Appendix A Toxicity Profiles for COPCs

General

1,1,2-Trichloroethane (also known as ethane trichloride; 1,1,2-TCE; beta-trichloroethane; 1,2,2-trichloroethane; vinyl trichloride; trichloroethane (non-specific name) and commonly abbreviated to **1,1,2-TCA**) is a predominantly man-made chemical. 1,1,2-TCA is a chemical intermediate in the production of 1,1-dichloroethene. 1,1,2-TCA has limited use as a solvent for fats, oils, waxes and resins. It is also released to the environment as a result of anthropogenic activity and it has also been identified as an intermediate in the biodegradation of 1,1,2,2-tetrachloroethane (another man-made chemical). It is formed commercially by the chlorination of ethylene with chlorine or by the oxychlorination of ethylene with HCl and oxygen.

Properties

1,1,2-TCA is a non-flammable, colourless, volatile liquid with a pleasant, sweet odour. It is insoluble in water and miscible with alcohol, ether and many organic liquids. Key properties are presented below (ATSDR 1989 and USEPA 2002):

CAS No.	79-00-5
Chemical Formula	$C_2H_3Cl_3$
Molecular Weight	133.41
Vapour Pressure	22.49 mmHg at 25^{o}C
Vapour Density	4.63
Density	1.4 g/ml at 20^{o}C
Solubility (Water)	4420 mg/L at 20^{o}C
Air Diffusion Coefficient	0.078 cm^2/s
Water Diffusion Coefficient	8.8 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.000913 atm.m^3/mol
	= 0.0374 at 25^{o}C (unitless)
Koc	50.1 cm^3/g
Odour Threshold	2.8 to 926.8 mg/m^3

Exposure

Exposure of the general population to 1,1,2-TCA may occur primarily through inhalation, however exposure via oral or dermal routes may occur but are expected to be insignificant. Exposure may occur in the workplace where it is used as a solvent.

If released into the environment the following can be noted with respect to 1,1,2-TCA (ATSDR, 1989):

- Air: Most of the 1,1,2-TCA released to the environment enters the atmosphere where it is fairly stable. In the atmosphere,1,1,2-TCA is degraded by photochemically-produced hydroxyl radicals with a half-life of approximately 49 days.

- Soil and Water: Following releases to soil, 1,1,2-TCA is expected to partially volatilise, with the remainder leaching into the subsurface soil profile and groundwater. If released to surface water most would volatilise with the remainder dissolving in water. The chemical would not be expected to show appreciable adsorption to sediment or suspended organic material.

- Biodegradation: 1,1,2-TCA may undergo slow biodegradation under anaerobic. Anaerobic degradation occurs predominantly through reductive dehalogenation which forms vinyl chloride. Aerobic degradation occurs via substitutive and oxidative mechanisms with the production of trichloroethyl alcohol. Aerobic degradation and hydrolysis are not likely to be an important fate processes for 1,1,2-TCA.

- 1,1,2-TCA has a low tendency to bioconcentrate in aquatic or marine organisms.

Health Effects

General

The following information is available from USDOE (1995) and ATSDR (1989). There is no clinical disease which is unique to 1,1,1-TCA toxicity.

1,1,2-TCA is rapidly and extensively absorbed into the body following inhalation exposures (principal route of exposure) and dermal exposure.

One absorbed, 1,1,2-TCA is distributed widely in body tissues (including the liver, fatty tissue, kidneys, blood and brains, heart, spleen and lungs). The primary metabolites identified are chloroacetic acid, S-carboxymethylcysteine, and thiodiacetic acid. Elimination occurs via exhalation and urine (including elimination of metabolites).

No information is available on the acute effects of 1,1,2-TCA in humans from inhalation or oral exposures. Tests involving acute exposure of mice and rats have shown 1,1,2-TCA to have moderate and high acute toxicity from inhalation and oral exposures, respectively. Studies on dermal exposure to 1,1,2-TCA in humans have reported stinging and burning sensations and transient whitening of the skin. Animal studies have reported effects on the liver, kidney, and central nervous system (CNS) from acute inhalation and oral exposure.

No information is available on the chronic effects of 1,1,2-TCA in humans from inhalation or oral exposure. Animal studies have not observed adverse effects from chronic inhalation exposure to 1,1,2-TCA, however effects on the liver and immune system have been noted in chronic oral studies.

No information is available regarding developmental or reproductive effects of 1,1,2-TCA in humans from inhalation or oral exposure. Animal studies have not reported developmental or reproductive effects from oral exposure to 1,1,2-trichloroethane.

Genotoxic Effects

Potential for genotoxicity of 1,1,2-TCA was reviewed by Woodward-Clyde (1996) which indicated that the available data were inadequate to enable a proper evaluation of genotoxic potential. In particular, there were a lack of gene mutation assays using mammalian cells and *in vivo* chromosome damage assays. Review of genotoxicity by OECD (2000) recommended further work such as an *in vivo* genotoxicity study. This was undertaken and reported in 2003 (OECD, 2003) which showed negative results. Hence the weight of evidence suggests that 1,1,2-TCA is not genotoxic *in vivo*.

Cancer	No studies are available regarding cancer in humans from inhalation or oral exposure. A study reported liver tumours and adrenal tumours in mice, but no tumours in rats from exposure to 1,1,2-TCA by gavage. Initiation/promotion screening studies on male rat liver demonstrated that the chemicals has neither initiation nor promotion activity. A carcinogenic study in skin of rats indicted no chemical related changes.

Toxicity Classification

1,1,2-TCA has been classified as a "possible" human carcinogen (Category C) by the USEPA on the basis of hepatocellular carcinomas and pheochromcytomas in one strain of mice.

IARC (1999) has classified 1,1,2-TCA in Group 3 (not classifiable as to its carcinogenicity to humans) based on no epidemiological data and limited evidence in experimental animals for carcinogenicity.

The National Occupational Health and Safety Commission (NOHSC) and NICNAS have not classified the potential carcinogenicity of 1,1,2-TCA.

Exposure Limits/Toxicity Evaluations

Australia

The Australian Drinking Water Guidelines (NHMRC, 1996 and 2004) have not derived a drinking water guideline for 1,1,2-TCA.

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment". For 1,1,2-TCA, the following have been established:

TWA: 10 ppm, equivalent to 55 mg/m^3

STEL: NA

WHO

The WHO (Drinking Water Guideline 1996 and 2004) have not derived a drinking water guideline value for 1,1,2-TCA.

The WHO (2000, 2000b) have not evaluated or provided an inhalation guideline values for 1,1,2-TCA.

EU

No assessment of 1,1,2-TCA is available from the EU.

US

The USEPA (IRIS current in 2004) has derived the following for 1,1,2-TCA:

- Non-cancer effects: oral reference dose ***(RfD) of 0.004 mg/kg/day*** on the basis of clinical serum chemistry in mice. No review of inhalation effects are provided.

- Cancer effects: ***oral slope factor of 0.057 (mg/kg/day)$^{-1}$*** has been derived using the linearised multistage procedure associated with hepatocellular carcinoma in mice. An ***inhalation unit risk of 1.6x10^{-5} (µg/m3)$^{-1}$*** has been derived using the oral exposure assessment.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with 1,1,2-TCA. The levels established (valid in 2004) are:

– Acute oral MRL = 0.3 mg/kg/day based on neurological effects

– Intermediate oral MRL = 0.04 mg/kg/day based on hepatic effects

The California Air Resources Board (CARB and OEHHA) has adopted the USEPA (IRIS) inhalation unit risk for the assessment of inhalation exposure to 1,1,2-TCA.

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. With respect to 1,1,2-TCA, intakes from soil, water and food can be considered to be insignificant. Based on data available from urban air in Brisbane and Perth (Hawas, 2001, WA DEP 2000) 1,1,2-TCA is generally not detected in urban air and hence background intake can be considered to be negligible.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for 1,1,2-TCA following review of the available information in general accordance with enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**Oral RfD = 0.004 mg/kg/day** (USEPA based on oral exposure study) 1,1,2-TCA is not a genotoxic carcinogen and hence use of a slope factor is not considered appropriate.
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**RfD = 0.004 mg/kg/day** (USEPA oral RfD adopted. There are no threshold guidelines established bsed on inhalation studies hence the oral data is used) Occupational inhalation exposure (NOHSC): **TWA: 10 ppm, equivalent to 55 mg/m^3** **STEL: NA**

References

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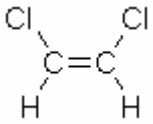
GENERAL

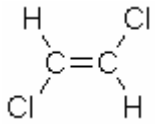
1,2-Dichloroethene (also known as **1,2-DCE**, 1,2-dichloroethylene, acetylene dichloride and dioform) exists in two isomeric forms, *cis*-1,2-dichloroethene and *trans*-1,2-dichloroethene, that are colourless, volatile liquids with a slightly acrid odour. 1,2-Dichloroethene is prepared commercially by either the direct chlorination of acetylene or by the reduction of 1,1,2,2-tetrachloroethane with fractional distillation used to separate the two isomers. 1,2-Dichloroethene can also be formed as a by-product during the manufacture of other chlorinated compounds. Commercial use is not extensive, but *trans*-1,2-dichloroethene and mixtures of *cis*- and *trans*-1,2-dichloroethene have been used as intermediates in the production of other chlorinated solvents and compounds, as well as low temperature extraction solvents for dyes, perfumes, and lacquers Although not used extensively in industry, 1,2-dichloroethene is used in the production of other chlorinated solvents and as a solvent for dyes, perfumes, and lacquers.

PROPERTIES

Both *cis*- and *trans*-1,2-DCE are colorless, volatile liquids with ethereal and slightly acrid odors. 1,2-DCE is slightly soluble in water, but is very soluble in alcohol, ether, acetone and most other organic solvents. Both forms are moderately flammable and react with alkalies to form chloracetylene gas, which spontaneously ignites in air. Additionally, *cis*- and *trans*-1,2-DCE react violently with potassium hydroxide, sodium, and sodium hydroxide and form shock-sensitive explosives when combined with dinitrogen tetraoxide. 1,2-Dichloroethene emits chlorine gas when heated to decomposition (US DOE 1994). Key properties are presented below (ATSDR 1996, WHO 2003, USEPA 2004 and ORNL Database 2006):

Property	**cis-isomer**	**trans-isomer**
CAS No:	156-59-2	156-60-5
Chemical Formula	$C_2H_2Cl_2$	$C_2H_2Cl_2$
Molecular Weight	96.95	96.95
Vapour Pressure	180 mmHg at 20^{o}C	265 mmHg at 20^{o}C
Vapour Density	1.6	1.8
Density	1.28 g/ml at 20^{o}C	1.26 g/ml at 20^{o}C
Solubility	3500 mg/L at 20^{o}C	6300 mg/L at 20^{o}C
Air Diffusion Coefficient	0.0736 cm^2/s	0.0707 cm^2/s
Water Diffusion Coefficient	1.1 x 10^{-5} cm^2/s	1.2 x 10^{-5} cm^2/s
Henry's Law Coefficient	0.00408 atm.m^3/mol = 0.167 at 25^{o}C (unitless)	0.00938 atm.m^3/mol = 0.384 at 25^{o}C (unitless)
Koc	35.5 cm^3/g	52.5 cm^3/g
Log Kow	2.09	2.09
Odour Threshold	NA	0.332 to 68 mg/m^3
Dermal Absorption	0.01 (unitless)	0.01 (unitless)
Permeability Constant	0.0149	0.0149





EXPOSURE

Because of its volatility, the primary route of 1,2-DCE exposure to humans is by inhalation, however exposure via oral or dermal routes may occur but are expected to be insignificant. Exposure may occur in the workplace.

Cis-1,2-DCE may be released to the environment in emissions and wastewater during its production and use. Under anaerobic conditions that may exist in groundwater, landfills or sediment, 1,2-DCE can be formed as breakdown products from the reductive dehalogenation of trichloroethene, tetrachloroethene and 1,1,2,2-tetrachloroethane. The *cis*-1,2-DCE isomer is the more common isomer found although it is commonly mistakenly listed as the *trans*-isomer. The *trans*-isomer, is more commonly analysed for and the analytical procedures generally used do not distinguish the isomers.

If released into the environment the following can be noted with respect to 1,2-DCE (ATSDR, 1996):

- Air: In the atmosphere 1,2-DCE will be lost by reaction with photochemically produced hydroxyl radicals (half life 8 days for *cis*-isomer and 3.6 days for *trans*-isomer) and scavenged by rain. Most of the 1,2-DEC removed by rain will probably re-enter via volatilisation. Because it is relatively long lived in the atmosphere, considerable dispersal from source areas should occur.

- Soil: If 1,2-DCE (*cis* or *trans*) is released on soil, it should evaporate and/or leach into the groundwater where very slow biodegradation should occur. Adsorption of 1,2-DCE to soil, sediment or suspended solids in water is not a significant fate process.

- Water: If released into water, 1,2-DCE (*cis* or *trans*) will be lost mainly through volatilization (half life 3 hr in a model river).

- Biodegradation: Biodegradation, adsorption to sediment, and bioconcentration in aquatic organisms should not be significant. In groundwater 1,2-DCE may undergo anaerobic biodegradation with a biodegradation half life of approximately 13-48 weeks. Aerobic biodegradation processes have also been observed. 1,2-DCE is commonly found in mixtures with other chlorinated solvents and hence half-lives can only be approximated.

- 1,2-DCE has a low tendency to bioconcentrate in aquatic or marine organisms.

HEALTH EFFECTS

General

The following information is available from WHO (2003), USDOE (1994) and ATSDR (1996). There is no clinical disease which is unique to 1,2-DCE toxicity.

1,2-DCE is rapidly absorbed by the lungs. Once absorbed, the chemical is metabolised by the liver to form dichloroethanol and dichloroacetic acid via the epoxide intermediate. Animal studies indicate that the metabolism of the *cis*-isomer occurs faster than that of the *trans*-isomer. As the *cis* and *trans*-isomers are lipid soluble of low molecular weights, they would be expected to be readily absorbed by the oral or dermal routes.

Toxicokinetic data are very limited for both human and animals exposures to 1,2-DCE. Although the compound is relatively lipophilic, there is no good evidence of accumulation in the liver, brain, kidney and adipose tissue. 1,2-DCE is likely to be metabolised to more hydrophilic by-products and therefore eliminated quickly by the kidney as metabolites.

Workers exposed to 1,2-DCE have been reported to suffer from drowsiness, dizziness, nausea, fatigue, and eye irritation. Acute and sub-chronic oral and inhalation animal studies of *trans*-1,2-DCE and acute inhalation animal studies of *cis*-1,2-DCE suggest that the liver is the primary target organ. The toxicity is expressed in increased activities of liver associated enzymes, fatty degeneration, and necrosis. Secondary target organs include the central nervous system and lung. No information is available concerning the chronic, developmental, or reproductive toxicity of *cis*-1,2-DCE or *trans*-1,2-DCE.

Cancer and Genotoxic Effects

No studies are available regarding carcinogenicity.

In vitro investigations of the genotoxic potential of 1,2-DCE indicated negative results for both isomers. 1,2-DCE was not found to be mutagenic and neither isomer induced chromosomal aberrations or sister chromatid exchanges in a study in Chinese hamster lung fibroblasts (WHO, 2003).

In vivo studies indicate that *cis*-, and possibly the *trans*-, isomer may be genotoxic (WHO, 2003). The *cis*-isomer was found to be mutagenic in two mice studies where chromosomal aberrations in mouse bone marrow cells were observed. The *trans*-isomer yielded negative results in these studies.

Review of 1,2-DCE by RIVM (2001) with respect to genotoxicity and carcinogenicity conclude that *cis*-1,2-DCE should be considered as a genotoxic agent *in vivo*, producing gene mutations and chromosome aberrations. However, carcinogenicity data are not available and hence the estimation of risk has to be based on non-carcinogenic (threshold) toxicity data. The *trans*-isomer was negative in *in vivo* test systems, but has induced aneuploidy in an *in vitro* test. For the induction of this kind of genotoxic effect the threshold approach is applicable.

TOXICITY CLASSIFICATION

USEPA has placed both *cis*-1,2-DCE and *trans*-1,2-DCE in weight-of-evidence group D, not classifiable as to human carcinogenicity, based on the lack of human or animal carcinogenicity data and on essentially negative mutagenicity data. Oral and inhalation slope factors have not been calculated for these isomers.

1,2-DCE has not been evaluated by the IARC or the National Occupational Health and Safety Commission (NOHSC) or NICNAS with respect to carcinogenicity.

EXPOSURE LIMITS AND TOXICITY EVALUATIONS

Australia

The Australian Drinking Water Guidelines (NHMRC 2004) have derived a drinking water guideline of 0.06 mg/L for 1,2-DCE (both isomers) following guidance from the WHO (refer below).

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment" (available within the Hazardous Substances Information System, NIOSH 2006). For 1,2-DCE, the following have been established:

TWA: 200 ppm, equivalent to 793 mg/m^3

STEL: NA

WHO

The WHO (Drinking Water Guidelines 2004) has derived a guideline of 0.05 mg/L based on a TDI of 0.017 mg/kg/day based on a NOAEL of 17 mg/kg from a 90 day study in mice administered *trans*-1,2-DCE in drinking water and an uncertainty factor of 1000.

The WHO (2000, 2000b) have not evaluated or provided an inhalation guideline values for 1,2-DCE.

EU

No assessment of 1,2-DCE is available from the EU.

RIVM

Review of 1,2-DCE by RIVM (2001) has provided tolerable daily intakes and tolerable concentrations in are relevant for *cis*- and *trans*-isomers.

A TDI of 0.006 mg/kg/day has been established for *cis*-1,2-DCE based on a NOAEL of 32 mg/kg/day from a 90 day oral rat study and an uncertainty factor of 5000. For *trans*-1,2-DCE a TDI of 0.017 mg/kg/day was established using the same study and approach presented by the WHO.

Inhalation tolerable concentrations (TC) were derived for *cis*-1,2-DCE using route extrapolation from the oral study, resulting in a TC of 0.030 mg/m^3. A TC of 0.060 mg/m^3 was established for *trans*-1,2-DCE based on a LOAEL of 185 mg/m^3 (continuous exposure) derived from liver and lung effects from an inhalation study on rats and applying an uncertainty factor of 3000. Both these inhalation values are considered to be provisional due to route extrapolation (*cis*-isomer) or poor database (*trans*-isomer).

US

The USEPA (IRIS current in 2006) has derived the following for 1,2-DCE:

- Non-cancer effects: oral reference dose (RfD) of 0.02 mg/kg/day for *trans*-1,2-DCE on the basis of a 90 day mouse study with drinking water (same study as used by WHO).
- No carcinogenic or review of inhalation effects for *trans*-1,2-DCE are provided.
- No data is available for oral or inhalation exposure (carcinogenic or non-cancer) to *cis*-1,2-DCE.

HEAST (1994) has provided a provisional peer reviewed chronic oral reference dose of 0.01 mg/kg/day for *cis*-1,2-DCE based on decreased haemoglobin and hematocrits in rats from a 90 day oral rat study. This value currently under review. The oral RfD available from IRIS for *trans*-1,2-DCE and the provisional RfD from HEAST for *cis*-1,2-DCE have been used by a number of state agencies (including Region IX) in the US in establishing remediation goals or screening levels. The oral values have been extrapolated for the evaluation of inhalation exposures.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with 1,2-DCE. The levels established (valid in 2006) are:

- Acute and intermediate inhalation MRL for *trans*-isomer= 0.2 ppm based on liver effects from inhalation study in rats (same study as used by RIVM);
- Acute oral MRL for *cis*-isomer = 1 mg/kg/day based on haematological effects;
- Intermediate oral MRL for *cis*-isomer = 0.3 mg/kg/day based on haematological effects;
- Intermediated oral MRL for *trans*-isomer = 0.2 mg/kg/day based on hepatic effects.

The California Air Resources Board (CARB and OEHHA) has not established an acute or chronic reference exposure level or unit risk values for 1,2-DCE.

SUGGESTED TOXICITY VALUES FOR RISK CHARACTERISATION

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. With respect to 1,2-DCE, intakes from soil, water and food can be considered to be

insignificant. 1,2-DCE is not considered to be a typical urban air contaminant and little data is available from data collected in Australian cities. *Cis*-1,2-DCE has been detected in VOC sampling from Perth (WA DEP 2000) with average concentrations of 0.2 ppb (0.8 µg/m^3) and a maximum reported concentration of 2.1 ppb (8.3 µg/m^3). These values were comparable to average concentrations reported in air in the US and used by RIVM (2001) following WHO methodology to estimate background intake of 1,2-DCE (both isomers) of approximately 0.13 µg/kg/day. This intake is essentially negligible in comparison with the available TDI and RfDs available from WHO, RIVM and US authorities.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for 1,2-DCE following review of the available information in general accordance with guidelines from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

	***Cis*-1,2-DCE**	***Trans*-1,2-DCE**
	The *cis*-isomer is considered potentially genotoxic, however there is a lack of carcinogenic data – hence no non-threshold evaluation is available. Evaluation of exposure via all routes must be undertaken on the basis of a threshold approach.	The *trans*-isomer is not considered genotoxic and any effects identified in studies are considered appropriate to be evaluated on the basis of a threshold approach.
Oral	**RfD = 0.01 mg/kg/day** (USEPA, provisional peer reviewed value in HEAST based on oral exposure study using *cis*-isomer, which is similar to the TDI derived by RIVM of 0.006 mg/kg/day)	**TDI = 0.017 mg/kg/day** (WHO 2004 based on oral exposure study using *trans*-isomer. This value is used for both isomers, but is only derived from studies on the *trans*-isomer)
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.	
Inhalation	No inhalation studies are available for the evaluation of exposure to *cis*-1,2-DCE, hence the oral value has been used for the evaluation of inhalation exposures. **RfD = 0.01 mg/kg/day** (it is noted that the RIVM present a provisional TC for the *cis*-isomer based on the oral study. The value presented by RIVM is equal to the oral RfD adopted and hence the oral RfD has been used for the assessment of inhalation exposures). Occupational inhalation exposure (NOHSC) for 1,2-DCE (both isomers): TWA: 200 ppm, equivalent to 793 mg/m^3 STEL: NA	Limited inhalation studies are available for the evaluation of exposure to *trans*-1,2-DCE, hence the oral TDI has been used for the evaluation of inhalation exposures. **TDI = 0.017 mg/kg/day** (it is noted that the RIVM present a provisional TC for the *trans*-isomer based on a limited inhalation study. The value presented by RIVM is equal to the oral TDI and hence the oral TDI has been used for the assessment of inhalation exposures). Occupational inhalation exposure (NOHSC) for 1,2-DCE (both isomers): TWA: 200 ppm, equivalent to 793 mg/m^3 STEL: NA
Background	Negligible	Negligible

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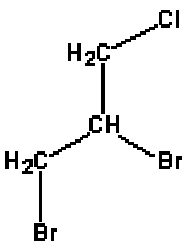
GENERAL



1,2-Dibromo-3-chloropropane (also known as dibromochloropropane and abbreviated to **DBCP**) is a simple man-made halogenated hydrocarbon that is used as a laboratory reactant, intermediate in organic synthesis and commercial preparation of the flame retardant tris(2,3-dibromopropyl)phosphate. The chemical was registered for use as a pesticide and soil fumigant, however in many places it is not longer registered.

If released to the atmosphere, DBCP will exist solely in the vapour phase in the ambient atmosphere where it is degraded by reaction with photochemically-produced hydroxyl radicals with an estimated half-life of about 37 days. Products of 1,2-dibromopropanol, chlorobromopropanol, and 1-bromo-3-chloro-2-propanone are formed during this process. DBCP released to soil will likely volatilise or leach. In water, DBCP is expected to volatilise. In groundwater, DBCP is expected to persist due to its low estimated rate of hydrolysis (half-life of approximately 141 years). In surface waters, biodegradation may occur, but is expected to be slow relative to the rate of volatilization. Sorption to sediments and bioconcentration are not expected to be important fate processes.

EXPOSURE AND HEALTH EFFECTS

Probable routes of human exposure to DBCP are inhalation, ingestion, and dermal contact, with exposure is expected to result primarily from inhalation and ingestion of drinking water, particularly from groundwater sources. Occupational exposure to DBCP is likely via inhalation and dermal contact with vapours, water, and products containing 1,2-dibromo-3-chloro-propane.

DBCP is a moderate central nervous system (CNS) depressant and an eye, skin, and respiratory tract irritant. Acute overexposure to DBCP in humans by inhalation may cause CNS effects, with symptoms including drowsiness, narcosis, and pulmonary congestion. Chronic inhalation exposure has been reported to cause kidney and liver effects in rats and mice (OEHHA, 2007).

Chronic occupational exposure to DBCP caused decreased sperm counts in men; however, no association between paternal exposure and birth defects, prematurity, mortality, or spontaneous abortions was noted. Testicular effects and decreased sperm count were observed in rabbits chronically exposed to DBCP by inhalation (OEHHA, 2007).

DBCP is metabolically activated via cytochrome P450-catalysed oxidation and glutathione conjugation to form several protein- and DNA-binding products in the rat and mouse. It is also activated in human testicular cells *in vitro*. It disturbs spermatogenesis and has caused male infertility in humans. On the basis of data from studies on different strains of rats and mice, DBCP was determined to be carcinogenic in both sexes by the oral, inhalation, and dermal routes. It was also determined to be a reproductive toxicant in humans and several species of laboratory animals. Recent epidemiological evidence suggests an increase in cancer mortality in individuals exposed to high levels of DBCP (WHO 2004 and IARC 1999).

DBCP is a bacterial mutagen in the presence of metabolic activation. It causes DNA damage and genotoxicity in animal cells *in vitro* and *in vivo* (IARC, 1999).

PROPERTIES

DBCP is a colourless (when pure) or amber to dark brown (technical grade) liquid with a pungent odour. Key properties are presented below (ATSDR 1992, USEPA 2004 and ORNL Database 2007):

CAS No	96-12-8
Chemical Formula	$C_3H_5Br_2Cl$
Molecular Weight	236.33
Vapour Pressure	0.058 mmHg at 20^oC
Vapour Density	8.2
Density	2.093 g/ml at 20^oC
Solubility	1230 mg/L at 20^oC
Air Diffusion Coefficient	0.0212 cm^2/s
Water Diffusion Coefficient	7.02 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.000147 $atm.m^3/mol$
	= 0.00601 at 25^oC (unitless)
Koc	130.8 cm^3/g
Log Kow	2.96
Odour Threshold	0.965 mg/m^3
Dermal Absorption	0.01 (unitless)
Permeability Constant	0.00871 cm/hr

SUGGESTED TOXICITY VALUES FOR RISK CHARACTERISATION

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. No data is available regarding environmental levels of DBCP in Australia. Limited data presented by WHO (2004) suggest low concentrations are reported in groundwater (detected at levels up to 20 µg/L. DBCP has also been identified as a contaminant I vegetables grown in soils treated with the fumigant. Limited data is available and DBCP is considered a low-level contaminant in air.

As DBCP is donsider4d to be a genotoxic carcinogen, it is primarily assessed on the basis of a non-threshold approach that does not require consideration of background intakes. If background intakes were required to be considered (for the assessment of non-carcinogenic effects) based on available data, background intakes would be considered negligible.

Toxicity Values

Review of available data with respect to DBCP indicates that based on the limited data available, the chemical is considered to be carcinogenic and genotoxic. On this basis it is considered relevant (in accordance with guidance from enHealth (2002)) to consider potential exposures to DBCP on the basis of a non-threshold approach where data is available.

Toxicity data relevant for use in the characterisation of risk to human health have been selected for DBCP following review of the available information in general accordance with guidelines from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Classification	USEPA: B2 probable human carcinogen. Note carcinogen assessment currently under review. IARC: Group 2B possibly carcinogenic to humans.

Toxicity Values:	
Oral	Slope Factor = 0.35 $(mg/kg/day)^{-1}$ (WHO, 2004 based on incidence of stomach, kidney and liver tumours in rats – also considered to provide adequate margin of safety for the protection of reproductive toxicity).
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	Limited inhalation data are available, however an inhalation unit risk of $6.9x10^{-7}(\mu g/m3)^{-1}$ which is equivalent to 0.0024 $(mg/kg/day)^{-1}$ was available from the USEPA, however it is currently withdrawn pending review. No occupational data is available from ASCC (2007), however the following is available from NIOSH (current to 2007): TWA: 0.001 ppm = 0.0097 mg/m^3 STEL: NA
Background	Negligible

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General

1,2-Dichloroethane (also known as ethylene dichloride, ethylene chloride, glycol dichloride, freon 150, dutch liquid, 1,2-ethylene dichloride, alpha, beta-dichloride and commonly abbreviated to **EDC**) is a synthetic product which is primarily used in the production of the vinyl chloride monomer. It is also an intermediate in the manufacture of fluorocarbons and chlorinated solvents such as trichloethane, trichloroethylene, perchloroethylene and vinylidene. These solvents are used to remove dirt, grease, resins and glue as well as in the manufacture of polystyrene and SBR latex. EDC is also added to leaded petrol as an anti-knock compound and has been used as a fumigant.

EDC is one on the most widely produced chemicals in the world. The majority of EDC released to the environment is in emissions to air. It is moderately persistent in the air, however it is not considered to be an ozone depleting substance.

Properties

EDC is a volatile, colourless liquid at room temperature with a pleasant smell and sweet taste. EDC evaporates into air very quickly and is soluble in water and several organic solvents such as alcohol, chloroform and ether. Key properties are presented below (ATSDR 2001 and USEPA 2002):

CAS No.	107-06-2
Chemical Formula	$C_2H_4Cl_2$
Molecular Weight	98.96
Vapour Pressure	79.1 mmHg at 25^{o}C
Vapour Density	3.4
Density	1.23 g/ml at 20^{o}C
Solubility (Water)	8690 mg/L at 20^{o}C
Air Diffusion Coefficient	0.104 cm^2/s
Water Diffusion Coefficient	9.9 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.0011 atm.m^3/mol
	= 0.0401 at 25^{o}C (unitless)
Koc	17.4 cm^3/g
Odour Threshold	48.6 to 405 mg/m^3

Exposure

Exposure of the general population to EDC may be by inhalation, oral or dermal routes. In most cases inhalation is the primary route of exposure. Exposure may also occur through oral ingestion and dermal contact with drinking/household water and/or soils. Intake from food sources is expected to be negligible. Children maybe exposed via the same pathways as adults. EDC has been detected in human milk and hence infancies could be exposed via breast-feeding. Occupational exposures (particularly inhalation and dermal contact) may occur in industries which handle the product.

If released into the environment the following can be noted with respect to EDC:

- Air: EDC is expected to remain in vapour phase where it is moderately persistent with an estimated half-life of between 43 and 111 days. Once EDC reaches the troposphere, it undergoes photo-oxidation to produce formyl chloride, chloroacetyl chloride, hydrochloric acid, carbon monoxide and carbon dioxide EDC is transported to the stratosphere where photolysis may produce chloride radicals which may in turn reach with ozone. EDC is not expected to contribute to ozone depletion. Due to its persistence in the troposphere there in the potential for long-range transport of EDC.

- Soil and Water: EDC is not expected to adsorb strongly in soils and may leach to groundwater where it has the potential to persist for years. EDC is expected to volatilise from surface soils and water.

- Biodegradation: Biodegradation is expected to occur slowly with hydrolysis and photolysis is not expected to be important fate processes. The potential for bioaccumulation in aquatic or terrestrial organisms appears to be low.

Health Effects

General	There is no clinical disease which is unique to EDC toxicity. Primary effects are associated with the liver, kidneys and neurological, cardiovascular and immune systems.
	EDC is readily absorbed into the body via inhalation, ingestion and dermal exposure. Following absorption into the body, EDC is widely distributed throughout the body. In animals the highest concentrations were generally within adipose tissue; however it is also distributed to the blood, liver, kidney, brain and spleen. EDC is metabolised extensively. Un-metabolised EDC is eliminated in expired air, while its metabolites (principally sulphur containing metabolites) are largely excreted in the urine. Although EDC is eliminated more slowly from adipose tissue than from blood or other tissues (lung and liver) following exposure, it is unlikely to bioaccumulate significantly.
	The following summary has been derived from ATSDR (2001).
Death	Acute inhalation and oral exposure of EDC has been known to result in death in humans. Cause of death is typically attributed to cardiac arrhythmia.
Hepatic Effects	Liver effects have been identified following acute inhalation or ingestion of EDC by humans and animals. Hepatic effects in animals were not limited to any specific route or duration of exposure and included increased levels of serum markers of liver dysfunction, increased liver weight and fatty degeneration.
Renal Effects	EDC is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects in humans include diffuse necrosis, tubular necrosis and kidney failure. Renal effects in animals include increased kidney weight, cloudy swelling of the tubular epithelium, tubular degeneration and regeneration, karyomegaly, dilation, protein casts and mineralisation.
Immunological Effects	Immunological effects have not been reported in humans. In mice, immunological effects have been reported following both acute inhalation and oral exposure. Due to interspecies differences in immunotoxicity, it is unclear whether the immune system may be a target of EDC in humans based on the mice studies.

Neurological Effects	Neurological effects reported by people acutely exposed to high concentrations of EDC via inhalation or ingestion include headache, irritability, drowsiness, tremors, partial paralysis and coma. Animal studies indicate the CNS is a target of high concentrations of EDC. Available data do not enable characterisation of the potential for EDC to cause more subtle neurotoxic effects following low-level prolonged exposures by inhalation, oral or dermal exposure.
Cardiovascular Effects	Cardiac effects (arrhythmias, insufficiency and haemorrhage) have been observed in humans acutely exposed to high concentrations of EDC. The available animal data suggests that the heart could be a target of EDC following acute high level exposure and possibly longer-term inhalation exposure.
Developmental Effects	Some developmental effects have been reported in humans and animals. However, the available information does not indicate that EDC is a developmental toxicant in animals at doses below those that cause other toxic effects.
Genotoxic Effects	The genotoxicity of EDC has been extensively investigated in non-mammalian and mammalian test systems. Following review of the available data by WHO (1998), EDC has been identified as genotoxic in *in vitro* and *in vivo* assays, and binds to DNA in rodents *in vivo*. Review of genotoxicity by Woodward-Clyde (1996) indicated that the available evidence in animals suggests that EDC is genotoxic.
Cancer	Available data on the carcinogenicity of EDC in humans are limited. There are no epidemiological studies which show an associated between EDC exposure and cancer. There is convincing evidence of increases in the incidence of both common and rare tumours in experimental animals at several sites (including squamous cell carcinomas of the stomach, haemangiosarcomas, fibromas of the subcutaneous tissue and adenocarcinomas and fibroadenomas of the mammary gland in rats; and alveolar/bronchiolar adenomas, mammary gland adenocarcinomas, endometrial stromal polyp or endometrial stromal sarcoma combined and hepatocellular carcinomas in mice) following oral exposure studies (WHO, 1998). The incidence of benign lung papillomas was significantly increased in mice following long-term dermal application of EDC, while a non-significant increase in the number of pulmonary adenomas per animal was reported in a screening bioassay on mice and in the incidence of benign mammary gland tumours in rats exposed by inhalation for 2 years (WHO 1998).

Toxicity Classification

EDC was classified as a "probable" human carcinogen (Category B2) by the USEPA for all routes of exposure based upon evidence from animal studies.

IARC (1999) has classified EDC in Group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans for carcinogenicity and sufficient evidence in experimental animals.

NICNAS has classified not classified EDC.

Exposure Limits/Toxicity Evaluations

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004 and derived from WHO, see below) have derived a drinking water guideline of 0.003 mg/L for EDC based on an lifetime excess cancer risk of 1 in 1,000,000. The slope factor used in the derivation of the drinking water guideline can be calculated as follows:

SF (mg/kg/day)$^{-1}$ *= Risk/Intake(mg/kg/day)*

= [Risk x Body Weight]/[Concentration (water) x Ingestion Rate)]

= [1 x10^{-6} x 70kg]/[0.003mg/L x 2 L/day]

= 0.012 (mg/kg/day)$^{-1}$

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment". For EDC, the following have been established:

TWA: 10 ppm, equivalent to 40 mg/m^3

STEL: NA

It should be noted that this chemical is flagged for further review based on carcinogenic potential.

WHO

The WHO (Drinking Water Guideline 1993 and 2004) established a guideline of 0.03 mg/L using a linearised multistage model and an excess lifetime cancer risk of 1 in 100,000. This corresponds to an ***oral slope factor of 0.012 (mg/kg/day)$^{-1}$*** (as used by NHMRC).

The WHO also notes that data indicate that EDC is less potent when inhaled.

WHO (2000) has undertaken a review of EDC for inhalation exposures. The review indicates that there is sufficient evidence of carcinogenicity in animals based on oral ingestion data. However, animal inhalation data do not provide sufficient evidence of carcinogenicity. Because of deficiencies in extrapolating oral data to inhalation, neither the oral slope factor nor any inhalation value has been recommended by the WHO in this assessment. A guideline value of 0.7 mg/m^3 for a 24-hour average has been derived for non-carcinogenic endpoints by the WHO (2000) based on a lowest-observed-adverse-effect level from animal studies. It is noted that this guideline value is of short duration exposures only and is recommended for the assessment of accidental release episodes or specific indoor pollution problems.

WHO (2000b) have published a parallel review from a task force which had the aim of providing a more global application of air quality guidelines, in conjunction with the Air Quality Guidelines for Europe (WHO, 2000). WHO (2000b) provide a range of inhalation unit risk values for exposure to EDC in air based on tumour formation in rats. The range of inhalation unit risk values is (0.5 to 2.8)x10^{-6} (μg/m^3)$^{-1}$ (i.e. for an air concentration of 1 μg/m^3, the lifetime risk is estimated to be (0.5 to 2.8)x10^{-6}). This is equivalent to the following inhalation slope factor:

SF (mg/kg/day)$^{-1}$ = *Risk/Intake(mg/kg/day)*

= *[Risk x Body Weight]/[Concentration (in air) x Inhalation Rate)]*

= *[(0.5 to 2.8) x10^{-6} x 70kg]/[0.001mg/m^3 x 20 m^3/day]*

= ***0.0018 to 0.0098 (mg/kg/day)$^{-1}$***

The higher value in the range presented above for inhalation exposures is considered the more conservative (higher risk). This value is approximately equal to the NHMRC slope factor used to derive the drinking water guideline, namely 0.012 (mg/kg/day)$^{-1}$ and is recommended for a conservative evaluation of inhalation exposures.

EU

The European Commission published a directive in 1990 in which limit values for emission of EDC were specified for various types of industrial plants. These limits ranged from 0.1 mg/litre (monthly) for plants using EDC for degreasing metals away from an industrial site to 12 mg/litre (daily) for plants producing EDC and processing or using the substance at the site (WHO, 1998). No other assessment of EDC is available from the EU.

US

The USEPA (IRIS current in 2004) has derived an ***oral slope factor of 0.091 (mg/kg/day)$^{-1}$*** for EDC based on a linear multistage model based on hemangiosarcomas in rats; and an ***inhalation unit risk of 2.6x10^{-5} (μg/m3)$^{-1}$*** using a linear multistage model based on oral data used to derive the oral slope factor. The USEPA does not present any data relevant to the assessment of non-carcinogenic effects for EDC.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with EDC. The levels established (valid in 2004) are:

- Chronic (and intermediate) inhalation MRL = 0.6ppm based on liver histopathology in rats; and
- Intermediate oral MRL = 0.2 mg/kg/day based on increased kidney weights in rats.

The California Air Resources Board (CARB 2002, OEHHA 2000) has established ***inhalation unit risk value of 2.1x10^{-5} (μg/m^3)$^{-1}$***and a ***chronic reference exposure level for EDC of 0.4 mg/m^3*** based on hepatotoxicity (elevated liver enzyme levels in serum of rats).

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. However, as EDC has been evaluated to be a genotoxic carcinogen it is considered appropriate to evaluate exposure using a slope factor for oral, inhalation and dermal exposures where an incremental probability of cancer is calculated. Hence background intake is not relevant in the evaluation of non-threshold dose response chemicals.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for EDC following review of the available information in general accordance with guidance provided by enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**Oral Slope Factor = 0.012 (mg/kg/day)$^{-1}$ (NHMRC, 2004)**
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**Inhalation unit risk of 2.8x10^{-6} (per μg/m^3),** equivalent to **0.0098 (mg/kg/day)$^{-1}$** (WHO 2000b). Occupational inhalation exposure (NOHSC): **TWA: 10 ppm, equivalent to 40 mg/m^3** **STEL: NA**

References

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General

Dichloromethane (also commonly known as methylene chloride as well as methane dichloride, methylene bichloride, methylene dichloride or **DCM**) is a synthetic compound, which is not known to occur naturally in the environment. DCM is primarily used as a solvent, especially for grease, plastics and various paint-binding agents. Among its uses are: as a component of paint and varnish strippers, and adhesive formulations; solvent in aerosol formulations; extractant in food and pharmaceutical industries; process solvent in cellulose ester production and fibre and film forming; process solvent in polycarbonate production; blowing agent in flexible polyurethane foams; the extraction of fats and paraffins; plastics processing, and metal and textile treatment; a vapour degreasing solvent in metal-working industries. The main use in consumer products is in paint strippers, where DCM is the main constituent (70-75%). The second important use is in hairspray aerosols, where it acts as a solvent and vapour pressure modifier. Other types of DCM-containing products are household cleaning products and lubricating, degreasing and automotive products, some of which may be in aerosol form. DCM is produced by the reaction of methanol with hydrogen chloride which is then reacted with chlorine. Chloroform and, to a lesser extent, carbon tetrachloride are also produced.

Properties

DCM is a non-flammable, colourless liquid with a with a penetrating ether-like odour. It is soluble in alcohol, ether, acetone, chloroform and carbon tetrachloride. The pure dry compound is very stable. DCM hydrolyses slowly in the presence of moisture, producing small quantities of hydrogen chloride. Commercial DCM normally contains small quantities of stabilisers to prevent decomposition. Key properties are presented below (ATSDR 2000 and USEPA 2002):

CAS No.	75-09-2
Chemical Formula	CH_2Cl_2
Molecular Weight	84.93
Vapour Pressure	349 mmHg at 20^{o}C
Vapour Density	2.9
Density	1.32 g/ml at 25^{o}C
Solubility (Water)	13200 mg/L at 20^{o}C
Air Diffusion Coefficient	0.101 cm^2/s
Water Diffusion Coefficient	1.2 x 10^{-5} cm^2/s
Henry's Law Coefficient	0.00219 atm.m^3/mol
	= 0.0898 at 25^{o}C (unitless)
Koc	11.7 cm^3/g
Odour Threshold	540 to 2160 mg/m^3

Exposure

Human exposure to DCM occurs principally through inhalation. However exposure may also occur via oral and dermal routes particularly during occupational or consumer use of DCM containing products. The chlorination of drinking water also produces DCM. NHMRC (1996) indicate that DCM has not been found in Australian drinking waters.

If released into the environment the following can be noted with respect to DCM (ATSDR 2000 and WHO 1996):

- Air: Nearly all DCM released to the environment will ultimately be present in the atmosphere due to its volatility, where it will degrade by reaction with photochemically produced hydroxyl radicals with a lifetime of 6 months. Transport can occur to regions far removed from the emission source. DCM is expected to have no significant impact on stratospheric ozone depletion nor will it contribute significantly to photochemical smog formation.

- Soil and Water: Following releases to soil, most DCM is expected to volatilise and low soil adsorption. Most of the remaining DCM will travel through the soil because of its low adsorption onto soils (and hence high mobility) with leaching to groundwater considered to be a significant pathway. Volatilisation is considered to be the main process for the removal of DCM from aquatic systems. DCM is not expected to adsorb significantly to sediment or suspended organic matter in surface water.

- Biodegradation: DCM undergoes slow hydrolysis in water and hence it is not considered to be a significant degradation process in water. Both aerobic and anaerobic biodegradation may be important for DCM in water. Degradation of DCM in soils was found to occur with the rate of degradation dependant on the soil type, concentration and redox state of the soil with degradation observed under both aerobic and anaerobic conditions. Biodegradation of DCM appears to be accelerated by the presence of elevated levels of organic carbon.

- Bioaccumulation of DCM is not expected to be significant.

Health Effects

General

The following information is available from WHO (1996) and ATSDR (2000). There is no clinical disease which is unique to DCM toxicity.

Humans and animals readily absorb DCM from the lungs and the gastrointestinal tract into systemic circulation. The compound is also absorbed to some extent through intact skin.

Following absorption, DCM concentrations rapidly increase in the blood to reach equilibrium levels that depend primarily on exposure concentrations. A fairly uniform distribution to heart, liver, and brain is reported with increased concentrations also reported in adipose tissue. DCM is quite rapidly excreted, mostly via the lungs in the exhaled air. It can cross the blood-brain barrier and be transferred across the placenta, and small amounts can be excreted in urine or in milk.

Extensive toxicokinetic studies have shown that DCM is metabolised by two pathways: (1) a mixed function oxidase (MFO) pathway mediated by the P-450 system yielding CO and CO_2 and (2) a glutathione-dependent (GST) pathway yielding only CO_2. Other metabolites of DCM include formaldehyde and formic acid.

Tests involving acute exposure of animals have shown DCM to have moderate acute toxicity from oral and inhalation exposure. Case studies of DCM poisoning during paint stripping operations have demonstrated that inhalation exposure to extremely high levels can be fatal to humans. Acute inhalation exposure to high levels of DCM in humans has resulted in effects on the central nervous system (CNS) including decreased visual, auditory, and psychomotor functions, but these effects are reversible once exposure ceases. DCM also irritates the nose and throat at high concentrations.

The major effects from chronic inhalation exposure to DCM in humans are effects on the CNS, such as headaches, dizziness, nausea, and memory loss. Animal studies indicate that the inhalation of DCM causes effects on the liver, kidney, CNS, and cardiovascular system.

Animal studies have demonstrated that DCM crosses the placental barrier, however in the studies available DCM is not a reproductive toxicant nor is it a developmental toxicant via inhalation or oral pathways.

Genotoxic Effects

Review of genotoxicity (WHO 1996 and Woodward-Clyde 1996) indicates that the available data indicate that DCM or its metabolites are capable of interacting with DNA. However, with the exception of mouse studies, *in vivo* studies using high levels of DCM exposure have not provided clear evidence of genotoxicity. The evidence suggests that DCM genotoxicity in the mouse results from the metabolism of DCM to genotoxic metabolites and this is a species specific phenomenon which does not appear to occur in other species including humans. Therefore the relevance of the genotoxicity in mice to humans is considered limited and there is no conclusive evidence that DCM in genotoxic.

Cancer

Review of carcinogenicity (WHO 1996 and Woodward-Clyde 1996) indicates that DCM has been found to be carcinogenic in the mouse, causing both lung and liver tumours, following exposure to high concentrations in air. These tumours were not seen in the rat or the hamster.

Metabolism and biochemical studies, and mutagenicity assays in bacteria and $B6C3F_1$ mice have provided a plausible explanation for the mechanism of action and the species differences in the carcinogenicity of DCM to the lung and liver. This explanation is based on the existence of an isoenzyme of glutathione- *S*-transferase which specifically metabolises DCM to the reactive intermediates responsible for tumour induction in the mouse. This is an important pathway only in mice and then only at high doses. It is not a major pathway for rats, hamsters of humans. The mouse appears to be unique in its response to DCM and is not an appropriate model for humans.

Benign mammary tumours observed in rats exposed at high doses to DCM are the result of high serum prolactin levels which is not expected to occur at low levels of exposure and has not been observed in humans exposed to DCM.

On the basis of the available information, the carcinogenic potency of DCM in humans is expected to be low.

Toxicity Classification

DCM has been classified as a "probable" human carcinogen (Category B2) by the USEPA based on increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in mice and benign mammary tumours in rats.

IARC (1999) has classified DCM in Group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans and sufficient evidence in experimental animals for carcinogenicity.

The National Occupational Health and Safety Commission (NOHSC) has classified DCM as Category 3 carcinogen (possible human carcinogen). NICNAS has classified not classified DCM.

Exposure Limits/Toxicity Evaluations

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004) have derived a drinking water guideline for DCM of 0.004 mg/L using a ***TDI of 0.0012 mg/kg/day*** derived from a lowest effect level based on a 2 year drinking water study on rats and the application of 5000 safety factor.

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment". For DCM, the following have been established:

TWA: 50 ppm, equivalent to 174 mg/m^3

STEL: NA

WHO

The WHO (Drinking Water Guideline 1996 and 2004) provide a guideline value for DCM of 0.02 mg/L based on a ***TDI of 0.006 mg/kg/day*** derived from hepatotoxic effects in a 2-year drinking water study in rats.

Review of DCM by the WHO in 1996 has concluded that "*Effects on the CNS have been observed in both animals and humans and a threshold in humans has been defined, based on the level of metabolite carbon monoxide in the blood, leading to exposure limits in the order of 177 mg/m^3*" (500ppm).

The WHO (2000) review of DCM has identified that carcinogenicity is not the critical end point for risk assessment purposes. The formation of carbon monoxide in blood (COHb is a more direct indication of a toxic effect, it can be monitored and is a more suitable basis for the derivation of a guideline. A ***guideline value of 3 mg/m^3*** has been derived for the assessment of 24-hour exposures based on a 0.1% increase in COHg. In addition, it is noted that the weekly average concentration should not exceed one-seventh of this guideline (0.45 mg/m^3). As this is a short term exposure value, it was not selected for risk assessment.

EU

The European Commission (TNO, 1999, CSTEE 2000) has commissioned a review of methylene chloride in the European Union. With respect to the assessment of risk by the general public via environmental exposures, the following criteria have been derived:

- Short-term exposure :- 7 mg/m^3 (consumers/general public) and 250 mg/m^3 (occupational exposure limit)

- Long-term exposure: 1.25 mg/m^3 (consumers/general public)

In addition the report discusses the potential for DCM to be an animal carcinogen and the potential for evaluation on the basis of non-threshold approach. A chronic standard of 0.2 mg/m^3 has been derived by the TNO based on 1x10^{-4} incremental risk level, using the NTP (USEPA) inhalation unit risk value of 4.7x10^{-7} (μg/m^3)$^{-7}$.

Review of the TNO report by the Scientific Committee for Toxicity, Ecotoxicity and the Environment for the EC (2000) indicated a number of deficiencies with the report. While the opinions in this report are not considered EU guidance as it has not been adopted by the Member States, the following is noted with respect to the evaluation of exposures by the general public:

- Chronic inhalation exposures have been evaluated on the basis of liver effects in the rat, leading to a NOAEL of 125 mg/m^3 continuous exposure, which, with a MOS of 100, reduces to a limit of 1.25 mg/m^3.

- The chronic standard of 0.2 mg/m^3 has been derived based on 1x10^{-4} incremental risk level is not considered to be acceptable.

- The review committee considered that the acceptable limit for long-term exposure of the general population should be based on consideration of the carcinogenic risk. A number of quantitative risk estimates for DCM inhalation exposure have been published, often varying by orders of magnitude. The exposure limit giving rise to a lifetime risk of 10^{-5}, calculated by the Swedish Institute of Environmental Medicine using a benchmark method without adjustment for species differences in kinetics, is 45 μg/m^3. The US EPA, using a model that includes toxicokinetic considerations, has calculated a value of 21 μg/m^3 for a similar level of risk. The Danish EPA (2001) have also established an air guideline value of 0.02 mg/m^3 on the basis of carcinogenic effects on the basis of 10^{-6} incremental lifetime risk.

US

The USEPA (IRIS current in 2004) has derived the following for DCM:

- Non-Cancer effects: Oral reference Dose ***(RfD) of 0.06 mg/kg/day*** based on liver toxicity in rats. A provisional inhalation Reference Concentration (RfC) of 3 mg/m^3 has also been calculated based on liver effects in rats.

- Cancer effects: An ***oral slope factor of 0.0075 (mg/kg/day)$^{-1}$*** has been derived using a linearised multistage model based on hepatocellular adenomas and carcinomas in mice. An ***inhalation unit risk value of 4.7x10^{-7} (μg/m^3)$^{-1}$*** has also been derived based on combined adenomas and carcinomas in mice.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with DCM. The levels established (valid in 2004) are:

– Acute inhalation MRL = 0.6 ppm (2.1 mg/m^3) based on CNS effects in humans (inhalation study)

– Intermediate inhalation MRL = 0.3 ppm (1.06 mg/m^3) based on liver effects in rats (inhalation study)

– Chronic inhalation MRL = 0.3 ppm (1.06 mg/m^3) based on liver effects in rats (inhalation study)

– Acute oral MRL = 0.2 mg/kg/day based on inhalation data

– Chronic oral MRL = 0.06 mg/kg/day based on liver effects in rats

The California Air Resources Board (CARB and OEHHA) has established the following with respect to DCM:

- Inhalation unit risk of $\boldsymbol{1.0x10^{-6}\ (\mu g/m^3)^{-1}}$.
- Chronic Inhalation reference Exposure Level (***REL) = 0.4 mg/m^3*** based on carboxyhemoglobin formation above 2% in workers.
- Acute inhalation ***REL = 14 mg/m^3*** (1 hour average) based on CNS effects.

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. With respect to DCM, intakes from soil, water and food can be considered to be insignificant. Based on data available from urban air in Brisbane and Perth (Hawas, 2001, WA DEP 2000) DCM intake from air may contribute to approximately 20% of the TDI. Hence, the suggested TDI values presented for the evaluation of DCM should be adjusted to account for 20% intake from background.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for DCM following review of the available information in general accordance with enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**TDI = 0.0012 mg/kg/day** (NHMRC 1996) **Adjusted intake for background = 0.00096 mg/kg/day (accounting for 20% background intake)** DCM is not a genotoxic carcinogen and hence use of a slope factor is not considered appropriate.
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**TDI = 1 mg/m^3** (chronic inhalation MRL from ATSDR, similar to the value suggested by TNO 1999 of 1.25 mg/m^3) **Adjusted intake for background = 0.8 mg/m^3 (accounting for 20% background intake)** DCM is not a genotoxic carcinogen and hence use of an inhalation unit risk (as

	available from TNO, Swedish Institute, Danish or US agencies) is not considered appropriate. Occupational inhalation exposure (NOHSC): **TWA: 50 ppm, equivalent to 174 mg/m^3** **STEL: NA**

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General

Hexachlorobenzene (also known as perchlorobenzene, pentachlorophenyl chloride and commonly abbreviated to **HCB**) is a synthetic organic compound that does not naturally occur. HCB can be produced by reacting benzene with excess chlorine in the presence of ferric chloride at 150-200^{o}C. HCB was primarily used as a grain fumigant on wheat, barley, oats and rye for the control of bunts. In most countries its use as a fungicide has been discontinued. HCB was also used in the production of pyrotechnic and military ordinance and in the manufacture of nitroso rubber for car tyres.

HCB has also been incidentally produced as a by product in the manufacture of chlorinated solvents such as tetrachloroethylene and carbon tetrachloride, chlorinated pesticide and other chlorinates compounds. Small amounts of HCB can also be produced during combustion processes such as burning of city wastes.

Properties

HCB is a clear white crystalline solid at room temperature that is practically insoluble in water. When heated to decomposition, it emits toxic fumes of chlorides. HCB is slightly soluble in ethanol, soluble in ethyl ether and very soluble in benzene. Key properties are presented below (ATSDR 2002 and USEPA 2002):

CAS No.	118-74-1
Chemical Formula	C_6Cl_6
Molecular Weight	284.79
Vapour Pressure	0.000011 mmHg at 20^{o}C
Vapour Density	9.8
Density	1.57 g/ml at 23^{o}C
Solubility (Water)	0.006 mg/L at 20^{o}C
Air Diffusion Coefficient	0.0542 cm^2/s
Water Diffusion Coefficient	5.91 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.0017 atm.m^3/mol at 25^{o}C
	= 0.0695 (unitless)
Koc	4 to 5 cm^3/g
Odour Threshold	Not available

Exposure

Exposures to HCB may occur and in the workplace and within the general environment. Work place exposure may occur through inhalation and dermal contact with this compound at workplaces where HCB is produced or used.

The general population may be exposed to HCB via inhalation of ambient air, ingestion of food and drinking water. The general population is not likely to be exposed to large amounts of HCB, however trace amounts have been reported in food and air with HCB reported in most people tested for HCB or its metabolite.

HCB is readily absorbed by the oral route and poorly via the skin. Intake from dietary sources is estimated to be the most significant intake mechanism in the general population, however intake from ambient air or drinking-water may increase in areas closer to emission sources.

The results of most studies of the levels of HCB in foods and human tissues over time indicate that exposure of the general population to HCB declined from the 1970s to the mid-1990s in many locations. Infants may be exposed to HCB from their mother *in utero* or via r human milk.

If released into the environment the following can be noted with respect to HCB (WHO, 2003):

- Air: HCB is expected to exist in both the vapour and particulate-phase in the ambient atmosphere. Vapour-phase HCB is degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals with an estimated atmospheric half-life of about 2.6 years. Particulate-phase HCB may be physically removed from the air by wet and dry deposition. Due to its persistence in the troposphere HCB meets the criteria for long-range transport in the atmosphere.

- Soil and Water: HCB is considered to be immobile in soils and sediment. Volatilisation of HCB from dry soil surfaces is not expected on the basis of the vapour pressure of the chemical. Volatilisation from moist soil surfaces may occur, however this process may be attenuated due to adsorption on to soil particles. HCB is not expected to biodegrade based on a measured half-life in soil of 3 to 6 years. In water, HCB is expected to adsorb to sediment or particulate matter. This compound may volatilise from the surface of water bodies, however adsorption may attenuate this process. The volatilisation half-life is estimated to be approximately 5 years if adsorption is considered.

- Biodegradation is not expected in water on the basis of biodegradation half-lives which have been estimated to be in the order of several years (2 to 10 years) in fresh waters.

- Bioconcentration in aquatic organisms is estimated to be very high on the basis of bioconcentration factors (BCF) in the range of 1,600 to 20,000 measured in fish.

On the basis of the potential for long-range transport, persistence in air, water, soil and sediment, bioaccumulation, toxicity and ecotoxicity, HCB meets the UN-ECE Persistent Organic Pollutant (POP) criteria (UNECE, 1998).

Health Effects

General

The following information is available from WHO (1997 and 2003) and ATSDR (2004). There is no clinical disease which is unique to HCB toxicity.

There is a lack of toxicokinetic information for humans. HCB is readily absorbed by the oral route in experimental animals and poorly via the skin (there are no data concerning inhalation). In animals and humans, HCB accumulates in lipid-rich tissues, such as adipose tissue, adrenal cortex, bone marrow, skin and some endocrine tissues, and can be transferred to offspring both across the placenta and via mothers' milk. HCB undergoes limited metabolism, yielding pentachlorophenol, tetrachlorohydroquinone and pentachlorothiophenol as the major metabolites in urine. Elimination half-lives for HCB range from approximately one month in rats and rabbits to 2 or 3 years in monkeys.

Acute toxicity of HCB is considered to be low via the oral and inhalation exposure pathways. In humans, toxicity has been observed following short-term repeated ingested exposure: with the liver, immune system, skin, tyroid and nervous systems the target organs of toxicity. In animals, similar effects have been noted. The most pronounced effect in both humans and animals is liver toxicity. HCB accumulates in the body over time.

Most data on the effects of HCB on humans originate from accidental poisonings that took place in Turkey in 1955-1959, in which more than 600 cases of porphyria cutanea tarda were identified from oral ingestion of HCB in bread. In this incident, disturbances in porphyrin metabolism, dermatological lesions, hyperpigmentation, hypertrichosis, enlarged liver, enlargement of the thyroid gland and lymph nodes, and (in roughly half the cases) osteoporosis or arthritis were observed, primarily in children. Breast-fed infants of mothers exposed to HCB in this incident developed a disorder called pembe yara (pink sore) and most died within a year. Animal studies have shown that HCB causes reproductive toxicity and increases the risk of cancer formation.

The primary systems for HCB are hepatic toxicity (porphyria), reproductive toxicity, developmental toxicity and carcinogenicity.

Genotoxic Effects

HCB has little capability to induce directly gene mutation, chromosomal damage and DNA repair. It exhibited weak mutagenic activity in a small number of the available studies on bacteria and yeast, although it should be noted that each of these studies has limitations. There is also some evidence of low-level binding to DNA *in vitro* and *in vivo*, but at levels well below those expected for genotoxic carcinogens.

On the basis of the available evidence (WHO 1997 and Woodward-Clyde 1996) HCB can be considered to be non-genotoxic.

Cancer

No association has been found between HCB levels in humans and the incidence of breast or other cancers. Several animal studies have demonstrated an increase in the incidence of tumour formation following oral exposure to HCB. Evidence of carcinogenicity is strongest in the liver (hyperplasia, benign tumours and malignant tumours). In addition HCB has been shown to induce renal metaplasia, adenomas and renal cell carcinomas; lymphosarcomas; adrenal hyperplasia; parathyroid adenomas and hemangioendothelioma and thyroid tumours.

On the basis of available metabolic and toxicological information the WHO considered that a TDI approach was appropriate for the assessment of non-neoplastic effects and neoplastic effects.

Toxicity Classification

HCB has been classified as a "probable" human carcinogen (Category B2) by the USEPA on the basis of the induction of tumours in the liver, tyroid and kidney in three rodent species following oral exposure.

IARC (2001) has classified HCB in Group 2B (possibly carcinogenic to humans) based on inadequate evidence in humans and limited evidence in experimental animals for carcinogenicity.

The National Occupational Health and Safety Commission (NOHSC) not evaluated HCB. NICNAS has classified not classified HCB.

Exposure Limits/Toxicity Evaluations

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004) have not derived a drinking water guideline for HCB.

Worksafe Australia (NOHSC) not evaluated HCB.

WHO

The WHO (1997) concluded that the available data were sufficient to develop guidance values for non-neoplastic effects and neoplastic effects for HCB.

For non-neoplastic effects a ***TDI of 0.17 mg/kg/day*** was derived based on primary hepatic effects in pigs and rats exposed via the oral route (NOEL of 0.05 mg/kg/day) and a 300 fold uncertainty.

The approach for neoplastic effects is based on the Tumorigenic $Dose_5$, or TD_5 i.e., the intake or exposure associated with a 5% excess incidence of tumours in experimental studies in animals. This is a benchmark approach in which the TD_5 is calculated directly from the experimental data rather than using the upper or lower confidence limits. Uncertainty factors are then applied to the TD_5 to obtain a guidance value. The TD_5 value was calculated from the results of a two-generation study in rats using a multistage model where the TD_5 values ranged from 0.81 mg/kg body weight per day for neoplastic liver nodules in females to 2.01 mg/kg body weight per day for parathyroid adenomas in males. The WHO Task Group decided that the most sensitive end-point (neoplastic nodules of the liver) would be used in the assessment. In calculating the suggested guidance value, it was agreed to use an uncertainty factor of 5000, based on consideration of the insufficient mechanistic data. The TD_5 was divided by this uncertainty factor to arrive at the ***suggested guidance value of 0.16 µg/kg body weight per day***. However, it is fully realized that national authorities may choose other end-points or uncertainty factors depending upon data evaluation and future scientific findings.

Although infants may have a high intake of HCB via breast milk for a short time, the TD_5 and TDI were considered to be protective of the health of this population because one of the long-term studies used in deriving these values included lactational exposure. However, it should be noted that the TD_5 and TDI values derived above should not be compared directly with intakes from breast milk by nursing infants, since the guidance values are based on a lifetime intake, whereas the duration of breast-feeding is relatively short.

The WHO Drinking Water Guideline (2003 and 2004) provides the guideline value of 0.001 mg/L for HCB as noted in 1996 calculated using the same approach. However an alternate, benchmark dose approach for deriving exposure associated with neoplastic effects based on the ***suggested guidance value of 0.16 µg/kg body weight per day*** using the TD_5 value approach.

The WHO (Drinking Water Guideline 1996) provide a guideline value for HCB of 0.001 mg/L based on the application of the linearised multistage model to a 2 year dietary study in rats (liver tumours) with an excess lifetime cancer risk of 10^{-5}. This approach was adopted because HCB has been shown to induce tumours in three animal species and at a variant of site, hence the linearised low-dose extrapolation model was considered appropriate in deriving a guideline value. The associated ***oral slope factor for HCB is 0.3 $(mg/kg/day)^{-1}$***.

The WHO (2000, 2000b) has not published any review of inhalation exposures to HCB.

EU

No assessment of HCB is available from the EU.

US

The USEPA (IRIS current in 2004) has derived an ***oral slope factor of 1.6 (mg/kg/day)$^{-1}$*** for HCB based on a linear multistage model based on hepatocellular carcinoma in rats; and an ***inhalation unit risk of 4.6x10^{-4} (μg/m^3)$^{-1}$*** using a linear multistage model based on oral data used to derive the oral slope factor. For the assessment of non-carcinogenic effects an oral reference dose (***RfD) of 0.0008 mg/kg/day*** has been established for HCB based on liver effects in rats. No reference concentration for the assessment of inhalation exposures (non carcinogenic effects) has been established.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with HCB. The levels established (valid in 2004) are:

– Acute oral MRL = 0.008 mg/kg/day based on hyperactivity in offspring rats (oral study)

– Intermediate oral MRL = 0.0001 mg/kg/day based on minimal ovarian effects in monkeys (oral study)

– Chronic oral MRL = 0.00005 mg/kg/day based on hepatic effects from a multigenerational study (oral study)

The California Air Resources Board (CARB and OEHHA) has derived an ***inhalation unit risk of 5.1x10^{-4} (μg/m^3)$^{-1}$*** for HCB.

The ACGIH (American Conference of Governmental Industrial Hygienists, 1998) has established a Threshold Limit Value ***(TLV) of 0.002 mg/m^3*** for HCB based on skin effects.

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. Some data is available regarding levels of HCB reported in breast milk as well as food. No data are available concerning ambient air levels in Australia, however HCB is not regarded as a common urban air contaminant and hence background intake from air is considered to be negligible. WHO (1997) calculated that the total background intake by an adult of HCB is between 0.0004 and 0.003 µg/kg body weight per day mostly derived from dietary exposures. This intake is essentially negligible compared to the TDI and guidance values derived fro the assessment of HCB. On this basis, the assessment of risk associated with potential intake of HCB does not need to be adjusted account for background.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for HCB following review of the available information in general accordance with guidelines from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**Guidance Value = 0.00016 mg/kg/day (**WHO 1997 2003 and 2004 based on neoplastic effects which is the most sensitive)

Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**Guidance Value = 0.00016 mg/kg/day** (equivalent to oral value as no inhalation specific data is available as US inhalation data has been derived from oral studies) Occupational inhalation exposure (ACGIH): **TLV: 0.002 mg/m^3** **STEL: NA**

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General

Hexachlorobutadiene (also known as perchlorobutadiene; 1,1,2,3,4,4-hexachloro-1,3-butadiene; 1,3-hexachlorobutadiene; dolen-pur; GP-40-66:120 and commonly abbreviated to **HCBD**) is a synthetic organic compound that does not naturally occur. HCBD is used as an intermediate in the production of rubber compounds. It is also used a s a solvent, a fluid for gyroscopes, a heat transfer fluid, hydraulic fluid and has been used as a fumigant. HCBD has also been used as a means of recovering chlorine containing gas (snift) in chloride production plants. It is a by-product in the manufacture of chlorinated solvents such as tetrachloroethylene and carbon tetrachloride.

Properties

HCBD is a colourless, oily liquid at room temperature with a turpentine like, pungent odour. HCBD is non-flammable, non-combustible, poorly soluble in water but miscible with ethanol and ether. Key properties are presented below (ATSDR 1994 and USEPA 2002):

CAS No.	87-68-3
Chemical Formula	C_4Cl_6
Molecular Weight	260.76
Vapour Pressure	0.15 mmHg at 25^{o}C
Vapour Density	9
Density	1.55 g/ml at 20^{o}C
Solubility (Water)	2 to 2.55 mg/L at 20^{o}C
Air Diffusion Coefficient	0.0561 cm^2/s
Water Diffusion Coefficient	6.16 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.0103 atm.m^3/mol
	= 0.421 at 25^{o}C (unitless)
Koc	5181 cm^3/g
Odour Threshold	12 mg/m^3

Exposure

Exposure of the general population to HCDB may by inhalation, oral or dermal routes. Exposure is most likely to occur in occupational environments which handle or produce the chemical. Other environmental exposures may be associated with inhalation, ingestion of HCBD in drinking water or ingestion of fish or other foods. HCBD has not been found in Australian drinking waters (NHMRC, 2004).

If released into the environment the following can be noted with respect to HCBD (UNECE, 2002):

- Air: Inter-compartmental transport of HCBD will occur by volatilisation (limited), adsorption to particulate matter, and subsequent deposition or sedimentation. In addition to deposition, reaction with hydroxyl radicals is assumed to be an important sink of HCBD in the troposphere with an estimated atmospheric half-life of up to 2.3 years. Due to its persistence in the troposphere HCBD meets the criteria for long-range transport in the atmosphere.

- Soil and Water: HCBD is expected to bind with soil and sediments. In water, HCBD is considered persistent unless there is high turbulence. Information available n the persistence of HCBD in water, sediment and soil shows conflicting results, however expert judgement has identified HCBD as persistent. Half lives in natural waters and soils have been reported to be 4-52 and 4-26 weeks respectively. There is conflicting data available about biodegradation. Based on the Structure of HCBD it can be expected that dechlorination is required before aerobic biodegradation can occur. Model calculations indicate that HCBD does not biodegrade fast. The substance has a high bioaccumulating potential as has been confirmed by both laboratory and field observations. Average steady-state bioconcentration factors of 5800 and 17 000, based on wet weight, have been determined experimentally in rainbow trout. Biomagnification has not been observed either in the laboratory or in the field (WHO, 1994).

HCBD is not listed as a key persistent organic pollutant under the Stockholm Convention. However, on the basis of the potential for long-range transport, persistence in water, soil and sediment, bioaccumulation, toxicity and ecotoxicity, HCBD meets the UN-ECE Persistent Organic Pollutant (POP) criteria (UNECE, 2002). On this basis evaluation of HCBD should consider the potential for persistence in the environment and bioaccumulation in the food chain.

Health Effects

General

The following information is available from WHO (1994) and ATSDR (1994). There is no clinical disease which is unique to HCBD toxicity. As there have been very few human studies, the evaluation of toxicity is mainly based on studies in experimental animals. However, limited human *in vitro* data suggest that the metabolism of HCBD in humans is similar to that observed in animals.

There is limited data available on the absorption of HCBD in animals. Oral experiments indicate that HCBD absorption is rapid and complete, however little data are available concerning absorption following dermal and inhalation exposures.

When orally administered, HCBD or its metabolites have been observed to be distributed primarily in the kidney (outer medulla) and adipose tissue. HCBD has also been located in the liver following intraperitoneal administration. HCBD and its metabolites are excreted in exhaled air, urine and faeces.

HCBD vapour is considered to be irritating to the mucous membranes of humans, and the liquid is corrosive. The compound should also be regarded a sensitising agent.

The main target organs for toxicity are the kidney and, to a much lesser extent, the liver. Reduced birth weight and neonatal weight gain has only been observed at maternally toxic doses, as was developmental toxicity.

Biotransformation to a reactive sulphur containing metabolite probably accounts for the observed nephrotoxicity, genotoxicity and carcinogenicity.

Genotoxic Effects

HCBD has been found to induce gene mutations, chromosomal aberrations, increased sister chromatid exchanges and unscheduled DNA synthesis, although some studies have reported negative results. There is limited evidence for the genotoxicity of HCBD in animals, and insufficient evidence in humans.

Cancer	There is limited evidence for carcinogenicity in animals and insufficient evidence in humans. Review of carcinogenicity by OEHHA (2000) indicated that there is sufficient evidence for the carcinogenicity of HCBD, based on the development of renal tubular neoplasms in rats. Review of HCBD by the WHO (guidelines 2003) also note the development of kidney tumours in a long-term oral study in rats. HCBD has not been shown to be carcinogenic by other routes of exposure. On the basis of available metabolic and toxicological information the WHO considered that a TDI approach was appropriate for the derivation of an oral drinking water guideline.

Toxicity Classification

HCBD has been classified as a "possible" human carcinogen (Category C) by the USEPA.

IARC (1999) has classified HCBD in Group 3 (not classifiable as to its carcinogenicity to humans) based on inadequate evidence in humans and limited evidence in experimental animals for carcinogenicity.

The National Occupational Health and Safety Commission (NOHSC) as Category 3 carcinogen (possibly carcinogenic to humans). NICNAS has classified not classified HCBD.

Exposure Limits/Toxicity Evaluations

Exposure limits and toxicity evaluations which are available in Australia, World Health Organisation, European Union and the US:

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004) have derived a drinking water guideline of 0.0007 mg/L for HCBD using a ***TDI of 0.0002 mg/kg/day*** based on a NOAEL of 0.2 mg/kg/day based on renal effects in rats and a 1000 fold safety factor.

Worksafe Australia (NOHSC) have established “Exposure Standards for Atmospheric Contaminants in the Occupational Environment”. For HCBD, the following have been established:

TWA: 0.02 ppm, equivalent to 0.21 mg/m^3

STEL: NA

Potential exposure via skin absorption is noted.

WHO

The WHO (Drinking Water Guideline 2004) provide a guideline value for HCBD of 0.0006 mg/L based on a ***TDI of 0.0002 mg/kg/day*** following the same approach outlined by NHMRC (as above).

The WHO has not published any review of inhalation exposures to HCBD.

EU

No assessment of HCBD is available from the EU.

US

The USEPA (IRIS current in 2004) has derived an ***oral slope factor of 0.078 (mg/kg/day)$^{-1}$*** for HCBD based on a linear multistage model based on renal tubular adenomas and adenocarcinomas in rats; and an ***inhalation unit risk of 2.2x10^{-5} (μg/m^3)$^{-1}$*** using a linear multistage model based on oral data used to derive the oral slope factor. The USEPA does not present any data relevant to the assessment of non-carcinogenic effects for HCBD. An oral reference dose of 0.0002 mg/kg/day was derived by the USEPA, however it was withdrawn in 1993.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with HCBD. The levels established (valid in 2004) are:

- Intermediate oral MRL = 0.0002 mg/kg/day based on kidney damage in mice

The California Air Resources Board (CARB and OEHHA) has not established any reference exposure levels (REL) or inhalation unit risk values for HCBD.

Suggested Toxicity Values for Risk Characterisation

Toxicity data relevant for use in the characterisation of risk to human health have been selected for HCBD following review of the available information in general accordance with enHealth (2002) and NEPM (1999).

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. No data is available regarding environmental levels of HCBD in Australia, other than noting that HCBD has not been found in drinking water in Australia (NHMRC). HCBD is not a common urban air contaminant and as such background intakes of HCBD are considered to be negligible. On this basis, the assessment of risk associated with potential intake of HCBD does not need to be adjusted account for background unless other sources of HCBD are present in the study area.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for HCBD following review of the available information in general accordance with guidance from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**TDI = 0.0002 mg/kg/day (NHMRC, 1996 and proposed 2002)**
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**TDI = 0.0002 mg/kg/day** (equivalent to oral TDI as no inhalation specific data is available. In addition, there is no data to suggest that inhalation exposures to HCBD should be evaluated using a non-threshold approach). Occupational inhalation exposure (NOHSC):

	TWA: 0.02 ppm, equivalent to 0.21 mg/m^3 **STEL: NA**

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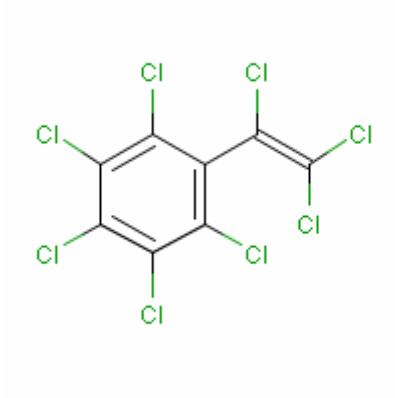
GENERAL



Octachlorostyrene (also known as pentachloro(trichloroethenyl)-benzene and commonly abbreviated to **OCS**) is a synthetic halogenated compound that does not naturally occur. OCS is not produced commercially for any application and is an unintentional by-product from several industrial processes (eg through chlorination of alkane/alkenes and chlorination of elementary carbon). As with chlorinated dioxins, chlorinated dibenzofurans and hexachlorobenzene, OCS is also formed during incomplete combustion in the presence of chlorine. Hence co-emissions of OCS and dioxins are likely to occur. OCS is a by-product of electrolyte refining of magnesium, electrolyte production of chlorine and aluminium foundry using hexachloroethane for degassing. OCS has structural similarities to hexachlorobenzene and dioxins/furans.

OCS is also considered a persistent organic pollutant (POP) and is being considered as a candidate for inclusion on the Stockholm convention priority list for POPs. It is listed by the USEPA within its Persistent Bioaccumulative and Toxic (PBT) Chemical Program.

PROPERTIES

OCS is a colorless liquid at room temperature that is practically insoluble in water and has a high thermal conductivity. Key properties are presented below (HSBD 2006):

CAS No	29082-74-4
Chemical Formula	C_8Cl_8
Molecular Weight	379.68
Vapour Pressure	0.000013 mmHg at 20^{o}C
Vapour Density	Not available
Density	Not available
Solubility	0.00174 mg/L at 20^{o}C
Air Diffusion Coefficient	0.036 cm^2/s
Water Diffusion Coefficient	2.9 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.00013 atm.m^3/mol = 0.0053 at 25^{o}C (unitless)
Koc	200,000 cm^3/g
Log Kow	6.29
Odour Threshold	Not available
Dermal Absorption	Not available, adopt 0.01 (unitless) as default for organics from ORNL (2006)
Permeability Constant	Not available, adopt 0.408 cm/hr considering hexachlorobenzene as surrogate

EXPOSURE

Potential human exposure pathways for OCS are through ingestion (especially of contaminated fish), inhalation, and absorption through the skin. Occupational exposure has been shown to result in elevated levels of OCS in the blood of workers at industrial facilities where OCS is a by-product (HSDB). OCS has been found in the blood of humans ingesting contaminated fish, and in the breast milk of non-occupationally exposed women (HSDB). OCS has also bee reported in breast milk.

The following is available from HSDB regarding the environmental fate of OCS:

- If released to air, it is expected that OCS will exist in both the vapour and particulate phases in the ambient atmosphere. Vapour-phase OCS will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 15 days. Particulate-phase OCS will be removed from the atmosphere by wet and dry deposition.

- If released to soil, OCS is expected to have no mobility based upon Koc values from 200,000 to 10,000,000. Volatilization from moist soil surfaces is expected to be an important fate process based upon an estimated Henry's Law constant of $2.3X10^{-4}$ atm-cu m/mole. However, adsorption to soil is expected to attenuate volatilization.

- If released into water, OCS is expected to adsorb to suspended solids and sediment based upon its Koc. Volatilization from water surfaces is expected to be an important fate process based upon this compound's estimated Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 13 hrs and 10 days, respectively. However, volatilization from water surfaces is expected to be attenuated by adsorption to suspended solids and sediment in the water column.

- BCF values ranging from 8,100 to 1,400,000 suggest bioconcentration in aquatic organisms is very high.

OCS is known to be a persistent chemical with degradation processes generally slow. OCS is listed in the priority 1 series of chemicals considered under the PBT program. The USEPA acknowledges that levels of OCS in the environment are decreasing. The estimated environmental half lives for OCS have been estimated (ILV 2006) as 170 hours in air, 5500 hours in water and 5500 to 55000 hours in soils and sediments. The potential for OCS to biomagnify is considered similar to that of hexachlorobenzene (ILV 2006).

HEALTH EFFECTS

General

The following information is available from USEPA (2000), IVL (2006) and HSDB and TOXLINE (online databases, current). There is no clinical disease which is unique to OCS toxicity.

The human toxicological properties of OCS are not well known. In laboratory animals, acute toxicity studies showed histological changes in liver, kidney and thyroid tissues, deemed "moderate to severe" for

the liver, but the impairment in function was not well quantified. Repeated doses of OCS have been shown to affect thyroid as well as liver, kidney and hematopoietic system.

The USEPA has developed and begun implementing a screening program for estrogenic substances to determine the relationship between exposure to suspected endocrine disrupting chemicals and associated adverse effects in humans. Suspected substances, including OCS, have been slated for testing under the endocrine screening program. Endocrine disrupting chemicals are thought to harm male and female reproductive systems, cause thyroid damage, cause a range of other problems affecting developing fetuses and newborns, including low IQs and genital malformations, cause low sperm counts and infertility, and possibly also cause cancer.

In its recent action of adding OCS (along with several other chemicals) to the Toxics Release Inventory (TRI) as a reportable chemical, the USEPA found that "all of the chemicals proposed for addition were found to be reasonably anticipated to cause serious or irreversible chronic human health effects at relatively low doses or ecotoxicity at relatively low concentrations, and thus are considered to have moderately high to high chronic toxicity or high ecotoxicity".

OCS is lipophilic and as such, is expected to (and has been reported to) accumulate within adipose tissue.

Genotoxic Effects

Based on limited data OCS has not been shown to be genotoxic.

Cancer

OCS has not been evaluated with respect to carcinogenicity with limited data not reporting significant findings with respect to carcinogenicity. Some studies suggest similarity to hexachlorobenzene and hexachlorobutadiene with respect to carcinogenicity, however limited data is available. OCS may act as a "promoter" of mutagenicity, and thus also as a promoter of carcinogenicity, though there are not studies available to confirm this hypothesis.

TOXICITY CLASSIFICATION

OCS has not been classified by USEPA or IARC. While OCS is listed in the Australian Inventory of Chemicals Substances (AICS), NICNAS has not conducted an assessment of classification of the chemical (NICNAS 2002).

EXPOSURE LIMITS AND TOXICITY EVALUATIONS

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004) have not derived a drinking water guideline for OCS.

Worksafe Australia (NOHSC) not evaluated OCS.

WHO

The WHO has not evaluated OCS.

EU

No assessment of OCS is available from the EU.

US

The USEPA has not evaluated OCS.

Other

Health Canada has established a Minimum Risk Intake or tolerable intake for OCS from food of 0.31 µg/kg bodyweight/day (as listed by USEPA 2000). It is noted that the state of New York has derived a tolerable intake of 0.03 µg/kg bodyweight/day (IVL, 2006).

The tolerable daily intake of 0.31 µg/kg bodyweight/day presented by Health Canada is similar to a surrogate value proposed (Hoover S.M, 1999) of 0.4 µg/kg bodyweight/day based on the median tolerable daily intakes associated with persistent organochlorins (that have relevant acceptable or tolerable daily intakes available from peer reviewed sources).

SUGGESTED TOXICITY VALUES FOR RISK CHARACTERISATION

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. No data are available concerning background levels of OCS in any media within Australia. Data from Canada (HSDB, current) and Sweden (IVL, 2006) suggests that OCS has been reported in air and fish with levels reported in the body including breast milk. Levels reported are low (<1 pg/m3 in air, approximately 1 ng/g in some fish (mostly not detected with concentrations of hexachlorobenzene reported to be higher in the fish where OCS was detected) and breast milk between 0.05 and 2.16 ng/g (7% detection rate)). As with hexachlorobenzene, the potential intake of OCS is potentially essentially negligible compared to the TDI. On this basis, the assessment of risk associated with potential intake of OCS does not need to be adjusted account for background.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected for OCS following review of the available information in general accordance with guidelines from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	TDI = 0.00031 mg/kg/day (Health Canada as listed by USEPA, 2000)
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	No dermal guidelines are available, hence it has been assumed that inhalation toxicity is equivalent to oral toxicity. Occupational inhalation exposure – no data is available. It is suggested that the value available for hexachlorobenzene be adopted as a surrogate. The occupational value suggested is (ACGIH): TLV: 0.002 mg/m^3 STEL: NA
Background	Negligible

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General

Tetrachloroethene (also known as tetrachloroethylene, perchloroethylene, ethylene tetrachloride, per, perc, perchlor, 1,1,2,2-tetrachloroethylene and commonly abbreviated to **PCE**) is a synthetic chemical that is widely used for dry cleaning of fabrics and for metal-degreasing operations. It is also used as a building block for making other chemicals and is used in some consumer products. PCE manufacture in Australia ceased in 1991. Use in Australia has declined from 1995, consistent with declining use worldwide. PCE is primarily imported in its "pure" form with approximately 80 % used in the dry cleaning industry in Australia.

PCE is widespread in the environment and is found in trace amounts in water, aquatic organisms, air, foodstuffs, and human tissue. The highest environmental levels of PCE are found in the commercial dry-cleaning and metal-degreasing industries. The Australian Drinking Water Guidelines (2004) indicate that PCE has not been detected in Australian drinking water supplies.

PCE may degrade in the environment to more toxic compounds, including vinyl chloride.

Properties

PCE is a volatile, colourless liquid. It is a non-flammable liquid at room temperature which evaporates easily into the air and has a sharp, sweet odour. PCE is practically insoluble in water but miscible with ethanol, ether and oils. Key properties are presented below (ATSDR 1997 and USEPA 2002):

CAS No.	127-18-4
Chemical Formula	C_2Cl_4
Molecular Weight	165.83
Vapour Pressure	18.5 mmHg at 25^{o}C
Vapour Density	5.8
Density	1.62 g/ml at 20^{o}C
Solubility (Water)	200 mg/L at 20^{o}C
Air Diffusion Coefficient	0.072 cm^2/s
Water Diffusion Coefficient	8.2 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.0184 atm.m^3/mol
	= 0.754 at 25^{o}C (unitless)
Koc	155 cm^3/g
Odour Threshold	6.8 mg/m^3 (ATSDR) and 33.9 mg/m^3 (NOHSC)

Exposure

Exposure to PCE may be derived from environmental and occupational sources as well as from consumer products. Common background levels of PCE in the environment are generally several thousand times lower than levels found in some workplaces. Background levels are found in the air, water, and food. The most significant exposure pathway is via the air, particularly in the workplace. PCE gets into air by evaporation from industrial or dry cleaning operations and released from stores of chemical wastes. It is frequently found in surface water.

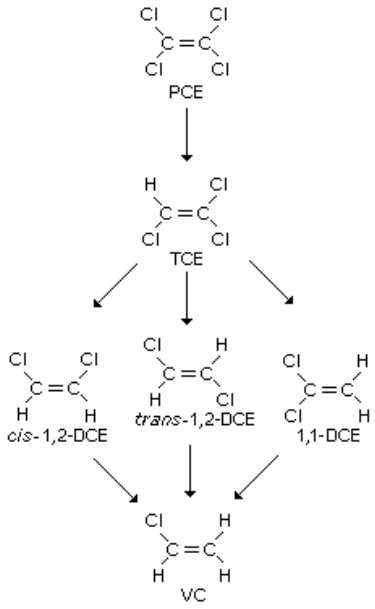
Common consumer products that may contain PCE include water repellents, silicone lubricants, fabric finishers, spot removers, adhesives, and wood cleaners. Although uncommon, small amounts of PCE have been found in food, especially food prepared near a dry cleaning facility. PCE has also been detected in the breast milk of mothers who have been exposed to the chemical. PCE is considered (NICNAS, 2001) to have a low potential for bioaccumulation.

If released into the environment the following can be noted with respect to PCE:

- Air: PCE is expected to remain in vapour phase. Removal is primarily through reaction with hydroxyl radicals, or chlorine atoms produced through photo-oxidation of PCE, which results in half-lives of 1 hour to 2 months.
- Soil and Water: PCE is expected to volatilise from surface soils and water. PCE has a low to medium mobility in soil and may leach slowly through soil into groundwater where it may persist for years. Depending on conditions reductive dehalogenation to vinyl chloride may occur. Under anaerobic conditions PCE and TCE can be intrinsically biodegraded to form DCE and vinyl chloride (below).

Figure 1. Pathway for anaerobic microbial degradation of chlorinated ethenes to form vinyl chloride (from: WHO, 1999)

NB. PCE=tetrachloroethene, TCE=trichloroethene, DCE=dichloroethene



Health Effects

General

There is no clinical disease which is unique to PCE toxicity. PCE is absorbed mainly through inhalation, causing both irritation and neurobehavioral effects. Skin burns, blistering and erythema can occur from severe direct contact with PCE. Some skin absorption can occur but does not appear to be of major significance. The amount of the chemical in the body increases with increasing exposure level and with an increase in physical exercise during exposure. It accumulates to a limited extent in the

	fatty tissues of man and of animals. Because of its affinity for fat, PCE is found in milk. PCE has also been shown to cross the placenta and distribute to the foetus. PCE is eliminated slowly through the lungs. A small amount is metabolised to trichloroethanol and trichloroacetic acid The concentrations of the compound in blood and breath can be used for estimating exposure levels in man. At high concentrations, PCE causes central nervous system depression. Lower concentrations of PCE have been reported to damage the liver and the kidneys. The following summary has been derived from ATSDR (1997).
Death	At high concentrations PCE is a potent anaesthetic agent and a cardiac sensitiser. Hence death resulting from excessive depression of the respiratory centre or the onset of fatal cardiac arrhythmia may occur. Deaths associated with PCE exposure (inhalation and ingestion) have been reported.
Respiratory Effects	Exposure to high concentrations of PCE has been associated with respiratory irritation.
Gastrointestinal Effects	Acute inhalation exposure to PCE has resulted in nausea and vomiting.
Hepatic Effects	The liver is a target organ in humans exposed to high concentrations of PCE in air. In animals, liver effects are characterised by hypertrophy, fatty degeneration and peroxisome proliferation. Hepatic lesions are also induced in experimental animals during inhalation exposure to PCE. The liver has not been shown to be a target organ in humans exposed via the oral route, however it is a target organ in animals exposed orally.
Renal Effects	Symptoms of renal dysfunction (including proteinuria and hematuria) have been associated with exposure to anaesthetic concentrations of PCE vapour. Weak (or no) effects have reported in people with chronic occupational exposures. Adverse renal effects have been observed in rodents exposed to PCE via inhalation and oral ingestion.
Dermal/Ocular Effects	Exposure to high doses of PCE through contact with the air or skin has resulted in burning or stinging in the eyes, transient eye irritation, acute burning and maculapapular rashes. Skin burns, blistering and erythema can occur from severe direct contact with PCE.
Body Weight Effects	Body weight loss has been reported in rats exposed to PCE in air and via oral ingestion.
Immunological Effects	No significant effects have been reported following inhalation exposures. Limited data supports immunotoxic effects on B cells/humoral immunity associated with oral exposures.
Neurological Effects	The nervous system is a major target organ in humans exposed to PCE via inhalation and ingestion. Anaesthetic and preanesthetic central nervous system effects (including mood changes, ataxia, faintness, dizziness, loss of motor coordination collapse, coma and seizures) have been reported from exposures over different periods of time. While acute symptoms seem to improve after cessation of exposure, chronic exposure has been associated with chronic encephalophy (memory and

	concentration impairment) is persistent after cessation of exposure. Neurological effects and biochemical changes in the brain have been reported in animals exposed to PCE.
Reproductive Effects	Some adverse reproductive effects in occupationally exposed women have been reported which include increased risk of spontaneous abortion. Animal studies indicate reproductive effects associated with PCE exposure.
Developmental Effects	Limited animal studies indicate the potential for a slight increase in maternal and foetal toxicity following inhalation exposure to PCE. Animal studies associated with oral exposure to PCE indicate maternal toxicity, increased numbers of postnatal deaths and increased micro/anophthalmia. Acute studies indicate developmental neurotoxicity (with the LOAEL utilised by the ATSDR in the establishment of an acute oral MRL).
Genotoxic Effects	Assays of clastogenic effects in humans have shown inconsistent results in occupational human studies. No animal studies show genotoxic effects. From weight of evidence, PCE is considered to be non-genotoxic (WHO 2000). Lack of strong genotoxic effects is considered (by ATSDR) to be consistent with the metabolism of the compound. Review of PCE undertaken by Woodward-Clyde (1996) indicated that the weight of evidence indicates that PCE is non-genotoxic. However, genotoxicity is observed when PCE is stabilised with known genotoxicants such as compounds containing epoxide groups.
Cancer	Some epidemiological studies indicate a possible association between chronic exposure to PCE and an increased cancer risk, however the evidence provided is considered to be inconclusive. This is mainly due to concurrent exposure to other petroleum solvents as well as PCE, confounding factors (smoking, alcohol, socio-economic status) and small numbers of cancers in the studies. An association between exposure to PCE (inhalation and ingestion) and an increased risk of cancer (mononuclear cell leukaemia and hepatic tumours) in animals has been suggested. Review of PCE by Woodward-Clyde (1996) indicates that PCE is a non-genotoxic animal carcinogen. Review of the possible mechanisms of tumour formation by PCE in animals suggests that the tumours observed may have little relevance for humans. Therefore a threshold type of exposure parameter would be relevant as a basis for human health risk assessment. NICNAS has classified PCE as a Carcinogen Category 3, which is a substance regarded as a possible risk of irreversible effects.

Toxicity Classification

PCE was classified as a "probable" human carcinogen (Category B2) by the USEPA for all routes of exposure based upon evidence from animal studies. This classification has been withdrawn pending further review (not finalised as of June 2004).

IARC has classified PCE in Group 2A (probably carcinogenic to humans) based in limited evidence in humans (epidemiological studies showed elevated risks for oesophageal cancer, non-Hodgkin's lymphoma and cervical cancer) and sufficient evidence in experimental animals (induce peroxisome proliferation in mouse liver and induced leukaemia in rats).

Exposure Limits/Toxicity Evaluations

Exposure limits and toxicity evaluations which are available in Australia, World Health Organisation, European Union and the US are presented below:

Australia

The Australian Drinking Water Guidelines (NHMRC 2004) has followed the WHO Drinking Water Guidelines (1996) which established health based guidelines derived from a **TDI of 0.014 mg/kg/day**. The TDI was derived from both a 6 week mice study and 90 day rat oral drinking water study, both of which indicated a NOAEL of 14 mg/kg/day. An uncertainty factor of 1000 was applied to the NOAEL (100 for inter- and intraspecies variation and 10 for carcinogenic potential). On this basis, the TDI established by WHO can be used for the evaluation of oral exposures to PCE.

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment". For PCE, the following have been established:

TWA: 50 ppm, equivalent to 335 mg/m^3

STEL: 150 ppm, equivalent to 1020 mg/m^3

WHO

Oral TDI used to derive drinking water guidelines (1996) as outlined above in the derivation of Australian Drinking Water Guidelines. The guideline has remained unchanged in the latest WHO guideline (WHO 2004).

Review of inhalation evaluations for PCE as presented by the WHO (2000, 2000b)indicates the following:

Reference	Inhalation Guideline Value	Averaging Time	Basis
WHO 2000	GV = 0.25 mg/m^3	24 hours	Non-carcinogenic LOAEL associated with kidney effects from long-term occupational study
WHO 2000	GV = 8 mg/m^3	30 minutes	Non-carcinogenic odour annoyance level
WHO 2000b	GV = 0.25 mg/m^3	annual	Non-carcinogenic kidney effects in workers (as per WHO 2000) above.

There appears to be some inconsistency in air quality guideline values published by the WHO, particularly with respect to the relevant averaging time for the GV of 0.25 mg/m^3. It should also be noted that the WHO (2000b) indicates that the guideline value is established based on non-carcinogenic end-points and that review of possible carcinogenic end points should be undertaken in the future.

US

The USEPA have established an oral reference dose (RfD) of 0.01 mg/kg/day (available from IRIS 2004) based on hepatotoxicity in mice and increased liver and kidney weights in rats over 13 weeks. An uncertainty factor of 1000 was used to derive the RfD. The USEPA provides no data relevant to non

carcinogenic inhalation or carcinogenicity. The slope factor previously provided by the USEPA (0.051 $mg/kg/day)^{-1}$) based on mouse liver tumour data has been withdrawn (1990).

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with PCE. The levels established (valid in 2004) are:

- Acute inhalation MRL = 0.2ppm based on neurological effects in humans;
- Chronic inhalation MRL = 0.04ppm based on neurological effects in rats; and
- Acute oral MRL = 0.05 mg/kg/day based on developmental effects in mice.

The California Air Resources Board (CARB, current to 2004) has listed PCE as a toxic air contaminant and evaluated cancer and non cancer effects. Cancer effects for PCE have been evaluated on the basis of an inhalation unit risk of $5.9x10^{-6}$ $(\mu g/m^3)^{-1}$ (equivalent to 0.021 $(mg/kg/day)^{-1}$, provided in 1991). Values established to evaluate non cancer effects include and acute inhalation value of 20000 $\mu g/m^3$ (reviewed 1999) based on CNS effects and a chronic inhalation value of 35 $\mu g/m^3$ (reviewed in 2000) based on effects to the kidney, liver and gastrointestinal system.

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI, GV or RfD in assessing potential exposures to site related chemicals. With respect to PCE, intakes from soil, water and food can be considered to be insignificant. Intakes from air have been calculated from industrial air concentrations in reported in Brisbane (Hawas O. et. Al., 2001), with the average and maximum concentrations reported of 0.015 mg/m^3 and 0.085 mg/m^3 respectively (consistent with data from other cities, NICNAS 2001). This represents up to 34% intake from background air sources. On this basis, the oral TDI and inhalation GV identified should be reduced to account for approximately 34% background intake.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected following review of the available information in general accordance with enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**Oral TDI = 0.014 mg/kg/day** (NHMRC 1996 and WHO 1996) **Adjusted tolerable intake = 0.0092 mg/kg/day** (background intake of 34%)
Dermal	No dermal guidelines are available; hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**Inhalation GV = 0.25 mg/m^3** (WHO, 2000b) based on an annual average.

	Adjusted GV = 0.17 mg/m^3 (background intake of 34%) Occupational inhalation exposure levels (NOHSC): **TWA: 50 ppm, equivalent to 335 mg/m^3** **STEL: 150 ppm, equivalent to 1020 mg/m^3**

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General

Trichloroethene (also known as 1,1,2-trichloroethylene, ethylene trichloride, and commonly abbreviated to **TCE**) is a synthetic product that was first prepared in 1864 by the reduction of hexachloroethane with hydrogen. It is mainly used as a liquid or vapour degreasing solvent, particularly in the metal fabricating industry. International concern about the environmental and health and safety concerns of chlorinated solvents has reduced the use of TCE.

TCE was manufactured in Australia from the 1950's to the early 1980's, with current demand met by imports of the chemical. TCE is also recycled in Australia. TCE is used widely in both large and small industries in Australia for vapour degreasing, cold cleaning as well as use in adhesives, waterproofing agents, paint strippers, carpet shampoos and some other cleaning products. It is also an effective cleaning agent for organic materials as it has a low latent heat of vaporisation and is non-flammable.

Properties

TCE is a volatile, colourless or blue mobile liquid with a sweet chloroform-like odour. TCE evaporates into air very quickly and dissolves slightly in water. Key properties are presented below (ATSDR 1995 and USEPA 2002):

CAS No.	79-01-6
Chemical Formula	C_2HCl_3
Molecular Weight	131.4
Vapour Pressure	74 mmHg at 25^{o}C
Vapour Density	4.53
Density	1.465 g/ml at 20^{o}C
Solubility (Water)	1100 mg/L at 20^{o}C
Air Diffusion Coefficient	0.079 cm^2/s
Water Diffusion Coefficient	9.1 x 10^{-6} cm^2/s
Henry's Law Coefficient	0.0103 atm.m^3/mol
	= 0.422 at 25^{o}C (unitless)
Koc	166 cm^3/g
Odour Threshold	115 mg/m^3 (recognition of TCE, WHO 2000)

Exposure

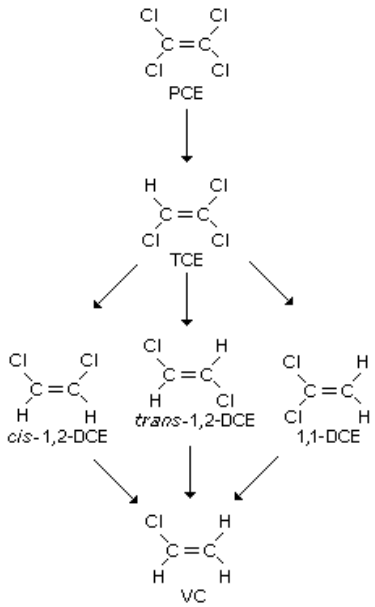
Exposure of the general population to TCE may be by inhalation, oral or dermal routes. In most cases inhalation is the primary route of exposure. Exposure may occur through oral ingestion of drinking water or soils, however exposure to TCE in food is generally low. Apart from occupational exposures, the primary concern is inhalation indoors. TCE in the outdoor air may originate from indoor or outdoor sources. Outdoor sources include outdoor air, contaminated soils or groundwater. Indoor air sources include new building construction materials or home cleaning products. The potential for bioaccumulation of TCE is considered to be low.

If released into the environment the following can be noted with respect to TCE:

- Air: TCE is expected to remain in vapour phase. Removal is primarily through reaction with hydroxyl radicals to produce low levels of phosgene, dichloroacetyl chloride, formyl chloride and other degradation products. Half-life pf TCE varies from 1 day to months.
- Soil and Water: TCE is expected to volatilise from surface soils and water. TCE may leach through soil into groundwater where it may persist for years.
- Water: Depending on conditions reductive dehalogenation to vinyl chloride may occur. Under anaerobic conditions TCE can be intrinsically biodegraded to form DCE and vinyl chloride (below).

Figure 1. Pathway for anaerobic microbial degradation of chlorinated ethenes to form vinyl chloride (from: WHO, 1999)

NB: PCE=tetrachloroethene, TCE=trichloroethene, DCE=dichloroethene



Health Effects

General

There is no clinical disease which is unique to TCE toxicity. In the past, TCE was used as a human anaesthetic. TCE has also been inhaled by people intentionally for its narcotic effect. Hence most toxicological data is associated with inhalation exposures. Primary effects are associated with the central nervous system (CNS).

TCE can be absorbed into the body via inhalation, ingestion and dermal exposure. Following absorption into the body, TCE is distributed to the blood, then transported to various tissues where it is metabolised. The toxicities associated with TCE are thought to be mediated by metabolites rather than the parent compound. Major sites of TCE distribution appear to be the body fat and liver.

Humans and animals excrete un-metabolised TCE via expiration, while the metabolites are excreted primarily in urine. Urinary metabolites include

	trichloroacetaldehyde, trichloroethanol, and trichloroacetic acid; the reactive epoxide TCE oxide is an essential feature of the metabolic pathway.
	The following summary has been derived from NICNAS (2000) and ATSDR (1995).
Death	Acute inhalation and oral exposure of TCE has been known to result in death in humans. Cause of death is typically attributed to hepatorenal failure (ingestion), ventricular fibrillation or CNS depression.
Gastrointestinal Effects	Acute inhalation exposure to TCE has results in nausea and vomiting. Chronic exposure to TCE in the occupation environment has been associated with anorexia and vomiting.
Hepatic Effects	There is some evidence for TCE inducted hepatotoxic effects in humans. Reports (occupational) support the liver as the end point of TCE toxicity. Studies in animals (inhalation and oral) over acute and intermediate periods indicate liver enlargement.
Dermal/Ocular Effects	Exposure to high doses of TCE through contact with the air or skin has resulted in skin irritation and rashes. Stevens-Johnson syndrome (severe erythema), dermatitis and scleroderma have been reported in occupational environments. Adverse effects have not been reported from exposure to dilute aqueous solutions of TCE.
	Ocular effects such as mild eye irritation have been observed in occupational environments.
Body Weight Effects	Body weight loss has been reported in humans occupationally exposed to TCE in air for intermediate of chronic durations at concentrations resulting in neurological effects. No significant effects were observed from oral studies.
Immunological Effects	No significant effects have been reported following inhalation an oral exposures and animal studies.
Neurological Effects	Primary effects identified following inhalation exposures to TCE are associated with the CNS. Effects include headache, vertigo, fatigue, nausea, memory loss, decreased word associations, depression of the CNS, and anaesthesia. Animal studies have reported neurotoxicity and neuropathology effects following oral exposure studies. These effects in part are thought to be due to the sedative properties of the metabolite trichloroethanol (TCOH).
Reproductive Effects	Reproductive effects (increases in miscarriages) have been observed in following exposure to TCE in humans and animals.
Developmental Effects	Other than reproductive effects, no significant developmental effects have been identified following inhalation exposures to TCE. Evidence of birth defects following TCE exposure in drinking water is not clear, however animal studies indicate TCE can act as a developmental toxicant following oral exposure.
Genotoxic Effects	Studies are not conclusive but may be suggestive of clastogenic effects. No human oral studies are available, and animal oral studies indicate conflicting findings. Review of TCE by Woodward-Clyde (1996) indicates that the weight of evidence suggests that TCE has a limited ability to cause genotoxicity. TCE is only weakly mutagenic in bacteria and yeast and the ability of TCE to interact with DNA in whole animals is observed only at high doses. Review by NICNAS (2000) indicates that TCE can be classified a category 3 mutagen – "*as a substance which cause*

	concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damage."
Cancer	No clear unequivocal evidence is available that TCE inhalation exposure is linked to increased cancer risk. The link between oral exposure to TCE and cancer in humans is controversial. Studies in rats and mice have indicated TCE and its metabolites are carcinogenic in animals. TCE has been shown to induce lung and liver tumours in various strains of mice at toxic doses. However, there are no conclusive data that the chemical causes cancer in other species. Review of TCE by Woodward-Clyde (1996) indicates similar findings.

Toxicity Classification

TCE was classified as a "probable" human carcinogen (Category B2) by the USEPA for all routes of exposure based upon evidence from animal studies. This classification has been withdrawn pending further review (not finalised as of June 2004).

IARC has classified TCE in Group 2A (probably carcinogenic to humans) based in limited evidence from several human epidemiological studies and on sufficient evidence from animal studies.

NICNAS has classified TCE as a Carcinogen Category 2, which is a substance regarded as if it is carcinogenic to humans, on the basis of the occurrence of tumours in experimental animals and limited evidence in workers.

Exposure Limits/Toxicity Evaluations

Exposure limits and toxicity evaluations which are available in Australia, World Health Organisation, European Union and the US:

Australia

The Australian Drinking Water Guidelines (NHMRC, 2004) have indicated that there are no long-term studies available to establish a no effect level associated with TCE, hence the available data was considered inadequate to establish an Australian guideline.

Worksafe Australia (NOHSC) have established "Exposure Standards for Atmospheric Contaminants in the Occupational Environment". For TCE, the following have been established:

TWA: 50 ppm, equivalent to 270 mg/m^3

STEL: 200 ppm, equivalent to 1080 mg/m^3

It should be noted that changes have been proposed to these levels. Changes have been issued by NOHSC for public comment in November 2003. They have not been adopted as of June 2004, however the proposed changes are noted:

TWA: 10 ppm, equivalent to 54 mg/m^3

STEL: 40 ppm, equivalent to 216 mg/m^3

WHO

The WHO (Drinking Water Guideline 1996 and 2004) established a ***TDI of 23.8 µg/kg of body weight*** (including allowance for 5 days per week dosing). This was calculated by applying an uncertainty factor of 3000 to a LOAEL of 100 mg/kg of body weight per day for minor effects on relative liver weight in a 6-week study in mice. The uncertainty factor components are 100 for inter- and intra-species variation, 10 for limited evidence of carcinogenicity, and an additional factor of 3 in view of the short duration of the particular study and the use of a LOAEL rather than a NOAEL.

Draft review of TCE by the WHO in 2004 as part of the rolling revision to the guidelines (not endorsed at this stage) has provided a provisional guideline value for cancer effects and non-cancer effects. With respect to the evaluation of cancer effects, the LSM was used to calculate a unit risk (slope factor) for kidney tumours observed in rates. Use of the LMS model is considered relevant based on possible genotoxicity associated with some TCE metabolites (particularly DCVC and DCVG). The slope factor derived was ***$7.8x10^{-4}$ (mg/kg/day)$^{-1}$*** following review of data from oral and inhalation studies. Review of non-cancer effects has resulted in the derivation of a TDI (which is lower than that presented by WHO in 1996 and 2004). The TDI was derived using a LOAEL from a developmental toxicity study, applying a benchmark dose approach to estimate a NOAEL, and application of an uncertainty factor of 100. The TDI derived was ***0.00146 mg/kg/day***. As these values are only available for review and are not endorsed, they have not been considered as approved values for the purpose of selecting relevant toxicity values following enHealth guidance.

The WHO (2000) provided toxicity data for a range of chemicals which were considered to have carcinogenic endpoints. TCE was one of those chemicals identified and an inhalation unit risk of $4.3x10^{-7}$ (per µg/m^3) for the assessment of exposures to TCE in air has been established. (i.e. for an air concentration of 1 µg/m^3, the lifetime risk is estimated to be $4.3x10^{-7}$). The unit risk has been established by the WHO based on increase tumours in lungs and testes in animal bioassays. In utilising this data, the WHO note that "*it cannot be conclusively established whether a threshold with regard to carcinogenicity in the action of TCE may be assumed.*" Hence a conservative approach (deriving a unit risk) has been adopted by the WHO.

The unit risk value is equivalent to the following slope factor:

$SF\ (mg/kg/day)^{-1}$ = *Risk/Intake(mg/kg/day)*

= *[Risk x Body Weight]/[Concentration (in air) x Inhalation Rate)]*

= $[4.3x10^{-7}$ *x 70kg]/[0.001mg/m*^{3} *x 20 m*^{3}*/day]*

= ***0.0015 (mg/kg/day)***$^{-1}$

EU

Review of TCE by the European Union (EU) in 2004 indicates that TCE gives rise to concern for humans owing to possible mutagenic and carcinogenic effects and because it is not possible to identify a threshold exposure level below which these effects would not be expressed. TCE is an *in vitro* mutagen in the presence of an exogenous metabolic activation system. Conflicting data exists, however the weight of evidence indicates that TCE can also exhibit genotoxic activity in somatic tissues *in vivo*. TCE is considered to have the potential to cause cancer in humans. The evaluation of exposure by the EU has focused on workers, consumers and environmental exposures. The evaluation has reviewed relevant

toxicity end points, evaluated body burden associated with exposure and calculated a Margin of Exposure (MOE). The most sensitive threshold effect evaluated was associated with CNS disturbance following repeated dose where a NOAEL of 38 mg/kg/day was used.

The EU has presented a calculation of lifetime cancer risk based on the T25 method in relation to non-Hodgkin lymphoma. From an inhalation study in female mice a HT25 dose descriptor for humans was derived as 130 mg/kg/day. Following the approach presented the EU calculated increased cancer risk for TCE for all groups using an ***equivalent slope factor of 0.0019 (mg/kg/day)$^{-1}$***. This value was used in the quantification of risk associated with exposure from oral, dermal and inhalation pathways.

US

The USEPA has withdrawn the slope factor and reference dose for TCE in 1994, pending review. Prior to being withdrawn, the USEPA had determined an oral slope factor of 0.013 (mg/kg/day)$^{-1}$ and an inhalation slope factor of 0.006 (mg/kg/day)$^{-1}$.

The USEPA issued an evaluation of TCE as a draft for review in 2001. The evaluation indicated that mechanistic research indicates that TCE-induced carcinogenesis is complex, involving multiple carcinogenic metabolites acting through multiple modes of action. Under EPA's proposed (1996, 1999) cancer guidelines, TCE can be characterized as ``highly likely to produce cancer in humans." For effects other than cancer, an oral reference dose (***RfD) of 3x10^{-4} mg/kg/d*** was based on critical effects in the liver, kidney, and developing fetus. An inhalation reference concentration (***RfC) of 4x10^{-2} mg/m^3*** was based on critical effects in the central nervous system, liver, and endocrine system. Several cancer slope factors were developed, with most between 0.02 and 0.4 per mg/kg/d. Several sources of uncertainty have been identified and quantified. The review process has not been completed to date.

The ATSDR has established Minimum Risk levels (MRLs) associated with non-carcinogenic effects associated with TCE. The levels established (valid in 2004) are:

- Acute inhalation MRL = 2ppm based on neurological effects in humans
- Intermediate inhalation MRL = 0.1ppm based on neurological effects in rats
- Acute oral MRL = 0.2 mg/kg/day based on developmental effects in mice

The California Air resources Board (CARB, 1990) has established an inhalation unit risk for the evaluation of chronic exposure to TCE. The inhalation unit risk is 2x10^{-6} to 3x10^{-6} (µg/m^3)$^{-1}$.

Suggested Toxicity Values for Risk Characterisation

Background Intake

For common contaminants, intakes from background sources such as food, water and/or air must also be considered in the evaluation and use of the ADI, TDI or RfD in assessing potential exposures to site related chemicals. With respect to TCE, intakes from soil, water and food can be considered to be insignificant. Intakes from air have been calculated from industrial air concentrations in reported in Brisbane (Hawas O. et. Al., 2001), with the maximum concentration reported of 0.000546 mg/m^3 (representing an intake of approximately 0.00018 mg/kg/day). Hence background intakes of TCE can be considered to be low and does not affect the use of available ADI, TDI or RfD values.

Toxicity Values

Toxicity data relevant for use in the characterisation of risk to human health have been selected following review of the available information in general accordance with guidance from enHealth (2002) and NEPM (1999), accounting for background intake where relevant.

Oral	**TDI = 0.0238 mg/kg/day** (WHO Drinking Water Guidelines, 2004)*
Dermal	No dermal guidelines are available, hence it has been assumed that dermal toxicity is equivalent to oral toxicity.
Inhalation	**Inhalation unit risk of $4.3x10^{-7}$ (per $\mu g/m^3$),** equivalent to **$0.0015 (mg/kg/day)^{-1}$** (WHO 2000, also similar to that derived by EU 2004). Occupational inhalation exposure evaluated using the proposed levels (NOHSC, proposed November 2003): **TWA: 10 ppm, equivalent to 54 mg/m^3** **STEL: 40 ppm, equivalent to 216 mg/m^3**

* Proposed revision to this value is available from WHO, however as these values are only available for review and have not been endorsed, they have not been considered in this assessment. Once endorsed, the oral exposure to TCE will be revised accordingly.

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