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Indoor air reference levels for chronic exposure to volatile organic compounds

2024

Water and Air Quality Bureau
Health Canada

Canada

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List of acronyms

ANSES	Agence nationale de sécurité sanitaire, de l'alimentation, de l'environnement et du travail (France)
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	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)
CAS RN	Chemical Abstract Service registry number
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
MRL	minimal risk level
NOAEL	no observed adverse effect level
OEHHA	California Office of Environmental Health Hazard Assessment
PBPK	physiologically based pharmacokinetics
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 in The Netherlands
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

Context

The purpose of this document is to present Health Canada's Indoor Air Reference Levels (IARLs). IARLs are health-based screening values developed for volatile organic compounds (VOCs) that were identified through partner and stakeholder consultation, from Government of Canada priorities, and/or are found in indoor air in Canada. IARLs are selected from available toxicological reference values (TRVs) from authoritative health and environmental organizations. They are associated with an acceptable level of risk following long-term exposure (over several months or years) in non-occupational scenarios for each specific VOC, as determined by the organization that performed the risk assessment. IARLs are selected for VOCs that are not addressed by Residential Indoor Air Quality Guidelines (RIAQG) and may be used to support risk assessment, risk management, and research needs of Health Canada, our partners and stakeholders.

1.0 Introduction

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.

To assist public health professionals who may need to assess the possible risk from exposure to VOCs potentially found in indoor air, Health Canada has selected Indoor Air Reference Levels (IARLs). For a given VOC, the IARL is an estimate of a concentration 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 an acceptable excess cancer risk level of 1 in 10^5. The IARL applies to the general population, including biologically susceptible subgroups.

IARLs are intended to supplement Health Canada's Residential Indoor Air Quality Guidelines (RIAQGs), which are based on comprehensive literature reviews, are externally peer-reviewed, and are posted for public consultation. In developing IARLs, the Health Canada review is limited to hazard assessments from internationally recognized health and environmental organizations and the key studies, as described in these assessments. Health Canada did not perform any new risk assessments for the IARLs, but rather selected the most relevant reference level derived by other organizations.

This document provides a summary of IARLs —current as of April 2023—for chronic exposure to VOCs. It includes IARLs first published in 2017 as well as new IARLs developed for contaminants identified through the Health Canada Indoor Air Program partner and stakeholder consultation and prioritization processes (Health Canada 2023a). Both new IARL candidates and contaminants with existing IARLs were subject to an initial selection process to determine whether they were suitable for development of a new IARL or an update of the existing IARL.

[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.

This document, along with the selected 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 supplementary document entitled *Derivation of Health Canada Indoor Air Reference Levels: Methodology for Volatile Organic Compounds* (Health Canada 2023b), which is available upon request. The methodology describes criteria for selection of candidates, identification of appropriate hazard assessments, and evaluation of hazard assessments based on the strength of the underlying science as well as consistency with Health Canada risk assessment practices for indoor air pollutants. Information on the derivation of individual IARLs is available upon request.

2.0 Considerations in the determination of indoor air reference levels

Authoritative health and environmental agencies and organizations, including Health Canada, follow similar procedures for conducting hazard assessments for cancer and non-cancer endpoints. Many hazard assessments are used to derive TRVs. The TRV nomenclature varies among the different organizations and includes terms such as reference concentration (RfC), tolerable concentration (TC), and minimal risk level (MRL). All TRVs considered in the selection of an IARL provide a quantitative value below which adverse non-cancer health effects are not expected to be observed for durations of up to a lifetime of exposure and include consideration of highly exposed and susceptible subpopulations. For non-threshold carcinogenic effects, the TRVs may be referred to as cancer potency factors, slope factors, or inhalation unit risks. For these TRVs, the level of potential excess lifetime cancer risk that would be considered acceptable is determined. For the purpose of IARLs, an excess cancer risk level of 1 in 10^5 is retained, which is consistent with many other health and environmental agencies and organizations.

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 then typically selected based on the most conservative value of either the identified cancer or non-cancer TRVs but might vary depending on the mode of action of the VOC or other considerations. The full list of IARLs is presented in section 5.0.

3.0 Application of indoor air reference levels

The IARL methodology provides an expedited means of generating health-based quantitative exposure limits for priority contaminants that are present in an indoor environment, are of concern for Health Canada Indoor Air Program partners and stakeholders, and/or are departmental priorities. IARLs can provide scientific support for risk assessment, risk management, and research activities of Health Canada, partners and stakeholders, including:

- the development of product emission standards and regulations for building materials and consumer products
- the development of guides and guidance for professional and non-professional audiences
- the provision of advice to the general public and public health professionals for reducing exposure to indoor air contaminants

- the identification of VOCs that may be appropriate for development of a RIAQG or other risk assessment activities
- the interpretation of data (such as measured or modelled concentrations) in the context of a human health risk assessment in a variety of exposure scenarios

For human health risk assessment applications, when comparing measured or modelled concentrations with IARLs, a statistically significant sample size with a sampling time of at least 24 hours taken under normal conditions is recommended. Averaging of results of repeated samples taken at different times of the year will provide a more representative estimate of the average long-term exposure. In some cases, the mode of action of a particular substance may also justify the use of samples of short durations and their consideration in risk assessment. In general, and especially where these conditions cannot be met, professional judgement should be used to consider all uncertainties that may impact a conclusion of potential risk.

4.0 Uncertainties and assumptions of indoor air reference levels

The IARL selection process has been developed to provide screening values for priority VOCs in an efficient manner. However, as Health Canada did not conduct a full human health risk assessment supported by a comprehensive review of all available data for each VOC, uncertainties are inherent in the IARL process. The first uncertainty arises due to the selection of TRVs derived by health and environmental agencies outside of Health Canada. A concerted effort was made to select high-quality TRVs from authoritative agencies that use risk assessment practices that are compatible with those employed by the Health Canada Indoor Air Program. Nevertheless, each agency has its own approach and policies that may result in a TRV that differs from one that Health Canada would have derived, given the same information. The second uncertainty arises from the date of derivation of the TRVs under consideration and literature search cut-off dates of each assessment. The IARL process considers the date of the TRV derivation and whether key studies were available at the time of derivation. However, in most cases, this information comes from within the assessments themselves as a literature search is not normally conducted as part of the IARL process. In addition, as with most risk assessments, there may be studies not captured by the risk assessment or more recent studies published after the assessment that could change the outcome.

In general, all hazard assessments must consider the uncertainties in the underlying toxicological and epidemiological data. Uncertainty factors, exposure adjustments, and chemical-specific data are used in a precautionary manner to address key assumptions. This approach results in 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 uncertainties inherent in measuring or estimating indoor air concentrations in homes in Canada. Indoor air concentrations measured in homes in Canada can be expected to vary based on factors such as the type, location, and housing characteristics, occupant behaviours, and averaging time of air measurements. Likewise, indoor air concentrations modelled based on VOC emissions observed from products, either in homes or in chamber tests, may differ from actual indoor air concentrations due to factors such as the number, type, pattern of use, and age of source

materials; the rate of decay of the emissions over time; and environmental conditions (such as temperature, humidity, ventilation rate).

Given these uncertainties, comparison of estimated or measured indoor air concentrations with an IARL provides an indication of potential risk and not a measure of actual risk. The current list of IARLs is restricted to values for long-term (or lifetime) exposure and thus caution should be exercised when comparing an IARL with measured values from a single sample or multiple samples collected over a short period of time. VOC levels measured in indoor environments demonstrate a high level of temporal variability based on multiple factors such as seasonal changes. Best practises for the application of IARLs to human health risk assessment include comparison to a statistically significant sample size with a sampling time of at least 24 hours taken under normal conditions, and averaging the results of repeated samples taken at different times of the year to provide a more representative estimate of the long-term exposure. In some cases, the mode of action of a particular substance may also justify the use of samples of short durations and their consideration in risk assessment. Such data may not be available under certain circumstances, such as a contaminated, remote, or hard-to-access site. In such circumstances, the use of either fewer measurements or measurements of shorter duration may be unavoidable, and it is recommended to apply the maximum measured value to assess potential human health risks. Professional judgement should be used to consider how the associated uncertainties may impact conclusions. Health-based limits such as IARLs are best used to help identify sources of contaminants, to help identify the potential need to conduct further risk assessment activities, and/or to employ risk mitigation strategies to reduce exposure.

5.0 Indoor air reference levels

Table 1 summarizes the IARLs selected for 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.

Further information on the derivation of each IARL is available upon request (air@hc-sc.gc.ca).

Table 1. Indoor Air Reference Levels

VOC	CAS RN	IARL ($\mu g/m^3$)	Critical Effect		Reference	IARL Date
			Cancer	Non-Cancer		
1,1-Dichloroethylene	75-35-4	0.06	Kidney tumours	n/a	OEHHA (2017)	2023
trans-1,2-Dichloroethylene	156-60-5	40	n/a	Immunotoxicity	US EPA (2020a)	2023
1,3-Butadiene	106-99-0	1.7	Leukemia	n/a	EC/HC (2000)	2017[1]
1,4-Dichlorobenzene	106-46-7	60	n/a	Nasal lesions	ATSDR (2006a)	2017[1]
1,4-Dioxane	123-91-1	2	Tumours at multiple sites	n/a	US EPA (2013)	2023
2-Butoxyethanol	111-76-2	82	n/a	Nasal lesions	OEHHA (2018)	2023 (updated)
2-Ethoxyethanol	110-80-5	70	n/a	Testicular degeneration and hematological changes	OEHHA (2000)[2]	2017[1]
2-Ethylhexanol	104-76-7	0.4	n/a	Altered olfactory epithelia	US EPA (2019)	2023
3-Chloropropene	107-05-1	1	n/a	Peripheral nerve damage	US EPA (1991a)	2017[1]
Acetone	67-64-1	70 000	n/a	Developmental effects	VCCEP (2003)	2017[1]
Ammonia	7664-41-7	500	n/a	Respiratory symptoms, altered lung function	US EPA (2016a)	2023
Aniline	62-53-3	1	n/a	Effects on spleen	US EPA (1990a)	2017[1]
Carbon tetrachloride	56-23-5	1.7	Adrenal gland tumours	n/a	US EPA (2010a)	2017[1]
Chloroform	67-66-3	300	n/a	Kidney and liver toxicity	OEHHA (2000)[2]	2017[1]
Cyclohexane	110-82-7	6000	n/a	Reduced pup weight	US EPA (2003a)	2017[1]

VOC	CAS RN	IARL ($\mu g/m^3$)	Critical Effect		Reference	IARL Date
			Cancer	Non-Cancer		
Dichloromethane	75-09-2	600	n/a	Effects on liver	US EPA (2011a)	2017[1]
Epichlorohydrin	106-89-8	1	n/a	Histological changes in the nose	US EPA (1994a)	2017[1]
Ethylbenzene	100-41-4	2000	n/a	Effects on pituitary gland and liver	OEHHA (2000)[2]	2017[1]
Ethylene oxide	75-21-8	0.002	Lymphoid and breast cancer	n/a	US EPA (2016b)	2023 (updated)
Isopropyl alcohol	67-63-0	7000	n/a	Kidney lesions	OEHHA (2000)[2]	2017[1]
Isopropylbenzene	98-82-8	400	n/a	Effects on kidney	US EPA (1997)	2017[1]
Methyl ethyl ketone	78-93-3	5000	n/a	Developmental effects	US EPA (2003b)	2017[1]
Methyl isobutyl ketone	108-10-1	3000	n/a	Developmental effects	US EPA (2003c)	2017[1]
Propionaldehyde	123-38-6	8	n/a	Olfactory epithelium atrophy	US EPA (2008)	2017[1]
n-Propylbromide	106-94-5	1.7	n/a	Neurotoxicity	OEHHA (2022a)	2023
Propylene oxide	75-56-9	2.7	Nasal cavity tumours	n/a	US EPA (1990b)	2017[1]
Styrene	100-42-5	850	n/a	Neurotoxicity	ATSDR (2010a)	2017[1]
Tetrachloroethylene	127-18-4	40	n/a	Neurotoxicity, visual impairment, and neurobehavioural effects	US EPA (2012), ATSDR (2014)	2017[1]
Toluene diisocyanate	26471-62-5	0.008	n/a	Decreased lung function	OEHHA (2016)	2023 (updated)
Trichloroethylene	79-01-6	2	Kidney tumours, liver tumours, non-Hodgkin's lymphoma[3]	Thymus and cardiac effects[3]	US EPA (2011b)	2023
Vinyl Chloride	75-01-4	1.1	Liver tumours	n/a	US EPA (2000)	2023

EC/HC, Environment Canada, Health Canada[1] Not updated in 2023 as no new TRVs were identified.
[2] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA (2011, 2014a, 2014b, 2015).
[3] TRVs for non-cancer and cancer effects for trichloroethylene were close enough to be considered equivalent.

6.0 Tables of TRVs for individual VOCs

Toxicological reference values for 1,1-dichloroethylene (CAS RN 75-35-4) (added 2023)

	Cancer		Non-cancer			
Organization	**Health Canada[1]**	**OEHHA[2]**	**ATSDR**	**OEHHA**	**TCEQ**	**US EPA**
Year of publication	2013	**2017**	2022a	2000[3]	2007	2003d
Species	Mice	**Mice**	Rats	Guinea pigs	Rats, Squirrel monkeys, Beagle dogs	Rats
Endpoint	Pulmonary adenomas	**Renal tubule adenoma or carcinoma in males**	Nasal lesions (necrosis of olfactory epithelium)	Liver toxicity (mottled liver and increased enzymes)	Focal necrosis of the liver	Liver toxicity (minimal fatty change)
Unit risk	TC_{05} of 4.2 mg/m^3	**Slope factor of 0.129 (mg/kg-day)$^{-1}$ for male mice**	n/a	n/a	n/a	n/a
Concentration at 1 x 10^{-5} risk level (µg/m^3)	0.8	**0.06**	n/a	n/a	n/a	n/a
Point of departure	n/a	**n/a**	$BMCL_{10}$ = 6.3 mg/m^3 $BMCL_{HEC-ADJ}$ = 0.14 mg/m^3	NOAEL = 20 mg/m^3	NOAEL= 101 mg/m^3	$BMCL_{10}$ = 39 mg/m^3 $BMCL_{10HEC-ADJ}$= 6.9 mg/m^3
Uncertainty factors	n/a	**n/a**	30 (UF_H = 10, UF_A = 3)	300 (UF_H = 10, UF_A = 3, UF_S = 10)	300 (UF_H = 10, UF_A = 3, UF_S = 10)	30 (UF_H = 10, UF_A = 3)
Concentration (µg/m^3)	n/a	**n/a**	4	70	340	200
Critical study[4]	2	**1**	1	3	3	4
Comments	TC05 of 4.2 mg/m3 is 1/20 risk. Divide by 5000 to get total risk of 10-4	**The animal slope factor was converted by OEHHA to a slope factor of 0.80 (mg/kg-day)-1 for humans** **NSRL was presented as 0.88 µg/day for 10-5 risk. This converts to an air concentration of 0.06 µg/m3 assuming an inhalation rate of 15.1 m3 /day**	BMCLHEC-ADJ = BMCL x 5/7 days x 7/24 hours x 0.13 Where 0.13 is the RGDRET (rat:human)5 Note that ATSDR used ppm for units. MRL = 0.001 ppm	n/a	Quast et al. 1986 was a supporting study	BMCL10HEC-ADJ = BMCL10 x 5/7 days x 7/24 hours

NSRL, No significant Risk Level

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2013).

[2] The OEHHA cancer TRV was retained as the IARL.

[3] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA report 2014b.

[4] 1. NTP (2015): 14-week and 2-year inhalation study. 2. Maltoni et al. (1984a, 1985): 1-year inhalation study.3. Prendergast et al. (1967): 90-day continuous inhalation study. 4. Quast et al. (1986): 18-month inhalation study. [5] $RGDR_{ET}$ (rat: human) = regional gas dose ratio (rat:human) for the extrathoracic region of the respiratory tract.

Toxicological reference values for trans-1,2-dichloroethylene (CAS RN 156-60-5) (added 2023)

Organization	Non-cancer		
	ATSDR[1]	**RIVM[2]**	**US EPA[3,4]**
Year of publication	1996	2001	**2020a**
Species	Rats	Rats	**Rats**
Endpoint	Fatty degeneration of liver	Fatty degeneration of liver, effects in lungs	**Immunotoxicity (Decreased lymphocyte count)**
Point of departure	LOAEL = 200 ppm (800 mg/m^3)	LOAEL = 780 mg/m^3 $LOAEL_{ADJ}$ = 185 mg/m^3	**$BMCL_{HEC}$ = 109 mg/m^3**
Uncertainty factors	1000 (UF_H = 10, UF_A = 10, UF_L = 10)	3000 (UF_H = 10, UF_A = 10, UF_L = 10, UF_S = 3)	**3000 (UF_H = 10, UF_A = 3, UF_S = 10, UF_D = 10)**
Concentration (µg/m^3)	800	60	**40**
Critical study[5]	1	1	**2**
Comments	s/o	$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 8/24 hours	**$BMCL_{HEC}$ = BMCL x 5/7 days x 7/24 hours x 1 (default for RGDR as rat>human)**

[1] ATSDR derived an intermediate MRL.
[2] RIVM derived a provisional TC. The RIVM assessment was published under the authorship of Baars et al. (2001).
[3] The US EPA TRV was retained as the IARL.
[4] The US EPA derived a screening level provisional RfC.
[5] 1. Freundt et al. (1977): 8- and 16-week inhalation study; 2. Kelly (1998): 90-day inhalation study.

Toxicological reference values for 1,3-butadiene (CAS RN 106-99-0)

	Cancer			Non-cancer	
Organization	**Health Canada[1,2]**	**OEHHA**	**US EPA**	**OEHHA**	**US EPA**
Year of publication	**2000**	1992[3]	2002	2013[3]	2002
Species	**Humans**	Mice	Humans	Mice	Mice
Endpoint	**Leukemia**	Lung tumours	Leukemia	Ovarian atrophy	Ovarian atrophy
Unit risk ($\mu g/m^3)^{-1}$	**5.9×10^{-6}**	1.7×10^{-4}	3×10^{-5}	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	**1.7**	17	0.3	n/a	n/a
Point of departure	**n/a**	n/a	n/a	$BMCL_{05\ HEC}$ = 0.664 mg/m^3	$BMCL_{10\ HEC}$ = 2 mg/m^3
Uncertainty factors	**n/a**	n/a	n/a	300 (UF_H = 10, UF_A = 30)	1000 (UF_H = 10, UF_A = 3, UF_L = 10, UF_{DB} = 3)
Concentration ($\mu g/m^3$)	**n/a**	n/a	n/a	2.2	2
Critical study[4]	**2**	1	2	3	3
Comments	**TC_{01} = 1.7 mg/m^3** **Unit risk = (0.01)/TC_{01}**	n/a	LEC_{01} = 300 $\mu g/m^3$ 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 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 (2000).
[2] The Health Canada TRV was retained as the IARL: The same database was used for the US EPA and Health Canada cancer assessments, but the Health Canada TRV was selected as it used a methodology that was considered to be more consistent with Indoor Air Program practices.
[3] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[4] 1. Melnick et al. (1990): 2-year inhalation study; 2. Delzell et al. (1995): retrospective cohort; 3. NTP (1993): 2-year inhalation study.

Toxicological reference values for 1,4-dichlorobenzene (CAS RN 106-46-7)

	Cancer	Non-cancer				
Organization	**OEHHA**	**ATSDR[1]**	**Health Canada[2]**	**OEHHA**	**RIVM[3]**	**US EPA**
Year of publication	1999[4]	**2006a**	1993a; 1996	2001[4]	2001	1994b
Species	Mice	**Rats**	Rats	Rats	Rats	Rats
Endpoint	Liver tumours	**Nasal lesions**	Increased liver and kidney weights; increased urinary protein/coproporphyrin	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 weight
Unit risk ($\mu g/m^3)^{-1}$	1.1×10^{-5}	**n/a**	n/a	n/a	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.9	**n/a**	n/a	n/a	n/a	n/a
Point of departure	n/a	**LOAEL = 450 mg/m^3** **NOAEL = 120 mg/m^3** **$BMCL_{10}$ = 57 mg/m^3** **$BMCL_{10\ ADJ}$ = 10 mg/m^3** **$BMCL_{10\ HEC}$ = 1.6 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 = 900 mg/m^3 NOAEL = 300 mg/m^3 $NOAEL_{ADJ}$ = 78mg/m^3 $NOAEL_{HEC}$ = 78 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	n/a	**30** **(UF_H = 10, UF_A = 3)**	500 (UF_H = 10, UF_A = 10, UF_S = 5)	100 (UF_H = 10, UF_A = 3, UF_S = 3)	100 (UF_H = 10, UF_A = 10)	100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration ($\mu g/m^3$)	n/a	**60**	95	800	670	800
Critical study[5]	1	**2, 3**	5	4	6	4
Comments	n/a	**$BMCL_{10\ HEC}$ = $BMCL_{10}$ x 5/7 days x 6/24 hours x 0.16 (RGDR)**	$NOAEL_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 0.71 (breathing rate adjustment)	$NOAEL_{HEC}$ = NOAEL x 7/7 days x 6/24 hours x 1.0 (RGDR)	$NOAEL_{ADJ}$ = 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 ATSDR TRV was retained as the IARL: Linear low-dose extrapolation was not considered appropriate for a non-genotoxic carcinogen; therefore, the cancer TRV from OEHHA was not selected as the IARL. For the non-cancer endpoint, the ATSDR TRV was selected as it used a recent chronic inhalation study that was not available at the time of the other assessments.

[2].The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993a) and Health Canada (1996).

[3] The RIVM assessment was published under the authorship of Baars et al. (2001).

[4] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).

[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 1,4-dioxane (CAS RN 123-91-1) (added 2023)

Organization	Cancer		Non-cancer		
	OEHHA	US EPA[1]	ATSDR	OEHHA	US EPA
Year of publication	2011	**2013**	2012	2000[2]	2013
Species	Mice	**Rats**	Rats	Rats	Rats
Endpoint	Hepatocellular carcinoma and adenoma	**Multiple tumour sites**	Atrophy of the olfactory epithelium	No effects (inhalation study)	Atrophy and respiratory metaplasia of the olfactory epithelium
Unit risk $(\mu g/m^3)^{-1}$	7.7×10^{-6}	**5×10^{-6}**	n/a	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.3	**2**	n/a	n/a	n/a
Point of departure	n/a	**n/a**	LOAEL = 180 mg/m^3 $LOAEL_{HEC}$ = 32 mg/m^3	NOAEL= 400 mg/m^3 $NOAEL_{HEC}$ = 83 mg/m^3	LOAEL = 180 mg/m^3 $LOAEL_{HEC}$ = 32.2 mg/m^3
Uncertainty factors	n/a	**n/a**	300 (UF_A= 3, UF_L= 10, UF_H=10)	30 (UF_A= 3, UF_H= 10)	1000 (UF_A = 3, UF_H = 10, UF_L = 10, UF_{DB} = 3)
Concentration ($\mu g/m^3$)	n/a	**n/a**	100	3000	30
Critical study[3]	3	**1**	1	2	1
Comments	Linear multistage model Cancer potencies were adjusted using the factors (x 104/90 weeks)^3 and $(bw_h/bw_a)^{1/3}$. Route-to-route extrapolation (oral-to-inhalation) assuming a human body weight of 70 kg and an inhalation rate of 20 m^3 per day	**Multi-tumour BMD analysis to determine the combined BMC_{10} and the $BMCL_{10}$.** **$BMCL_{HEC}$ =BMCL x 6/24 hours x 5/7 days x 1 (where 1 is the default DAF)** **IUR = BMR / $BMCL_{HEC}$, where the BMR was 0.1**	$LOAEL_{HEC}$ = LOAEL x 6/24 hours x 5/7 days x 1 (where 1 is the default used when the ratio of animal to human blood: air partition coefficients is greater than 1)	$NOAEL_{HEC}$ = NOAEL x 7/24 hours x 5/7 days x 1 (where 1 is the default ratio of animal to human blood: air partition coefficients) Supported by liver, kidney, and hematological effects in drinking water study (NCI 1978)	$LOAEL_{HEC}$ = LOAEL x 6/24 hours x 5/7 days x 1 (where 1 is the default DAF)

[1] The US EPA cancer TRV was retained as the IARL: The cancer TRV from the US EPA assessment was selected as it used a more recent inhalation study, compared with the older oral study used by the OEHHA. The US EPA assessment was also more recent and incorporated mode of action data.
[2] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA report 2014b.
[3] 1. Kasai et al. (2009): 2-year inhalation study; 2. Torkelson et al. (1974): 2-year inhalation study; 3. National Cancer Institute (1978): 90-week drinking water study.

Toxicological reference values for 2-butoxyethanol (CAS RN 111-76-2) (Updated 2023)

	Non-cancer			
Organization	**ATSDR**	**Health Canada[1]**	**OEHHA[2]**	**US EPA**
Year of publication	1998	2002	**2018**	2010b
Species	Humans	Rats	**Rats**	Rats
Endpoint	Hematological effects	Hematological effects	**Hyaline degeneration of nasal olfactory epithelium**	Hemosiderin deposition
Point of departure	NOAEL = 2.9 mg/m^3	BMC_{05} = 5.3 mg/m^3	**$BMCL_{05,HEC}$ = 2.46 mg/m^3**	$BMCL_{10,HEC}$ = 16 mg/m^3
Uncertainty factors	3 (UF_H = 3)	0.5 (UF_H = 10, UF_A = 0.05)	**30** **(UF_H = 10, UF_A = 3)**	10 (UF_H = 10, UF_A = 1, UF_{DB} = 1)
Concentration (µg/m^3)	970	11 000	**82**	1600
Critical study[3]	1	2	**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 with rats.	**UF_A includes only the toxicodynamic portion, since the HEC accounted for toxicokinetics by use of the RGDR.**	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 OEHHA TRV was retained as the IARL.
[3]1. Haufroid et al. (1997): occupational study; 2. NTP (1998, 2000): 2-year inhalation study.

Toxicological reference values for 2-ethoxyethanol (CAS RN 110-80-5)

	Non-cancer		
Organization	**OEHHA[1]**	**US EPA**	**WHO**
Year of publication	**2000[2]**	1991b	2010a
Species	**Rabbits**	Rabbits	Rats
Endpoint	**Testicular degeneration and hematological changes**	Testicular degeneration and hematological changes	Teratogenicity (delayed ossification) and preimplantation loss
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	**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 (µg/m^3)	**70**	200	100
Critical study[3]	**1**	1	2, 3
Comments	**NOAEL$_{ADJ}$ = NOAEL x 6/24 hours x 5/7 days** **NOAEL$_{HEC}$ = NOAEL$_{ADJ}$ x 1 (RGDR)**	NOAEL$_{ADJ}$ = NOAEL x 6/24 hours x 5/7 days NOAEL$_{HEC}$ = NOAEL$_{ADJ}$ x 1 (RGDR) US EPA has medium confidence in the study, database and RfC.	NOAEL$_{ADJ}$ = NOAEL x 6/24 hours

[1]The OEHHA TRV was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2014a, 2014b, 2015).
[3]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 2-ethylhexanol (CAS RN 104-76-7) (added 2023)

Organization	Non-cancer US EPA[1]
Year of publication	**2019**
Species	**Mice**
Endpoint	**Diameter increase in the Bowman's glands in olfactory epithelium**
Point of departure	**LOAEL = 116 mg/m^3** **LOAEL$_{adj\text{-}HEC}$ = 4.17 mg/m^3** **BMCL$_{1SD\ (HEC)}$ = 1.1 mg/m^3**
Uncertainty factors	**3000 (UF$_A$= 3, UF$_{DB}$= 10, UF$_H$= 10, UF$_S$= 10)**
Concentration (µg/m^3)	**0.4**
Critical study[2]	**1**
Comments	**LOAEL$_{adj\text{-}HEC}$ = LOAEL x 5/7 days x 8/24 hours x RGDR$_{ET}$ (mouse: human)[3]** **The BMCL$_{1SD\ (HEC)}$ was used as the POD**

[1] The US EPA TRV was retained as the IARL.
[2] 1. Miyake et al. (2016): 3-month inhalation study.
[3] RGDR$_{ET}$ (mouse: human) = regional gas dose ratio (mouse:human) for the extrathoracic region of the respiratory tract.

Toxicological reference values for 3-chloropropene (CAS RN 107-05-1)

	Cancer	Non-cancer
Organization	**OEHHA**	**US EPA[1]**
Year of publication	1999[2]	**1991a**
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}	**n/a**
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.67	**n/a**
Point of departure	n/a	**NOAEL = 17 mg/m^3** **$NOAEL_{ADJ}$ = 3.6 mg/m^3** **$NOAEL_{HEC}$ = 3.6 mg/m^3**
Uncertainty factors	n/a	**3000** **(UF_H = 10, UF_A = 3, UF_S = 10, UF_{DB} = 10)**
Concentration ($\mu g/m^3$)	n/a	**1**
Critical study[3]	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 US EPA TRV was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2015).
[3]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)

Organization	Non-cancer ATSDR	VCCEP[1,2]
Year of publication	1994	**2003**
Species	Humans	**Rats**
Endpoint	Increased amplitude of visual evoked response	**Decreased fetal body weight**
Point of departure	LOAEL = 3000 mg/m^3	**NOAEL = 5300 mg/m^3** **NOAEL$_{HEC}$ = 2100 mg/m^3**
Uncertainty factors	100 (UF$_H$ = 10, UF$_L$ = 10)	**30** **(UF$_H$ = 10, UF$_A$ = 3)**
Concentration (µg/m^3)	31 000	**70 000**
Critical study[3]	1	**2**
Comments	n/a	**NOAEL$_{HEC}$ calculated using PBPK modelling**

[1]The VCCEP assessment was published under the authorship of the American Chemistry Council Acetone Panel (2003).
[2]The VCCEP TRV was retained as the IARL: The TRV from the ATSDR assessment was not considered appropriate as the key study had significant weaknesses, and the US EPA considered it insufficient for deriving an RfC. A Health Canada assessment also considered the 6-week study used by ATSDR as indicative of short-term rather than long-term effects. Therefore the value derived by the VCCEP was selected as the IARL.
[3]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 ammonia (CAS RN 7664-41-7) (added 2023)

Organization	Non-cancer			
	ATSDR	OEHHA	TCEQ	US EPA[1]
Year of publication	2004	2000[2]	2015	**2016a**
Species	Humans	Humans	Humans	**Humans**
Endpoint	Altered lung function, irritation	Altered lung function, irritation	Respiratory effects	**Altered lung function, respiratory symptoms**
Point of departure	NOAEL= 6500 µg/m^3 NOAEL$_{ADJ}$ = 1500 µg/m^3	NOAEL= 6500 µg/m^3 NOAEL$_{ADJ}$ = 2300 µg/m^3	NOAEL = 8800 µg/m^3 NOAEL$_{ADJ}$ = 3200 µg/m^3	**NOAEL = 13 600 µg/m^3** **NOAEL$_{ADJ}$ = 4900 µg/m^3**
Uncertainty factors	30 (UF$_H$= 10, UF$_{DB}$= 3)	10 (UF$_H$ = 10)	10 (UF$_H$ = 10)	**10 (UF$_H$ = 10)**
Concentration (µg/m^3)	71	200	320	**500**
Critical study[4]	1	1	1	**1**
Comments	NOAEL = mean TWA exposure concentration (9.2 ppm) NOAEL$_{ADJ}$ = NOAEL x 5/7 days x 8/24 hours	NOAEL = mean TWA exposure concentration (9.2 ppm) NOAEL$_{ADJ}$ = NOAEL x 5/7 days x 10/20 m^3/day	NOAEL = high exposure group (12.5 ppm) NOAEL$_{ADJ}$ = NOAEL x 5/7 days x 10/20 m^3/day	**NOAEL = 95% lower confidence bound of mean in the high exposure group** **NOAEL$_{ADJ}$ =** **NOAEL x 5/7 days x 10/20 m^3/day**

[1] The US EPA TRV was retained as the IARL: All of the TRVs were based on the same key study but used different methods for determining the point of departure. The US EPA used the frequency distribution of the exposure data to estimate the mean of the high exposure group and its 95% lower confidence bound, which was then used to derive the TRV; this comprehensive assessment was also the most recent and was therefore selected for the IARL.
[2] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA report 2014b.
[3] 1. Holness et al. (1989): occupational study.

Toxicological reference values for aniline (CAS RN 62-53-3)

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

[1]The US EPA TRV was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2015).
[3]1. CIIT (1982): 2-year ingestion study; 2.Oberst et al. (1956): 20- to 26-week inhalation study; 3. E.I. DuPont de Nemours and Company Inc. (1982): 2-week inhalation study.

Toxicological reference values for carbon tetrachloride (CAS RN 56-23-5)

	Cancer		Non-cancer				
Organization	**OEHHA**	**US EPA[1]**	**ATSDR**	**OEHHA**	**RIVM[2]**	**US EPA**	**WHO**
Year of publication	1987[3]	**2010a**	2005	2001[3]	2001	2010a	1999a
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}**	n/a	n/a	n/a	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.24	**1.7**	n/a	n/a	n/a	n/a	n/a
Point of departure	n/a	**n/a**	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	n/a	**n/a**	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 ($\mu g/m^3$)	n/a	**n/a**	190	40	60	100	(1) 6.1 (2) 6.7 (3) 11.4
Critical study[4]	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 x 5/7 days x 6/24 hrs x 1 (RGDR)	$LOAEL_{HEC}$ = LOAEL x 5/7 days x 7/24 hrs x 1.7 (RGDR)	$NOAEL_{HEC}$ = NOAEL x 5/7 days x 7/24 hrs	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 US EPA cancer TRV was retained as the IARL: The US EPA cancer TRV was selected as the IARL as it was based on a more recent inhalation study compared with the older, oral study used by the OEHHA.
[2] The RIVM assessment was published under the authorship of Baars et al. (2001).
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[4]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. Prendergast (1967): 90-day inhalation study.

Toxicological reference values for chloroform (CAS RN 67-66-3)

	Cancer			Non-cancer		
Organization	**Health Canada[1]**	**OEHHA**	**US EPA**	**ATSDR**	**OEHHA[2]**	**RIVM[3]**
Year of publication	2001a	1990[4]	2001	1997	**2000[4]**	2001
Species	Rats	Rats	Mice	Humans	**Rats**	Rats
Endpoint	Kidney tumours	Kidney tumours	Hepatocellular carcinoma	Liver toxicity	**Kidney and liver toxicity**	None
Unit risk $(\mu g/m^3)^{-1}$	n/a	5.3×10^{-6}	2.3×10^{-5}	n/a	**n/a**	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	n/a	1.9	0.4	n/a	**n/a**	n/a
Point of departure	n/a	n/a	n/a	LOAEL = 10 mg/m^3	**LOAEL = 120 mg/m^3 $LOAEL_{HEC}$ = 75 mg/m^3**	NOAEL = 110 mg/m^3
Uncertainty factors	n/a	n/a	n/a	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	n/a	n/a	100	**300**	100
Critical study[5]	1	1, 2, 3, 4	2	5	**6**	6
Comments	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.	Linear multistage procedure with PBPK. Based on a 1990 California Department of Health Services analysis.	Linearized multistage procedure, extra risk	n/a	**$LOAEL_{HEC}$ = LOAEL x 5/7 days x 7/24 hours x 3 (RGDR) OEHHA used a different part of the same study as RIVM.**	UF_S for 4 hours/day, 5 days/week, 6-month exposure. RIVM used a different part of the same study as OEHHA.

[1]The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (2001a).
[2]The OEHHA non-cancer TRV was retained as the IARL: Linear extrapolation was not considered appropriate for this non-genotoxic carcinogen. For non-cancer effects, a clearer point of departure could be determined from the animal study compared with the human study. The LOAEL identified by OEHHA for 7-hour per day exposure was considered more appropriate than the NOAEL identified by RIVM for 4-hour per day exposure.
[3] The RIVM assessment was published under the authorship of Baars et al. (2001).
[4] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[5]1. Jorgenson et al. (1985): 2-year drinking water study; 2. NCI (1976): 78-week gavage study; 3. Roe et al. (1979): 80-week study in toothpaste; 4. Tumasonis et al. (1985): 2-year drinking water study; 5. Bomski et al. (1967): 1- to 4-year occupational case-control study; 6. Torkelson et al. (1976): 6-month inhalation study.

Toxicological reference values for cyclohexane (CAS RN 110-82-7)

	Non-cancer
Organization	**US EPA[1]**
Year of publication	**2003a**
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	**300** **(UF_H = 10, UF_A = 3, UF_{DB} = 10)**
Concentration (µg/m^3)	**6000**
Critical study[3]	**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 US EPA TRV 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]1,2. DuPont HLR (1997); Kreckmann et al. (2000): 2-generation reproductive inhalation study.

Toxicological reference values for dichloromethane (CAS RN 75-09-2)

	Cancer				Non-cancer			
Organization	**Health Canada[1]**	**OEHHA**	**US EPA**	**ATSDR**	**ATSDR**	**OEHHA**	**RIVM[2]**	**US EPA[3]**
Year of publication	1993b	1989[4]	2011a	2000	2000	2000[3]	2001	**2011a**
Species	Mice	Mice	Mice	Rats	Rats	Humans	Humans	**Rats**
Endpoint	Lung tumours	Lung tumours	Lung and liver tumours	Effects on liver	Effects on liver	Increased carboxyhemoglobin	Increased carboxyhemoglobin	**Effects on liver**
Unit risk $(\mu g/m^3)^{-1}$	2.3×10^{-8}	1.0×10^{-6}	1.0×10^{-8}	n/a	n/a	n/a	n/a	**n/a**
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	435	10	1000	n/a	n/a	n/a	n/a	**n/a**
Point of departure	n/a	n/a	n/a	NOAEL = 170 mg/m^3 $NOAEL_{ADJ}$ = 31 mg/m^3	NOAEL = 170 mg/m^3 $NOAEL_{ADJ}$ = 31 mg/m^3	LOAEL = 139 000 $\mu g/m^3$ $LOAEL_{ADJ}$ = 48 700 $\mu g/m^3$	LOAEL = 90 mg/m^3 $LOAEL_{ADJ}$ = 3 mg/m^3	**$BMDL_{10}$ = 532 mg dichloromethane metabolized via CYP pathway/L liver tissue/day** **$HEC_{1\%}$ = 17.2 mg/m^3**
Uncertainty factors	n/a	n/a	n/a	30 (UF_H = 10, UF_A = 3)	30 (UF_H = 10, UF_A = 3)	100 (UF_H = 10, UF_L = 10)	1	**30** **(UF_H = 3, UF_A = 3, UF_{DB} = 3)**
Concentration ($\mu g/m^3$)	n/a	n/a	n/a	1000	1000	400	3000	**600**
Critical study[5]	1, 2	1, 2	1, 2	3	3	4	4	**3**
Comments	Based on the lowest PBPK modified $TD_{0.05}$ value.	n/a	Application of age-dependent adjustment factors results in a 70-year risk of 1.7×10^{-8}.	$NOAEL_{ADJ}$ = NOAEL x 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.	$NOAEL_{ADJ}$ = NOAEL x 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 Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993b).
[2]The RIVM assessment was published under the authorship of Baars et al. (2001).
[3]The US EPA non-cancer TRV was retained as the IARL: The US EPA assessments were the most recent and included BMD modelling and refinements to the PBPK model. The use of rat data for the non-cancer TRV was also considered more appropriate than those that used human data due to issues of study quality (that is., a low number of subjects and limited exposure information in the human studies).
[4]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[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 RN 106-89-8)

	Cancer		Non-cancer	
Organization	**OEHHA**	**US EPA**	**OEHHA**	**US EPA[1]**
Year of publication	1999[2]	1988	2001[2]	**1994a**
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}	n/a	**n/a**
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.43	8	n/a	**n/a**
Point of departure	n/a	n/a	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	n/a	n/a	100 (UF_H =10, UF_A = 3, UF_S = 3)	**300** **(UF_H = 10, UF_A = 3, $UF_{S,\ DB}$ = 10)**
Concentration ($\mu g/m^3$)	n/a	n/a	3	**1**
Critical study[3]	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 Konishi et al. (1980) study). Relevance of forestomach tumours in rodents to humans is unclear and not well addressed in this assessment.	n/a	$NOAEL_{ADJ}$ = NOAEL x 6/24 hours x 5/7 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 6/24 hours x 5/7 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, the study, and the database.**

[1]The US EPA non-cancer TRV was retained as the IARL: Tumours are related to exposure route; therefore the OEHHA cancer assessment based on forestomach tumours observed in an oral study was not considered appropriate for the IARL; the nasal tumours resulting from inhalation exposure were considered a more relevant endpoint.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[3]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 RN 100-41-4)

	Cancer		Non-cancer				
Organization[1]	**OEHHA**	**VCCEP**	**ATSDR**	**OEHHA[1]**	**RIVM[2]**	**US EPA**	**VCCEP**
Year of publication	2007[3]	2007	2010b	**2000[3]**	2001	1991c	2007
Species	Rats	Mice	Rats	**Rats and mice**	Rats and mice	Rabbits	Rats
Endpoint	Kidney tumours	Lung tumours	Effects on kidney	**Effects on pituitary gland and liver (mice)**	Effects on liver and kidney	Developmental effects	Auditory effects
Unit risk ($\mu g/m^3)^{-1}$	2.5×10^{-6}	n/a	n/a	**n/a**	n/a	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	4	n/a	n/a	**n/a**	n/a	n/a	n/a
Point of departure	n/a	40 500 mg metabolized in lung/kg lung/wk	LOAEL = 330 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
Uncertainty factors	n/a	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 = 10)	300 (UF_H = 10, UF_A = 3, UF_S = 10)	100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration ($\mu g/m^3$)	n/a	2100	260	**2000**	770	1000	1300
Critical study[6]	1	1	1	**1, 2**	3	4, 5	6
Comments	More recent evidence suggests ethylbenzene may be a threshold carcinogen.	n/a	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 Subchronic study	US EPA has low confidence in this derivation; published prior to NTP (1999).	Subchronic study supportive of chronic effects.

[1] The OEHHA non-cancer TRV was retained as the IARL: Linear low-dose extrapolation was not considered appropriate for a non-genotoxic carcinogen; therefore the cancer TRV from OEHHA was not selected. The non-cancer TRV from OEHHA was selected as the IARL as the key study was of chronic duration, with relevant endpoints.
[2] The RIVM assessment was published under the authorship of Baars et al. (2001).
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[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]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 et al. (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 RN 75-21-8) (updated 2023)

	Cancer				Non-cancer	
Organization	**Health Canada[1]**	**OEHHA**	**TCEQ**	**US EPA[2]**	**ATSDR**	**OEHHA**
Year of publication	2001b	1987[3]	2020	**2016b**	2022b	2001[3]
Species	Rats	Rats	Humans	**Humans**	Rats	Mice
Endpoint	Mononuclear leukemia	Mononuclear leukemia	Lymphoid cancer	**Lymphoid and breast cancer**	Decreased pup body weight	Neurological effects
Unit risk $(\mu g/m^3)^{-1}$	2.3×10^{-5}	8.8×10^{-5}	2.3×10^{-6}	**5.0×10^{-3}**	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.43	0.11	4.3	**0.002**	n/a	n/a
Point of departure	n/a	n/a	n/a	**n/a**	NOAEL = 18 mg/m^3 $NOAEL_{ADJ}$ = 3.8 mg/m^3	NOAEL = 18 mg/m^3 $NOAEL_{ADJ}$ = 3.2 mg/m^3
Uncertainty factors	n/a	n/a	n/a	**n/a**	30 (UF_H = 10, UF_A = 3)	100 (UF_H = 10, UF_A = 3, UF_S = 3)
Concentration ($\mu g/m^3$)	n/a	n/a	n/a	**n/a**	130	30
Critical study[4]	2	1	3	**3**	4	2
Comments	Unit risk of 2.3×10^{-5} $(\mu g/m^3)^{-1}$ estimated from TC_{05} value of 2.2 mg/m^3	Based on a 1985 US EPA analysis that considered human equivalent dose.	Age-dependent adjustment factors were applied to the adult UR.	**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 5.85/7 days x 6/24 hours Where 5.85 is the weighted average	$NOAEL_{ADJ}$ = 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 US EPA TRV was retained as the IARL.
[3]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).
[4]1. Snellings et al. (1981): 2-year inhalation study; 2. Snellings et al. (1984): 10- or 11-week inhalation study; 3. Steenland et al. (2003, 2004): retrospective cohort; 4. US EPA 1994c: 2-generation inhalation study.

Toxicological reference values for isopropyl alcohol (CAS RN 67-63-0)

Organization	Non-cancer OEHHA[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	**30** **(UF_H = 10, UF_A = 3)**
Concentration (µg/m^3)	**7000**
Critical study[3]	**1**
Comments	**$NOAEL_{HEC}$ = NOAEL x 5/7 days x 6/24 hours x 1 (RGDR)**

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

Toxicological reference values for isopropylbenzene (CAS RN 98-82-8)

Organization	Non-cancer 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	**1000** **(UF_H = 10, UF_A = 10, UF_S = 10)**
Concentration (µg/m^3)	**400**
Critical study[2]	**1**
Comments	**$NOAEL_{HEC}$ = POD x 5/7 days x 6/24 hours x 1 (RGDR)**

[1]The US EPA TRV was retained as the IARL.
[2]1. Cushman et al. (1995): 13-week inhalation study.

Toxicological reference values for methyl ethyl ketone (CAS RN 78-93-3)

Organization	Non-cancer US EPA[1]
Year of publication	**2003b**
Species	**Rats**
Endpoint	**Developmental effects**
Point of departure	**LEC_{10} = 5202 mg/m^3** **$LEC_{10\ HEC}$ = 1517 mg/m^3**
Uncertainty factors	**300** **(UF_H = 10, UF_A = 3, UF_{DB} = 10)**
Concentration (µg/m^3)	**5000**
Critical study[2]	**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 US EPA TRV was retained as the IARL.
[2]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 RN 108-10-1)

Organization	Non-cancer US EPA[1]
Year of publication	**2003c**
Species	**Rats and mice**
Endpoint	**Developmental effects**
Point of departure	**NOAEL = 4100 mg/m^3** **NOAEL$_{HEC}$ = 1026 mg/m^3**
Uncertainty factors	**300** **(UF_H = 10, UF_A = 3, UF_{DB} = 10)**
Concentration (µg/m^3)	**3000**
Critical study[2]	**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.**

[1]The US EPA TRV was retained as the IARL.
[2]1. Tyl et al. (1987): gestation day 6–15 developmental inhalation study.

Toxicological reference values for propionaldehyde (CAS RN 123-38-6)

	Non-cancer
Organization	**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	**1000** **(UF_H = 10, UF_A = 3, UF_S = 10, UF_{DB} = 3)**
Concentration (µg/m^3)	**8**
Critical study[2]	**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 US EPA TRV was retained as the IARL.

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[3]1. Union Carbide (1993): inhalation developmental study.

Toxicological reference values for n-propylbromide (CAS RN 106-94-5) (added 2023)

	Cancer		Non-cancer		
Organization	**OEHHA**	**US EPA**	**ATSDR**	**OEHHA[1]**	**US EPA[2]**
Year of publication	2022b	2020b	2017	**2022a**	2020b
Species	Mice	Mice	Humans (Epidemiological)	**Humans (Epidemiological)**	Rats
Endpoint	Combined alveolar/ bronchiolar adenoma or carcinoma in females	Combined alveolar/bronchiolar adenoma or carcinoma in females	Mild neurological impairment (decreased vibratory perception in feet)	**Reduction in distal peripheral nerve function (decreased vibratory perception in feet)**	Decreased traction time (time hanging from a suspended bar)
Unit risk $(\mu g/m^3)^{-1}$	3.7×10^{-6}	1×10^{-6}	n/a	**n/a**	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	2.7	10	n/a	**n/a**	n/a
Point of departure	n/a	n/a	LOAEL = 6.4 mg/m^3 $LOAEL_{ADJ}$ = 2.3 mg/m^3	**LOAEL: 14.13 mg/m^3** **$LOAEL_{ADJ}$ = 5.05 mg/m^3**	$BMCL_{1SD}$ = 92 mg/m^3 $HEC_{(consumer\ exposure)}$ = 30.5 mg/m^3
Uncertainty factors	n/a	n/a	30 (UF_L= 3, UF_H = 10)	**3000 (UF_L= $\sqrt{10}$, UF_S = 10, UF_H= 100)**	100 (UF_A = 10, UF_H = 10)
Concentration ($\mu g/m^3$)	n/a	n/a	100	**1.7**	300[3]
Critical study[4]	4	4	1	**2**	3
Comments	n/a	n/a	$LOAEL_{adj}$ = LOAEL x 5/7 days x 12/24 hours) REL[5] is 0.02 ppm after rounding	**$LOAEL_{adj}$ = LOAEL x 5/7 days x 10/20m^3)** **UF_H includes a toxicokinetic factor of 10 (to protect infants and children) and a toxicodynamic factor of 10 (for neurotoxicity)**	$HEC_{(consumer\ exposure)}$ = $BMCL_{1SD}$ x 8/24 hours) No TRV was derived. The UF of 100 was recommended to indicate a "target MOE" but not applied by US EPA An HEC of 30.5 mg/m^3 was also determined using the $BMCL_1$ of 116 mg/m^3 for post-implantation loss in a 2-generation rat study, adjusted for continuous exposure (x6/24 hr)

[1] The OEHHA non-cancer TRV was retained as the IARL.
[2] The US EPA published a risk assessment of 1-Bromopropane (2020b) but did not derive any TRVs.
[3] The value shown is what a TRV could be if the proposed uncertainty factors were applied to the HEC, but the US EPA 2020b assessment did not include an actual TRV derivation.
[4] 1. Li et al. (2010a): occupational study; 2. Li et al. (2010b): occupational study; 3. Honma et al. (2003): 3-week inhalation study; 4. NTP (2011): 105-week inhalation study.
[5] REL: recommended exposure limit

Toxicological reference values for propylene oxide (CAS RN 75-56-9)

	Cancer		Non-cancer	
Organization	**OEHHA**	**US EPA[1]**	**OEHHA**	**US EPA**
Year of publication	1999[2]	1990b	**2000[2]**	1990b
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}	**n/a**	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	2.7	2.7	**n/a**	n/a
Point of departure	n/a	n/a	**LOAEL = 71 mg/m^3** **$LOAEL_{HEC}$ = 3 mg/m^3**	LOAEL = 71 mg/m^3 $LOAEL_{HEC}$ = 3 mg/m^3
Uncertainty factors[2]	n/a	n/a	**100** **(UF_H = 10, UF_A = 3, UF_L = 3)**	100 (UF_H = 10, UF_A = 3, UF_L = 3)
Concentration ($\mu g/m^3$)	n/a	n/a	**30**	30
Critical study[3]	1, 2	1, 2	**3**	3
Comments	n/a	n/a	**$LOAEL_{HEC}$ = 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 US EPA non-cancer TRV was retained as the IARL: OEHHA adopted the cancer unit risk from the US EPA.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2014a, 2014b, 2015).

[3]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 RN 100-42-5)

Organization	Non-cancer ATSDR[1]	Health Canada[2]	OEHHA	RIVM[3]	US EPA	WHO
Year of publication	**2010a**	1993c	2000[4]	2001	1992	2000
Species	**Humans**	Rats	Humans	Humans	Humans	Humans
Endpoint	**Neurotoxicity**	Body weight change; neurotoxicity	Neurotoxicity	Neurotoxicity	Neurotoxicity	Neurotoxicity
Unit risk ($\mu g/m^3)^{-1}$	**n/a**	n/a	n/a	n/a	n/a	n/a
Concentration at 1 x 10^{-5} risk level ($\mu g/m^3$)	**n/a**	n/a	n/a	n/a	n/a	n/a
Point of departure	**LOAEL = 85.2 mg/m³** **$LOAEL_{ADJ}$ = 20.4 mg/m³**	LOEL = 260 mg/m³ $LOEL_{ADJ}$ = 65 mg/m³ $LOEL_{HEC}$ = 46 mg/m³	$BMCL_{05}$ = 7.2 mg/m³ $BMCL_{05ADJ}$ = 2.6 mg/m³	LOAEL = 107 mg/m³ $LOAEL_{ADJ}$ = 26 mg/m³	NOAEL = 106 mg/m³ Lower 95% confidence limit of the NOAEL = 94 mg/m³ $NOAEL_{ADJ}$ = 34 mg/m³	LOAEL = 107 mg/m³ $LOAEL_{ADJ}$ = 26 mg/m³
Uncertainty factors	**30** **(UF_H = 10, UF_L = 3)**	500 (UF_H = 10, UF_A = 10, UF_L = 5)	3 (UF_H = 3)	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**	92	900	900	1000	260
Critical study[5]	**1**	3, 4	2	2*	2	2
Comments	**$LOAEL_{ADJ}$ = LOAEL x 8/24 hours x 5/7 days**	$LOEL_{ADJ}$ = LOEL x 6/24 hours $LOEL_{HEC}$ = $LOEL_{ADJ}$ x [(0.11 m³/day / 0.35 kg)/ (12 m³/day/27 kg)]	$BMCL_{05ADJ}$ = $BMCL_{05}$ x 10 m³/20 m³ x 5/7 days	$LOAEL_{ADJ}$ = LOAEL x 8/24 hours x 5/7 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 m³/20 m³ x 5/7 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 ASTDR TRV was retained as the IARL: The ATSDR TRV was selected as the IARL as the assessment is the most recent, and the TRV is derived from a meta-analysis using data from nine studies.
[2] The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993c).
[3] The RIVM assessment was published under the authorship of Baars et al. (2001).
[4] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2014a, 2014b, 2015).
[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 RN 127-18-4)

	Cancer		Non-cancer				
Organization	**OEHHA**	**US EPA**	**ATSDR[1]**	**Health Canada[2]**	**RIVM[3]**	**US EPA[1]**	**WHO**
Year of publication	1991[4]	2012	**2014**	1993d	2001	**2012**	2010b
Species	Mice	Mice	**Humans**	Mice	Humans	**Humans**	Humans
Endpoint	Liver tumours	Liver tumours	**Neurobehavioural effects**	Nephrotoxicity, hepatotoxicity	Nephrotoxicity	**Neurotoxicity, visual impairment**	Nephrotoxicity
Unit risk ($\mu g/m^3)^{-1}$	5.9×10^{-6}	2.6×10^{-7}	**n/a**	n/a	n/a	**n/a**	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	1.7	40	**n/a**	n/a	n/a	**n/a**	n/a
Point of departure	n/a	n/a	**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]	n/a	n/a	**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 ($\mu g/m^3$)	n/a	n/a	**40**	360	250	**40 (rounded average of 15 and 56)**	250
Critical study[5]	1	2	**3, 4**	1	5	**3, 6**	5
Comments	n/a	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 ATSDR and US EPA non-cancer TRVs were retained as the IARL: The US EPA cancer TRV was selected as the IARL as the assessment used data that were not available at the time of the OEHHA assessment.
[2] The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993d).
[3] The RIVM assessment was published under the authorship of Baars et al. (2001).
[4] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2015).
[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. (1998): occupational neurobehavioural testing; 5. Mutti et al. (1992): occupational exposure study; 6. Echeverria et al. (1995): occupational neurobehavioural testing.

Toxicological reference values for toluene diisocyanate (mixed isomers) (CAS RN 26471-62-5) (updated 2023)

	Cancer	Non-cancer		
Organization	**OEHHA**	**ATSDR**	**OEHHA[1]**	**US EPA**
Year of publication	1999[2]	2018	**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}	n/a	**n/a**	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	0.91	n/a	**n/a**	n/a
Point of departure	n/a	AEL[3] = 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	n/a	100 (UF_H = 10, UF_L = 10)	**300** **(UF_H = 100, UF_S = 3)**	30 (UF_H = 10, UF_{DB} = 3)
Concentration ($\mu g/m^3$)	n/a	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 5/7 days**	$NOAEL_{ADJ}$ = NOAEL x 10 m^3/20 m^3 x 5/7 days US EPA has medium confidence in the study, database, and RfC.

[1]The OEHHA non-cancer TRV was retained as the IARL.
[2]Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA reports (2011, 2015, 2016).
[3]AEL: adverse effect level.
[4]1. NTP (1986c): 106-week ingestion study (gavage); 2. Clark et al. (1998): 5-year occupational study; 3. Diem et al. (1982): 5-year occupational study.

Cancer toxicological reference values for trichloroethylene (CAS RN 79-01-6) (added 2023)

Organization	Cancer					
	ANSES	Health Canada (DWG)	Health Canada (PSL) [1]	OEHHA	US EPA[2,3]	WHO
Year of publication	2018	2005	1993e	2011*	**2011b**	2010b*
Species	Human (epidemiological)	Rats	Rats	Mice	**Human (epidemiological)**	Rats
Endpoint	Kidney tumours	Renal tubular adenocarcinomas	Leydig cell tumours in testes	hepatocellular carcinomas, adenomas and hepatomas; pulmonary lymphomas and adenocarcinomas	**Kidney tumours, non-Hodgkin's lymphoma, liver tumours**	Leydig cell tumours in testes
Unit risk $(\mu g/m^3)^{-1}$	10^{-6}	1.2×10^{-7} (males) 8.1×10^{-8} (females)	6.1×10^{-7}	2.0×10^{-6}	**4.1×10^{-6}**	4.3×10^{-7}
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	10	83 (males) 120 (females)	16	5	**2**	23
Critical study[4]	5	1	1	1,2,3,4	**5,6**	7
Comments	Based on the kidney cancer portion of the combined excess risk per unit calculated by the US EPA (2011).	Linearized multistage modelling. Body weight-based scaling was used: $(bw_A/bw_H)^{1/4}$	TC_{05} derived using multistage modelling. Adjusted for continuous exposure (7/24 hours, 5/7 days). Scaled based on inhalation volume to bw ratio. IUR = $0.05/TC_{05}$	Linearized multistage modelling; PBPK modelling; geometric mean of IUR for 4 studies. *IUR derived in 1990.	**IUR= 0.01/ $LEC_{0.1}$ IUR derived for kidney tumours, then applied a factor of 4 to account for additional risk from non-Hodgkin's lymphoma and liver tumours**	*IUR derived in 2000.

DWG, Drinking Water Guidelines, PSL, Priority Substances List

[1] The Health Canada assessment was published under the authorship of Environment Canada and Health Canada (1993e).

[2] The US EPA TRV was retained as the IARL.

[3] US EPA - IRIS (2011) IUR was also adopted by Health Canada (CSD) and US EPA (TSCA).

[4] 1. Maltoni et al. (1986): 2-year inhalation study. 2. Bell et al. (1978): 2-year inhalation study; 3. Henschler et al. (1980): 78-week inhalation study; 4. Fukuda et al. (1983): 2-year inhalation study; 5. Charbotel et al. (2006): occupational study; 6. Raaschou-Nielsen et al. (2003): occupational study; 7. Maltoni et al. (1988): 104-week inhalation study.

Non-cancer toxicological reference values for trichloroethylene (CAS RN 79-01-6) (added 2023)

Organization	Non-cancer				
	ANSES	Health Canada (DWG)	OEHHA	RIVM[1]	US EPA[2,3]
Year of publication	2018	2005	2000[4]	2001	**2011b**
Species	Rats	Rats	Humans (epidemiological)	Mice	**Mice and rats**
Endpoint	Renal Toxicity	Fetal heart malformations	Symptoms of neurotoxicity (drowsiness, fatigue, headache); eye irritation	Hepatotoxicity	**Decreased thymus weight (mice); fetal heart malformations (rat)**
Point of departure	BMCL = 238 ppm $BMCL_{HEC\text{-}ADJ}$= 43.7 ppm	$BMCL_{10}$= 146 µg/kg bw per day	LOAEL: 170 mg/m^3 $LOAEL_{ADJ}$ = 60 mg/m^3	LOAEL= 200 mg/m^3	**Mouse:** **LOAEL = 0.35 mg/ kg/d** **$HEC_{99\text{-}LOAEL}$ = 0.0332 ppm (0.19 mg/m^3)** **Rat:** **$BMDL_{0.1}$: 0.0142mg TCE oxidized/kg bw/ $^{3/4}$day** **$HEC_{99\text{-}BMDL01}$ = 0.0037 ppm (0.019 mg/m^3)**
Uncertainty factors	75 (UF_A= 2.5; UF_H=10; UF_{DB}=3)	100 (UF_H = 10 UF_A = 10)	100 (UF_H = 10 UF_L = 10)	1000 (UF_A= 10; UF_H= 10; UF_L = 10)	**Mouse: 100 (UF_A= 3; UF_H= 3; UF_L = 10)** **Rat: 10 (UF_A= 3; UF_H= 3)**
Concentration (µg/m^3)	3.2	5	600	200	**Mouse: 1.9** **Rat: 2.1** **Overall: 2**
Critical study[5]	7	11	10	12	**8,9**
Comments	$BMCL_{ADJ}$ = BMCL x 5/7 days x 7/ 24 hours HEC was determined by PBPK modelling (dose metric = blood concentration of metabolite DCVC)	The TDI of 1.46 µg/kg bw per day was converted to an air concentration by IACAS (2013). Air concentration = TDI x allocation factor for air (0.8) x body weight (70kg) / inhalation rate (15 m^3/d)	$LOAEL_{ADJ}$ = LOAEL x 5/7 days x 10/20 m^3/day	n/a	**$HEC_{99\text{-}LOAEL}$ and $HEC_{99\text{-}BMDL01}$ were determined by PKPB modelling** **Overall RfC was the midpoint between 2 candidate RfCs.**

DWG, Drinking Water Guidelines

[1] The RIVM assessment was published under the authorship of Baars et al. (2001).

[2] The US EPA TRV was retained as the IARL.

[3] The US EPA (IRIS) (2011) value was adopted by ATSDR (2019) and Health Canada (CSD) (2021).

[4] Refers to the actual date of assessment. Toxicological reference value information was summarized from OEHHA report (2014b).

[5] 7. Maltoni et al. (1988): 104-week inhalation study; 8. Keil et al. (2009): 27-week drinking water study. 9. Johnson et al. (2003): gestational drinking water study; 10. Vandervort and Polnkoff (1973): occupational study; 11. Dawson et al. (1993): gestational drinking water study. 12. Kjellstrand et al. (1983): 30-day continuous inhalation study.

Toxicological reference values for vinyl chloride (CAS RN 75-01-4) (added 2023)

	Cancer				Non-cancer		
Organization	**ANSES**	**OEHHA**	**US EPA[1]**	**WHO**	**ATSDR[2]**	**US EPA**	**TCEQ**
Year of publication	2012	2000	**2000**	1999b	2006b	2000	2009
Species	Mice	Mice	**Rats**	Human	Rats	Rats	Rats
Endpoint	Liver angiosarcoma and hepatocellular carcinomas	Lung carcinoma	**Liver angiosarcoma, angioma, hepatoma, or neoplastic nodules**	All cancers	Hepatic centrilobular hypertrophy	Liver cell polymorphism and cysts	Centrilobular hypertrophy in the liver
Unit risk $(\mu g/m^3)^{-1}$	3.8×10^{-6}	7.7×10^{-5}	**For continuous lifetime exposure from birth: 8.8×10^{-6}** **For continuous lifetime exposure through adulthood: 4.4×10^{-6}**	1×10^{-6} (estimate)	n/a	n/a	n/a
Concentration at 1×10^{-5} risk level ($\mu g/m^3$)	2.6	0.13	**For continuous lifetime exposure from birth: 1.1** **For continuous lifetime exposure through adulthood: 2.3**	10	n/a	n/a	n/a
Point of departure	n/a	n/a	**n/a**	n/a	LEC_{10}= 5.08 ppm HEC = 1 ppm	HEC: 2.5mg/m^3 LOAEL: 25.3 mg/m^3	POD_{ADJ} ($BMCL_{10}$) = 0.680ppm
Uncertainty factors[3]	n/a	n/a	**n/a**	n/a	n/a	30 (UF_H = 10; UF_A = 3)	30 (UF_A= 3;UF_H = 10; UF_L= 1)
Concentration ($\mu g/m^3$)	n/a	n/a	**n/a**	n/a	80	100	60
Critical study[4]	4	5	**1**	6,7	3	2	3
Comments	n/a	n/a	**Linearized multistage modelling was used to derive the unit risk**	n/a	Intermediate MRL (15–364 days)	The inhalation RfC was derived from an oral exposure study: Til et al. 1983.	Study was chosen due to its publishing date and the study design.

[1] The US EPA cancer TRV was retained as the IARL: The mode of action for tumour development is dependent on liver metabolism; therefore, the OEHHA cancer TRV based on lung tumours was not considered appropriate, and the US EPA cancer TRV based on liver tumours was selected for the IARL.
[2] ATDSR developed an intermediate MRL, but not a chronic MRL.
[3] UF_A Interspecies, UF_H Intraspecies, UF_L LOAEL to NOAEL.
[4] 1. Maltoni et al. (1981, 1984b): 1-year inhalation study; 2. Til et al. (1983): Lifetime dietary study; 3. Thornton et al. (2002): 19-week inhalation study; 4. Hong et al. (1981): 28-week (mice) and 52-week (rat) inhalation study; 5. Drew et al. (1983): 2-year inhalation study; 6. Nicholson (et al). 1984; occupational study; 7. Equitable Environmental Health (1978): occupational study.

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