL$_{10}$ = 128 mg/m^3** **BMCL$_{10\ HEC}$ = 8.3 mg/m^3**
Uncertainty factors[2]	**1000** **(UF_H = 10, UF_A = 3, UF_S = 10, UF_{DB} = 3)**
Concentration (µg/m^3)	**8**
Critical study[3]	**1**
Comments	**BCML$_{HEC\ 10}$ = BMCL$_{10}$ x 7/7 days x 6/24 hours x 0.26 (RGDR)** **UF_{DB} for lack of a 2-generation reproductive toxicity study.** **US EPA has medium confidence in the critical endpoint, low to medium confidence in the study selected, and low confidence in overall database.**

[1]The TRV in the bolded column was retained as the IARL.
[2]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[3]1. Union Carbide (1993): inhalation developmental study

TOXICOLOGICAL REFERENCE VALUES FOR PROPYLENE OXIDE (CAS No. 75-56-9)

	NEOPLASTIC		NON-NEOPLASTIC	
Organization	CalEPA	**US EPA[1]**	**CalEPA**	**US EPA**
Year of publication	1999[2]	**1990**	2000[2]	1990
Species	Mice	**Mice**	Rats	Rats
Endpoint	Nasal cavity tumours	**Nasal cavity tumours**	Atrophy of olfactory epithelium and degeneration of respiratory epithelium	Atrophy of olfactory epithelium and degeneration of respiratory epithelium
Unit risk $(\mu g/m^3)^{-1}$	3.7×10^{-6}	**3.7×10^{-6}**		
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	2.7	**2.7**		
Point of departure			LOAEL = 71 mg/m^3 $LOAEL_{HEC}$ = 3 mg/m^3	LOAEL = 71 mg/m^3 $LOAEL_{HEC}$ = 3 mg/m^3
Uncertainty factors[3]			100 (UF_H = 10, UF_A = 3, UF_L = 3)	100 (UF_H = 10, UF_A = 3, UF_L = 3)
Concentration ($\mu g/m^3$)			30	30
Critical study[4]	1, 2	**1, 2**	3	3
Comments			$LOAEL_{HEC}$ = LOAEL x 5/7 days x 6/24 hours x 0.23 (RGDR) US EPA concluded there was medium confidence in the study selected, dataset, and resulting RfC.	$LOAEL_{HEC}$ = LOAEL x 5/7 days x 6/24 hours x 0.23 (RGDR) No studies in mice at lower concentrations than those in NTP (1985) were identified.

[1]The TRV in the bolded column was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[4]1. NTP (1985): 2-year inhalation study; 2. Renne et al. (1986): 2-year inhalation study; 3. Kuper et al. (1988): 2-year inhalation study

TOXICOLOGICAL REFERENCE VALUES FOR STYRENE (CAS No. 100-42-5)

Organization[1]	NON-NEOPLASTIC					
	ATSDR[a]	CalEPA	Health Canada	RIVM	US EPA	WHO
Year of publication	**2010**	2000[c]	1993	2001	1992	2000
Species	**Humans**	Humans	Rats	Humans	Humans	Humans
Endpoint	**Neurotoxicity**	Neurotoxicity	Body weight change; neurotoxicity	Neurotoxicity	Neurotoxicity	Neurotoxicity
Unit risk $(\mu g/m^3)^{-1}$						
Concentration at 1 x 10^{-5} risk level ($\mu g/m^3$)						
Point of departure	**LOAEL = 85.2 mg/m^3** **$LOAEL_{ADJ}$ = 20.4 mg/m^3**	$BMCL_{05}$ = 7.2 mg/m^3 $BMCL_{05ADJ}$ = 2.6 mg/m^3	LOEL = 260 mg/m^3 $LOEL_{ADJ}$ = 65 mg/m^3 $LOEL_{HEC}$ = 46 mg/m^3	LOAEL = 107 mg/m^3 $LOAEL_{ADJ}$ = 26 mg/m^3	NOAEL = 106 mg/m^3 Lower 95% confidence limit of the NOAEL = 94 mg/m^3 $NOAEL_{ADJ}$ = 34 mg/m^3	LOAEL = 107 mg/m^3 $LOAEL_{ADJ}$ = 26 mg/m^3
Uncertainty factors[4]	**30** **(UF_H = 10, UF_L = 3)**	3 (UF_H = 3)	500 (UF_H = 10, UF_A = 10, UF_L = 5)	30 (UF_H = 10, UF_L = 3)	30 (UF_H = 3, UF_{DB} = 3, UF_S = 3)	100 (UF_H = 10, UF_L = 10)
Concentration ($\mu g/m^3$)	**850**	900	92	900	1000	260
Critical study[b]	**1**	2	3, 4	2*	2	2
Comments	**$LOAEL_{ADJ}$ = LOAEL x 8 hours/24 hours x 5 days/7 days**	$BMCL_{05ADJ}$ = $BMCL_{05}$ x 10 m^3/20 m^3 x 5 days/7 days	$LOEL_{ADJ}$ = LOEL x 6 hours/24 hours $LOEL_{HEC}$ = $LOEL_{ADJ}$ x [(0.11 m^3/0.35 kg)/(m^3/0.35 kg)]	$LOAEL_{ADJ}$ = LOAEL x 8 hours/24 hours x 5 days/7 days *RIVM does not explicitly cite a critical study. It is likely Mutti et al. (1984).	Lower 95% confidence limit of the NOAEL = NOAEL x 0.88 $NOAEL_{ADJ}$ = lower 95% confidence limit of NOAEL x 10 m^3/20 m^3 x 5 days/7 days US EPA has medium confidence in the RfC and study, and medium to high confidence in the database.	LOAEL adjusted by a factor of 4.2 to convert from occupational to continuous exposure

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993a). The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_{DB} = database deficiency, UF_L = use of a LOAEL
[5]1. Benignus et al. (2005): meta-analysis of several occupational studies; 2. Mutti et al. (1984): occupational study (average exposure: 8.6 years); 3. Kishi et al. (1992a): gestational days 7-21, developmental study (in utero exposure of the pups via maternal inhalation exposure); 4. Kishi et al. (1992b): gestational days 7–21, developmental study (in utero exposure of the pups via maternal inhalation exposure).

TOXICOLOGICAL REFERENCE VALUES FOR TETRACHLOROETHYLENE (CAS No. 127-18-4)

	NEOPLASTIC		NON-NEOPLASTIC				
Organization[1]	**CalEPA**	**US EPA**	**ATSDR**	**Health Canada**	**RIVM**	**US EPA[2]**	**WHO**
Year of publication	1991[3]	2012	**2014**	1993	2001	**2012**	2010
Species	Mice	Mice	**Humans**	Mice	Humans	**Humans**	Humans
Endpoint	Liver tumours	Liver tumours	**Neurobehavioral effects**	Nephrotoxicity, hepatotoxicity	Nephrotoxicity	**Neurotoxicity, visual impairment**	Nephrotoxicity
Unit risk $(\mu g/m^3)^{-1}$	5.9×10^{-6}	2.6×10^{-7}					
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.7	40					
Point of departure			**LOAEL = 50.3 mg/m^3** **$LOAEL_{ADJ}$ = 12 mg/m^3**	LOAEL = 678 mg/m^3 $LOAEL_{ADJ}$ = 360 mg/m^3	LOAEL = 100 mg/m^3 $LOAEL_{ADJ}$ = 25 mg/m^3	**From two studies:** **Study 6** **LOAEL = 156 mg/m^3** **$LOAEL_{ADJ}$ = 56 mg/m^3** **Study 3** **LOAEL = 42 mg/m^3** **$LOAEL_{ADJ}$ = 15 mg/m^3**	LOAEL = 100 mg/m^3 $LOAEL_{ADJ}$ = 25 mg/m^3
Uncertainty factors[4]			**300** **(UF_H = 10, UF_L = 10, UF_{DB} = 3)**	1000 (UF_H = 10, UF_A = 10, UF_L = 10)	100 (UF_H = 10, UF_L = 10)	**1000** **(UF_H = 10, UF_L = 10, UF_{DB} = 10)**	100 (UF_H = 10, UF_L = 10)
Concentration ($\mu g/m^3$)			**40**	360	250	**40** **(rounded average of 15 and 56)**	250
Critical study[5]	1	2	**3, 4**	1	5	**3, 6**	5
Comments		**Unit risk calculated using PBPK modelling**	**$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 8/24 hours**	$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 6/24 hours x 3 (volume/body weight adjustment of mice to humans)	$LOAEL_{ADJ}$ = LOAEL x 40 hr/week/168 hr week	**$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 10/20 m^3/d, breathing rate.** **UF_{DB} for lack of neurological, developmental, and immunological studies.**	$LOAEL_{ADJ}$ = LOAEL x 40 hr/week / 168 hr week

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993b). The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRVs in the bolded column were retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2011).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL, UF_{DB} = database deficiency
[5]1. NTP (1986a): 2-year inhalation study; 2. JISA (1993): 2-year inhalation study; 3. Cavalleri et al. (1994): occupational neurobehavioural testing; 4. Gobba et al. (1994): occupational neurobehavioural testing; 5. Mutti et al. (1992): occupational exposure study; 6. Echeverria, White and Sampaio (1995): occupational neurobehavioural testing.

TOXICOLOGICAL REFERENCE VALUES FOR TOLUENE DIISOCYANATE (MIXED ISOMERS) (CAS No. 26471-62-5)

	NEOPLASTIC	NON-NEOPLASTIC		
Organization	CalEPA	**ATSDR**	**CalEPA[1]**	**US EPA**
Year of publication	1999[2]	2015	**2016**	1995
Species	Rats	Humans	**Humans**	Humans
Endpoint	Subcutaneous fibroma/fibrosarcoma	Decreased lung function	**Decreased lung function**	Decreased lung function
Unit risk $(\mu g/m^3)^{-1}$	1.1×10^{-5}			
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.91			
Point of departure		AEL = 0.0085 mg/m^3 AEL_{ADJ} = 0.00202 mg/m^3	**NOAEL = 0.006 mg/m^3** **$NOAEL_{ADJ}$ = 0.002 mg/m^3**	NOAEL = 0.006 mg/m^3 $NOAEL_{ADJ}$ = 0.002 mg/m^3
Uncertainty factors[3]		100 (UF_H = 10, UF_A = 10)	**300** **(UF_H = 100, UF_S = 3)**	30 (UF_H = 10, $UF_{S,D}$ = 3)
Concentration ($\mu g/m^3$)		0.02	**0.008**	0.07
Critical study[4]	1	2	**3**	3
Comments	Inhalation unit risk derived from an oral cancer potency factor in male rats exposed by gavage to a commercial mixture of toluene diisocyanate	AEL_{ADJ} = AEL x 5/7 days x 8/24 hours	**$NOAEL_{ADJ}$ = NOAEL x 10 m^3/20 m^3 x 5 days/7 days**	$NOAEL_{ADJ}$ = NOAEL x 10 m^3/20 m^3 x 5 days/7 days US EPA has medium confidence in the study, database and RfC.

[1]The TRV in the bolded columns was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2016, 2015, 2011).
[3]UF_H = intraspecies variability, UF_L = use of an adverse effect level, UF_S = extrapolation for study duration, UF_D = database deficiency
[4]1. NTP (1986c): 106-week ingestion study (gavage); 2. Clarket al. (1998): 5-year occupational study; 3. Diem et al. (1982): 5-year occupational study

TOXICOLOGICAL REFERENCE VALUES FOR XYLENES, MIXTURE (CAS No. 1330-20-7)

	NON-NEOPLASTIC					
Organization[1]	**ATSDR**	**CalEPA**	**Health Canada**	**RIVM**	**US EPA^**	**VCCEP**
Year of publication	2007	2000[3]	1993	2001	**2003**	2005
Species	Humans	Humans	Rats	Rats	**Rats**	Rats
Endpoint	Symptoms of neurotoxicity, sore throat, nose, and eye irritation	Symptoms of neurotoxicity, sore throat, nose, and eye irritation	Unspecified maternal effects and fetal skeletal retardation	Decreased rotarod performance in offspring	**Decreased latency in paw-lick response (i.e., sensitivity to pain)**	Decreased rotarod performance in males (i.e., decreased motor activity)
Point of departure	LOAEL = 61 mg/m^3	LOAEL = 61 mg/m^3 $LOAEL_{HEC}$ = 22 mg/m^3	LOEL = 250 mg/m^3 $LOEL_{HEC}$ = 180 mg/m^3	LOAEL = 870 mg/m^3	**LOAEL = 434 mg/m^3** **NOAEL = 217 mg/m^3** **$NOAEL_{HEC}$ = 39 mg/m^3**	LOAEL = 434 mg/m^3 NOAEL = 217 mg/m^3 $NOAEL_{ADJ}$ = 39 mg/m^3 $NOAEL_{HEC}$ = 66 mg/m^3
Uncertainty factors[4]	300 (UF_H = 10, UF_L = 10, UF_{DB} = 3)	30 (UF_H = 10, UF_L = 10)	1000 (UF_H = 10, UF_A = 10, UF_L = 10)	1000 (UF_H = 10, UF_A = 10, UF_L = 10)	**300 (UF_H = 10, UF_A = 3, UF_S = 3, UF_{DB} = 3)**	100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration (µg/m^3)	220	700	180	870	**100**	660
Critical study[5]	1	1	2	3	**4**	4
Comments	UF_{DB} for lack of chronic neurotoxicity data	Continuous exposure adjustment: multiplied PoD by [(10 m^3/d)/(20 m^3/d) x 5 d/7 d]	0.72 applied to PoD to account for inhalation volume/body weight of young rats relative to humans (i.e., rats [(0.11 m^3/day)/0.35 kg] to humans aged 5 to 11 years [(12 m^3/day)/27 kg). UF_L also included limitations of critical study.		**$NOAEL_{HEC}$ = NOAEL x 5/7 days x 6/24 hours UF_{DB} for lack of 2-generation reproduction study.**	$NOAEL_{ADJ}$ = NOAEL x 6/24 hours x 5/7 days $NOAEL_{HEC}$ = $NOAEL_{ADJ}$ X 1.7 (RGDR)

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993d). The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]The TRV in the bolded column was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b).
[4]UF_H = intraspecies variability, UF_A = interspecies variability, UF_L = use of a LOAEL, UF_S = extrapolation for study duration, UF_{DB} = database deficiency
[5]1. Uchida et al. (1993): occupational study; 2. Ungvary and Tatrai (1985): gestation day 7–15 developmental inhalation study; 3. Hass and Jakobsen (1993): developmental neurotoxicity inhalation study; 4. Korsak, Wisniewska-Knypl and Swiercz (1994): 3-month neurotoxicity inhalation study

7.0 TABLES OF TRVs FOR INDIVIDUAL VOCs (NO IARLSs RECOMMENDED)

TOXICOLOGICAL REFERENCE VALUES FOR 1,1,2,2-TETRACHLOROETHANE (CAS No. 79-34-5)

Organization	NEOPLASTIC CalEPA
Year of publication	1999[1]
Species	Mice
Endpoint	Liver tumours
Unit risk $(\mu g/m^3)^{-1}$	5.8×10^{-5}
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.17
Critical study[2]	1
Comments[3]	Based on a US EPA oral slope factor. US EPA did not derive an inhalation slope factor.

[1]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2011).
[2]1. NCI (1978a): 78-week gavage study
[3]No IARL was determined because of limited data on health effects from inhalation and the infrequent or lack of detection of these VOCs in Canadian homes.

TOXICOLOGICAL REFERENCE VALUES FOR 1,2-DICHLOROETHANE (CAS No. 107-06-2)

	NEOPLASTIC			NON-NEOPLASTIC	
Organization[1]	CalEPA	RIVM	US EPA	ATSDR	CalEPA
Year of publication	1985[2]	2001	1991	2001	2001
Species	Rats	Rats (assumed)	Rats	Rats	Rats
Endpoint	Hemangiosarcomas	Hemangiosarcomas	Hemangiosarcomas	No effects	Effects on liver
Unit risk $(\mu g/m^3)^{-1}$	2.1×10^{-5}	2.1×10^{-6}	2.6×10^{-5}		
Concentration at 1×10^{-5} risk level $(\mu g/m^3)$	0.48	4.8	0.38		
Point of departure				NOAEL = 222 mg/m^3	NOAEL = 40 mg/m^3 $NOAEL_{HEC}$ = 12 mg/m^3
Uncertainty factors[3]				90 (UF_H = 3, UF_A = 10, UF_{DB} = 3)	30 (UF_H = 10, UF_A = 3)
Concentration $(\mu g/m^3)$				2500	400
Critical study[4]	1	1, 2	1	3	4
Comments[5]	Based on gavage study	Based on gavage study Assessment in Dutch; summary available only in English	Based on gavage study As of 2000, under review by US EPA IRIS	One dose, no control group	$NOAEL_{HEC}$ = PoD x 5/7 days x 7/24 hours x 1.5 (RGDR)

[1]The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_{DB} = database deficiency
[4]1. NCI (1978b): 78-week gavage study; 2. Vemeire et al. (1991): gavage study (length of study unspecified); 3. Cheever et al. (1990): 2-year inhalation study; 4. Spreafico et al. (1980): 1-year inhalation study
[5]No IARL was determined as new data on inhalation health effects have become available and existing TRVs were derived from oral exposure studies. A 2014 Health Canada assessment for the derivation of a guideline for Canadian drinking water quality identified a 2006 inhalation study as the critical study.

TOXICOLOGICAL REFERENCE VALUES FOR 4,4'-METHYLENEDIANILINE (CAS No. 101-77-9)

	NEOPLASTIC	NON-NEOPLASTIC
Organization	**CalEPA**	**CalEPA**
Year of publication	1999[1]	2001[1]
Species	Mice	Guinea pigs
Endpoint	Liver tumours	Ocular toxicity
Unit risk $(\mu g/m^3)^{-1}$	4.6×10^{-4}	
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.02	
Point of departure		LOAEL = 440 mg/m^3 $LOAEL_{ADJ}$ = 52 mg/m^3 $LOAEL_{HEC}$ = 52 mg/m^3
Uncertainty factors[2]		3000 (UF_H=10, UF_A=3, UF_S=10, UF_L=10)
Concentration ($\mu g/m^3$)		20
Critical study[3]	1	2
Comments[4]	Inhalation unit risk derived from an oral cancer potency factor in male mice exposed to 4,4'-methylenedianiline dihydrochloride in drinking water	$LOAEL_{ADJ}$ = LOAEL x 4 hours/24 hours x 5 days/7 days $LOAEL_{HEC}$ = $LOAEL_{ADJ}$ x 1 (RGDR)

[1]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b, 2011).
[2]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration, UF_L = LOAEL uncertainty
[3]NTP (1983): 103-week ingestion study (drinking water); 2. Leong et al. (1987): 2-week inhalation study (nose-only)
[4]No IARL was determined because of limited data on health effects from inhalation and lack of detection in Canadian homes.

TOXICOLOGICAL REFERENCE VALUES FOR PHENOL (CAS No. 108-95-2)

	NON-NEOPLASTIC	
Organization[1]	CalEPA	**RIVM**
Year of publication	2000[2]	2001
Species	Rats, mice, and monkeys	Rats, mice, and monkeys
Endpoint	No effect on pulmonary, cardiovascular, hematological, hepatic or renal systems (NOAEL). Neurological and hepatic effects (LOAEL).	Not reported
Point of departure	NOAEL = 20 mg/m^3 $NOAEL_{HEC}$ = 20 mg/m^3	NOAEC = 20 mg/m^3
Uncertainty factors[3]	100 (UF_H = 10, UF_A = 3, UF_S = 3)	1000 ($UF_{H,A}$ = 100, UF_S = 10)
Concentration (µg/m^3)	200	20
Critical study[4]	1, 2	(1)
Comments[5]	$NOAEL_{HEC}$ = NOAEL x 1 (RGDR) LOAEL = 26 ppm	RIVM cited ATSDR (1998) as the source of the NOAEC. However, the updated ATSDR Toxicological Profile (2008) does not explicitly report a NOAEC and ATSDR considered the reviewed studies as inadequate. The NOAEC was likely derived from the summary of Sandage (1961) reported in ATSDR (1998).

[1]The RIVM assessment was published under the authorship of Baars et al. (2001).
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from CalEPA reports (2015, 2014a, 2014b).
[3]UF_H = intraspecies variability, UF_A = interspecies variability, UF_S = extrapolation for study duration
[4]1. Sandage (1961): 90-day inhalation study; 2. Dalin and Kristoffersson (1974): 15-day inhalation study.
[5]No IARL was determined because of a limited toxicological database

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