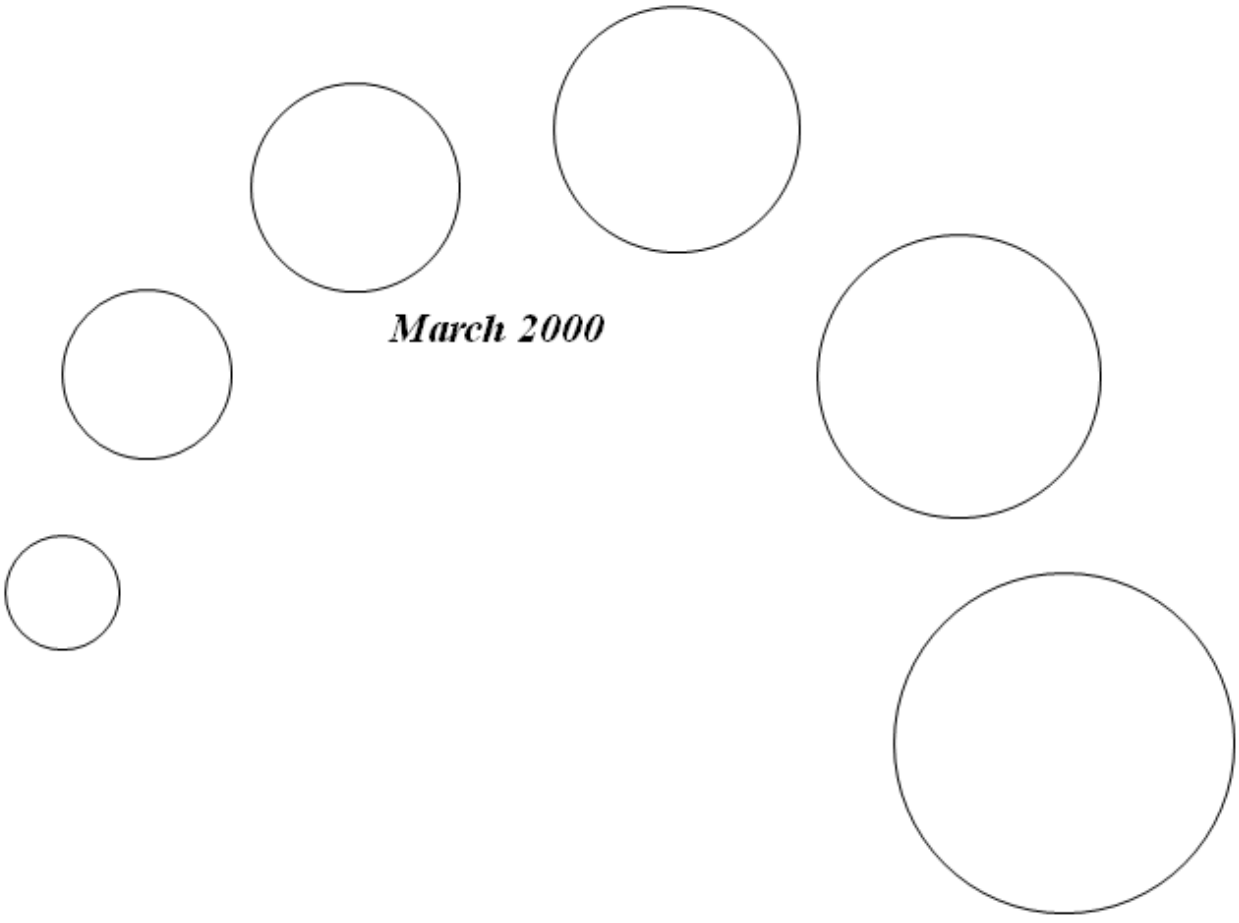
NICNAS

National Industrial Chemicals Notification and Assessment Scheme

Trichloroethylene

Priority Existing Chemical Assessment Report No. 8



March 2000

Number 8

ISBN 0 642 42202 8

Preface

This assessment was carried out under the National Industrial Chemicals Notification and Assessment Scheme (NICNAS). This Scheme was established by the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act), which came into operation on 17 July 1990.

The principal aim of NICNAS is to aid in the protection of people at work, the public and the environment from the harmful effects of industrial chemicals.

NICNAS assessments are carried out in conjunction with Environment Australia (EA) and the Therapeutic Goods Administration (TGA), which carry out the environmental and public health assessments, respectively.

NICNAS has two major programs: the assessment of the health and environmental effects of new industrial chemicals prior to importation or manufacture; and the other focussing on the assessment of chemicals already in use in Australia in response to specific concerns about their health/or environmental effects.

There is an established mechanism within NICNAS for prioritising and assessing the many thousands of existing chemicals in use in Australia. Chemicals selected for assessment are referred to as Priority Existing Chemicals (PECs).

This PEC report has been prepared by the Director (Chemicals Notification and Assessment) in accordance with the Act. Under the Act manufacturers and importers of PECs are required to apply for assessment. Applicants for assessment are given a draft copy of the report and 28 days to advise the Director of any errors. Following the correction of any errors, the Director provides applicants and other interested parties with a copy of the draft assessment report for consideration. This is a period of public comment lasting for 28 days during which requests for variation of the report may be made. Where variations are requested the Director's decision concerning each request is made available to each respondent and to other interested parties (for a further period of 28 days). Notices in relation to public comment and decisions made appear in the *Commonwealth Chemical Gazette.*

The draft trichloroethylene report was published in May 1998. Dow Chemical (Australia) Ltd and Orica Australia Pty Ltd submitted applications to vary the draft report with reference to the carcinogenicity and mutagenicity classification in the report. Following the Director's decision concerning these requests on 14 July 1998, Orica Australia Pty Ltd and Dow Chemical (Australia) Ltd lodged appeals with the Administrative Appeals Tribunal (AAT) to review the Director's decision. Orica Australia Pty Ltd withdrew their application before the hearing. The AAT hearing was held in Melbourne from 3-9 November 1999. Additional unpublished studies provided by applicants and articles published since preparation of the draft report were considered by the Tribunal. Appendix 5 contains a list of these article and studies. The Tribunal's decision was handed down on 31 December 1999 affirming all the decisions of the Director. The Tribunal's decision is reproduced in full in Appendix 6.

In accordance with the Act, publication of this report revokes the declaration of this chemical as a PEC, therefore manufacturers and importers wishing to introduce this chemical in the future need not apply for assessment. However, manufacturers and

importers need to be aware of their duty to provide any new information to NICNAS, as required under section 64 of the Act.

For the purposes of Section 78(1) of the Act, copies of Assessment Reports for New and Existing Chemical assessments may be inspected by the public at the Library, NOHSC, 92-94 Parramatta Road, Camperdown, Sydney, NSW 2050 (between 10 am and 12 noon and 2 pm and 4 pm each weekday). Summary Reports are published in the *Commonwealth Chemical Gazette*, which are also available to the public at the above address.

Copies of this and other PEC reports are available from NICNAS either by using the prescribed application form at the back of this report, or directly from the following address:

GPO Box 58

Sydney

NSW 2001

AUSTRALIA

Tel: +61 (02) 9577 9437

Fax: +61 (02) 9577 9465 or +61 (02) 9577 9465 9244

Other information about NICNAS (also available on request) includes:

- NICNAS Service Charter;
- information sheets on NICNAS Company Registration;
- information sheets on Priority Existing Chemical and New Chemical assessment programs;
- subscription details for the NICNAS Handbook for Notifiers; and
- subscription details for the Commonwealth Chemical Gazette.

Information on NICNAS, together with other information on the management of workplace chemicals can be found on the NOHSC Web site:

http://www.nohsc.gov.au/nicnas

Abstract

Trichloroethylene has been assessed as a Priority Existing Chemical under the National Industrial Chemicals Notification and Assessment Scheme. Trichloroethylene is a chlorinated solvent used mainly in metal cleaning. The most common form of metal cleaning using trichloroethylene is vapour degreasing, while cold cleaning, such as dipping and wiping, occurs to a lesser extent. Trichloroethylene is either used as a solvent neat or as an ingredient of products such as adhesives, electrical equipment cleaners, waterproofing agents, paint strippers and carpet shampoos. Most of these products are used for industrial purposes, although some are available for consumer use.

Exposure to trichloroethylene is mainly by inhalation, with skin contact significant in some cases, particularly cold cleaning. In a comprehensive NICNAS survey conducted in industry to investigate current uses, exposure levels, control technologies and environmental exposure, there was little evidence of routine exposure monitoring. Consequently, a special project was commissioned to undertake atmospheric and biological monitoring of workers using trichloroethylene as a neat solvent in cold cleaning and in products for various purposes. From the study and other exposure data, it was concluded that exposure to trichloroethylene vapours could be high during vapour degreasing and cold cleaning.

Trichloroethylene is absorbed via inhalational, dermal and oral routes, with the most significant uptake being through inhalation of the vapour. Absorbed trichloroethylene is distributed throughout the body and is deposited mainly in adipose tissue and liver. It readily crosses the placental and blood brain barriers. The liver is the primary site of metabolism. The major metabolites are trichloroethanol, trichloroacetic acid and trichloroethanol glucuronide. Other minor metabolites that have been identified are chloral hydrate, monochloroacetic acid, dichloroacetic acid and N-acetyl dichlorovinyl cysteine. A second pathway identified in humans and animals is conjugation with glutathione with the formation of dichlorovinyl cysteine in the kidneys. The major part of the absorbed trichloroethylene is excreted in urine as metabolites while a small amount is exhaled unchanged.

There are some species differences in the metabolism of trichloroethylene. The rate of metabolism of trichloroethylene to trichloroacetic acid in mice is more rapid than in rats. Saturation of the oxidative pathway has also been reported in rats at 200 to 500 mg/kg while in mice saturation is only seen at 2000 mg/kg. Saturation in humans has been predicted by physiologically based pharmacokinetic (PBPK) models to occur at 2000 mg/kg.

The predominant effect of acute exposure to trichloroethylene in humans is CNS depression. It is a skin and eye irritant but not a skin or respiratory sensitiser. The critical effect on repeated exposure is kidney toxicity, with an inhalational No Observed Adverse Effect Level (NOAEL) of 100 ppm observed in a two year study. Other affected systems are the lungs, nervous system and hearing. In animal reproductive toxicity studies, adverse effects were only observed at maternally toxic doses.

Trichloroethylene is weakly mutagenic *in vitro*. In the presence of metabolic activation, trichloroethylene tested positive in several bacterial and fungal gene mutation assays. Trichloroethylene also tested positive in a mouse lymphoma gene mutation assay, and unscheduled DNA synthesis (UDS) was reported in several studies. In somatic cell studies *in vivo*, both positive and negative results were obtained in micronucleus tests, with negative results obtained in studies for chromosome aberrations, sister chromatid exchange and UDS. Trichloroethylene induced DNA single strand breaks in the liver of rats and mice in one study, and in mice liver and kidneys in a second study. A mouse spot test was equivocal, however, a preliminary test for pink-eyed unstable mutation was clearly positive. In germ cell assays, dominant lethal tests were either negative or inconclusive. Studies in occupationally-exposed groups of workers were inconclusive. However, a study of somatic mutations in the von Hippel-Lindau gene in tissue from renal cancer patients reported that trichloroethylene acts on the gene. Further work is underway in Europe to confirm the effects of trichloroethylene on the VHL gene.

Trichloroethylene has been shown to induce tumours in mouse liver and lung and rat kidney and testis with all but the rat kidney tumours considered not relevant to humans. Peroxisomal proliferation is thought to be the mechanism of liver tumour formation and this has not been seen in humans. Lung tumours in mice are related to the accumulation of chloral hydrate in the Clara cells of the lung. Testicular tumours were observed only in one strain of rats with a high incidence in the control group. These tumours are rare in men and are often associated with peroxisomal proliferators. A number of epidemiological studies have investigated the carcinogenic potential of trichloroethylene. Most studies that were large enough to detect an effect individually did not show any association between cancer and occupational exposure to trichloroethylene. However two other studies, with some weaknesses in their conduct, indicated an apparent association between cancer and occupational exposure to trichloroethylene. The kidney tumours are thought to be related to the metabolism of trichloroethylene and are considered to be of concern to humans. The mechanism by which trichloroethylene causes rat kidney cytotoxicity is uncertain and is currently under investigation. It has been proposed that the likely mechanism of kidney tumours in rats is repeated cytotoxicity and regeneration. Some workers have postulated that kidney toxicity is due to formic acid while others have attributed it to the metabolite dichlorovinyl cysteine. Dichlorovinyl cysteine has been identified in the urine of workers exposed to trichloroethylene.

Based on the assessment of health effects, trichloroethylene meets the *Approved Criteria for Classifying Hazardous Substances* for classification as a skin and eye irritant (risk phrases R36/38 - irritating to eyes and skin), mutagen category 3 (R40(M3) Possible risk of irreversible effects, mutagen category 3) and carcinogen category 2 (R45 - May cause cancer).

The occupational risk assessment found that during formulation of products the risk of kidney effects is considered to be minimal. However, there is a concern during vapour degreasing as workers may be exposed to high vapour concentrations for prolonged periods. Use of trichloroethylene in cold cleaning is of concern as workers may be exposed to the vapour as well as absorption of liquid through the skin. Use of trichloroethylene products usually involves work activities of short duration. However there is a concern if workers are exposed on a prolonged basis to products containing high concentrations of trichloroethylene, especially if they are used as aerosols.

It is recommended that greater research and development be directed to substitute processes and non-hazardous substances because of concern that workers may be exposed to high trichloroethylene concentrations during vapour degreasing and cold cleaning.

To control worker exposure during vapour degreasing it is recommended that the vapour degreasing tank conform to the requirements of the Australian Standard AS 2661 - 1983 (Standards Association of Australia, 1983). This standard also describes the safety requirements for the operation of a vapour degreaser plant.

Use of trichloroethylene in cold cleaning is not supported by this assessment, and a phase out period of two years is recommended. The use of trichloroethylene may be unnecessary and/or excessive for some processes. Alternative processes and the substitutes available for some of the uses should be used. During the period where alternatives are being identified, for other uses, appropriate engineering controls such as local exhaust ventilation must be used to minimise exposure. Use of trichloroethylene products in an aerosol form is not supported by this assessment. Local exhaust ventilation will help to minimise exposure of workers to trichloroethylene during use of other products.

Gross deficiencies were noted in the MSDS and labels provided for assessment and it is recommended that suppliers amend these in accordance with regulatory requirements. The deficiencies and the recommendations to rectify them are detailed in the full report.

Trichloroethylene is not expected to present a risk to public health provided consumer products containing trichloroethylene are labelled in accordance with the requirements of the Standard for the Uniform Scheduling of Drugs and Poisons and the label instructions are followed.

The risk to the environment is expected to be low in Australia. Based on the available data it is predicted that trichloroethylene will not occur at concentrations potentially harmful to the aquatic environment or the atmosphere. There is no manufacture of trichloroethylene in Australia, and measures for handling and storing bulk trichloroethylene are in place, therefore except in the case of a major spill, contamination of groundwater is unlikely.

Contents

LIST OF FIGURES

LIST OF TABLES

Acronyms and Abbreviations

ABS	Australian Bureau of Statistics
ACGIH	American Conference of Governmental Industrial Hygienists
ACS	Australian Customs Service
ADG Code	Australian Code for the Transport of Dangerous Goods by Road and Rail
ALT	alanine aminotransaminase
AS	Australian Standard
AST	apartate aminotransamine
ATSDR	US Agency for Toxic Substances and Disease Registry
BEI	biological exposure index
CAS	Chemical Abstracts Service
CFC	chlorofluorocarbons
CNS	central nervous system
cm	centimeter
DNA	deoxyribonucleicacid
EA	Environment Australia
EC	European Commision
EC_{50}	concentration at which 50% of the test population are affected
ECD	electron capture detection
ECG	electrocardiograph
ECETOC	European Center for Ecotoxicology and Toxicology of Chemicals
EEG	electroencephalograph
EU	European Union
FID	flame ionisation detection
GC	gas chromatography
h	hour
HECD	Hall's electrolytic conductivity detection
HRGC	high resolution gas chromatography
HSE	Health and Safety Executive (UK)
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest observable adverse effect level
LOEC	lowest observed effect concentration
MAK	"Maximale Arbeitsplatz-Konzentration' (maximum workplace concentration)
min	minute
MOE	margin of exposure
MS	mass spectrometry
MSDS	Material Safety Data Sheet
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIOSH	National Institute for Occupational Safety and Health (US)

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOHSC	National Occupational Health and Safety Commission
NSW	New South Wales
NTP	National Toxicology Program (US)
NZS	New Zealand Standard
OSHA	Occupational Safety and Health Administration (US)
PBL	peripheral blood leucocytes
PCE	polychromatic erythrocytes
PEC	predicted environmental concentration
PPE	personal protective equipment
ppm	parts per million
ppt	parts per trillion
PVC	polyvinyl chloride
RR	risk ratio
SCE	sister chromatid exchange
SIAM	SIDS Initial Assessment Meeting
SIAR	SIDS Initial Assessment Report
SIDS	Screening Information Data Set
SIR	standardised incidence rate
SMR	standardised mortality rate
STEL	short term exposure limit
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
TCA	trichloroacetic acid
TCOH	trichloroethanol
TGA	Therapeutic Goods Administration
TLV	threshold limit value
TWA	time weighted average
UDS	unscheduled DNA synthesis
µg	microgram
VHL	von Hippel-Lindau
WA	Western Australia

1. Introduction

1.1 Declaration

Trichloroethylene (CAS No 79-01-6) was declared a Priority Existing Chemical under the *Industrial Chemicals (Notification and Assessment) Act 1989* (the Act) (Cwlth) by the Minister for Industrial Relations, by notice in the *Chemical Gazette* of 4 April 1995.

The grounds for declaring trichloroethylene a Priority Existing Chemical were:

- wide use as an industrial solvent with occupational and public exposure to a wide range of products containing the chemical;
- concerns that trichloroethylene may be used as a substitute for 1,1,1-trichloroethane after its phase out by the end of 1995, thereby increasing human and environmental exposure;
- exposure to trichloroethylene may give rise to adverse health effects;
- the differences of opinion regarding the carcinogenic status of the chemical.

1.2 Purpose of assessment

The purpose of this assessment is to:

- characterise current and potential occupational, public and environmental exposure to trichloroethylene;
- characterise the human health hazards and environmental effects/impact and in particular clarify the carcinogenic status of trichloroethylene;
- assess current risk management measures for trichloroethylene including occupational exposure standards and other current standards and guidelines;
- to make recommendations on control measures for the management of the risks to occupational/public health and appropriate hazard communication measures;
- to make recommendations on control measures for the management of environmental hazards along with information on disposal and waste management.

1.3 Data collection

In accordance with the Act manufacturers and importers of trichloroethylene who wished to continue manufacturing or importing trichloroethylene, whilst it was a Priority Existing Chemical were required to apply for assessment and supply information. Information for the assessment was also received from end users, formulators, unions and from a comprehensive literature search. Concurrent with this report has been the preparation of an initial Screening Information Data Set (SIDS) assessment report (SIAR) by the UK Health and Safety Executive (the UK SIAR). The UK draft SIAR was reviewed at the 4th OECD SIDS Initial Assessment Meeting (SIAM) and accepted with changes. Australia had the opportunity to review the report before finalisation as a member of the OECD.

To enhance the efficiency of the National Industrial Chemical Notification and Assessment Scheme (NICNAS) assessment the review of health effects on experimental animals and humans has been based on the UK SIAR. A number of relevant reviews were used to assess the mutagenic and carcinogenic potential of trichloroethylene. Information on mode of use and exposure was also obtained through a number of site visits. The Canadian Environmental Protection Act and German BUA Reports on trichloroethylene were used as the basis of the environmental fate and environmental toxicity review.

The additional data sources that were utilised are as discussed below:

Australian Bureau of Statistics (ABS)

Quantities of trichloroethylene imported in to Australia from 1988 -1997 were obtained from the ABS.

Australian Customs Services (ACS)

The import of trichloroethylene into Australia was monitored through information provided by the Australian Customs Service (ACS). Data on the importers and amounts imported into the country were obtained from the ACS.

Data supplied by applicants

Applicants supplied the following data:

- quantity of trichloroethylene imported;
- quantity of products containing trichloroethylene imported;
- uses of the chemical and products containing the chemical;
- information on recycling of trichloroethylene;
- MSDS and labels
- list of end users

No unpublished data on health or environmental effects of trichloroethylene were provided by applicants.

Surveys

All the applicants on-sell the imported trichloroethylene or trichloroethylene products and do not use the chemical and were unable to provide any data on occupational exposure during use of the chemical. NICNAS therefore conducted a survey to investigate the use processes, exposure levels, control technologies and environmental exposure to trichloroethylene.

Survey 1 Survey of users of trichloroethylene

A survey was undertaken by NICNAS in 1995 to obtain information on the use of trichloroethylene in Australia, to assist in the assessment of occupational and environmental exposure.

Survey 2 Atmospheric monitoring survey

Twenty-six companies identified from the user survey as conducting atmospheric monitoring were followed up with a questionnaire to obtain more detailed monitoring data. Results of 37 samples from 9 worksites were provided in response to the monitoring survey. In addition, monitoring data were also obtained from one bulk storage site and one recycler of trichloroethylene.

Atmospheric Monitoring Project

No atmospheric monitoring data was obtained for use of trichloroethylene in cold cleaning or during use of trichloroethylene products. A project was therefore specially commissioned to an external consultant to undertake atmospheric and biological monitoring of workers using trichloroethylene products for various purposes and neat trichloroethylene in cold degreasing.

Workplaces were identified and contacted by NICNAS. Seven workplaces were willing to participate, with one workplace using both neat trichloroethylene and a trichloroethylene product. The number of workers involved at each workplace depended on the work available. Atmospheric monitoring included personal monitoring and was conducted in accordance with Australian Standard AS 2986 and the samples were analysed by gas chromatography. Biological monitoring included estimation of trichloroacetic acid in urine and analysis of the urine samples by a method developed at the WorkCover Laboratories at Thornleigh.

2. Background

2.1 History

Trichloroethylene was first prepared in 1864 by Fischer by the reduction of hexachloroethane with hydrogen. Commercial production of trichloroethylene in Europe started in 1908 and in the USA in the 1920s. In the past, as is today, trichloroethylene has mainly been used as a liquid or vapour degreasing solvent in the metal fabricating industry.

International and national concern about the environmental and health and safety implications of chlorinated solvents has resulted in a number of regulations and controls that have impacted on the use of trichloroethylene.

2.2 International perspective

In general, there has been a continuing decline in demand for trichloroethylene over the years. New growth is possible in future due to concerns with some of the alternatives for trichloroethylene, for example the phasing out of 1,1,1-trichloroethane at the end of 1995 under the Montreal Protocol. Overseas, new growth in use has also been seen because of its use as a precursor in the manufacture of chlorofluorocarbons (CFC) alternatives such as HFC-134a or HCFC-123 (Anon, 1995). However, conversely, increasing trends in the recovery and recycling of trichloroethylene may reduce production of trichloroethylene. Such circumstances could introduce new sources of potential exposure.

2.2.1 United States

Severe restrictions by the US government in the use and emission of trichloroethylene led to a decrease in demand for trichloroethylene (Wolf & Chestnutt, 1987). The restrictions were as follows:

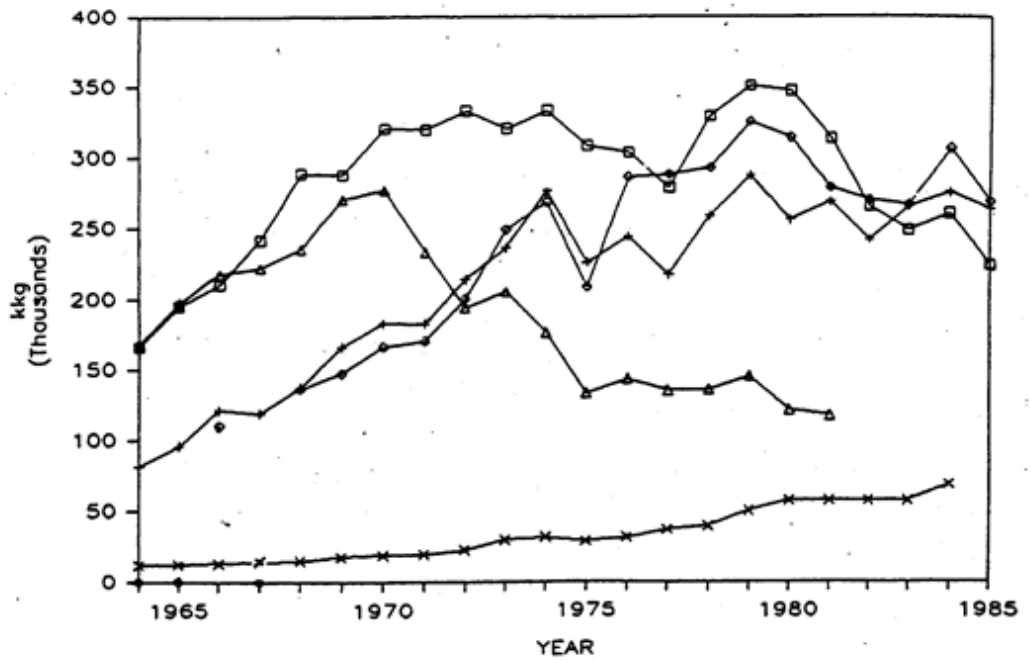
- In 1968, Los Angeles County adopted Rule 66 which limited emissions of trichloroethylene.
- By 1972, several other states enacted legislation similar to L.A. County's Rule 66. The original US Clean Air Act (1970) which regulated emissions of chlorinated solvents like trichloroethylene led to the chemical's replacement with 1,1,1-trichloroethane by many users (Shelley et al., 1993).
- In 1974 conversion from trichloroethylene to 1,1,1-trichloroethane proceeded rapidly in solvent and degreasing applications to comply with air pollution standards.
- By 1975, industry agreed that trichloroethylene was photoreactive and Federal and local governments severely restricted the use and emission of trichloroethylene in vapour degreasing plants in many areas of the country to reduce air pollution.

- In 1977, the US Environmental Protection Agency's recommended policy on the control of volatile organic compounds was announced and trichloroethylene was listed as photochemically reactive.

Another event that contributed to the decline in demand was a "Memorandum of alert" issued on trichloroethylene by the US National Cancer Institute in April 1975. Preliminary findings in bioassays of the solvent indicated that it had carcinogenic effects in mice. The alert resulted in a push for replacement by "safer" solvents such as tetrachloroethylene (perchloroethylene) and 1,1,1-trichloroethane.

The findings of photoreactivity and potential carcinogenicity of trichloroethylene led to a decline in production. For example, in the USA the demand for trichloroethylene dropped from 244,939 tons (540 million pounds) in 1971 to only 68,038 tons (150 million pounds) in 1990. Refer to Figure 1.

Figure 1 - Annual chlorinated solvents production (Wolf & Chestnutt, 1987)



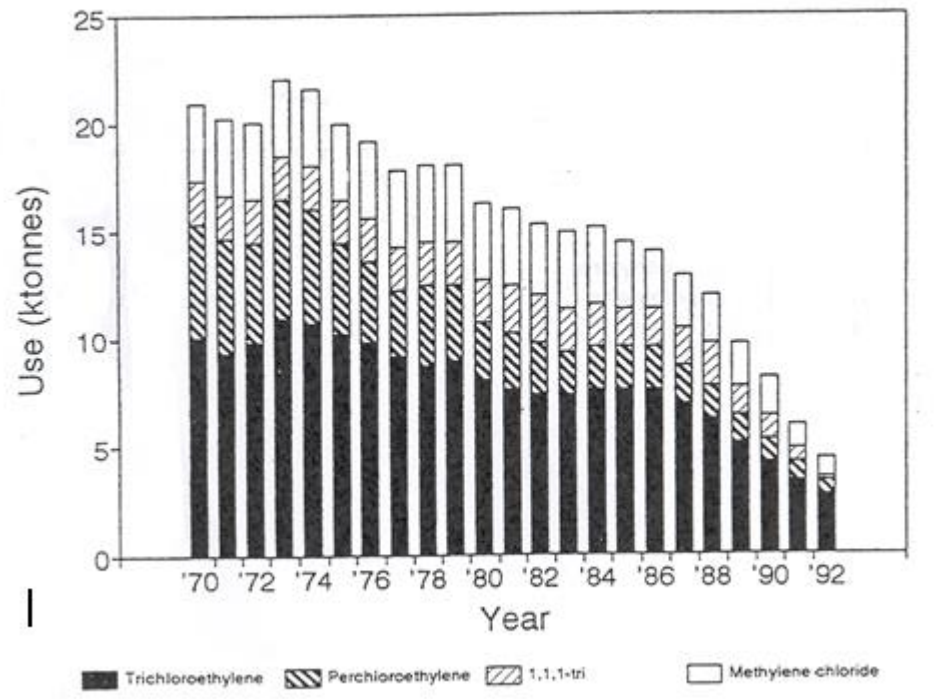
□ perchloroethylene
Δ trichloroethylene
X CF113
\+ methylene chloride
◊ methyl chloroform

2.2.2 European Union

The decline in use in the US has also been seen in other countries. For example, in the European Union (EU) the use of trichloroethylene has declined by over 50% since the mid-1970s (United Kingdom, 1996). The EU has rules limiting discharges to watercourses. Germany has introduced rules on the use of chlorinated solvents for degreasing, dry cleaning and extraction, designed to achieve substantial reductions in emissions. There are also regulations in Austria and Switzerland banning certain solvent applications.

More recently, in 1991 Sweden issued an Ordinance which banned the sale, transfer or use of chemical products containing trichloroethylene, methylene chloride, or tetrachloroethylene. The bans came into force with respect to consumer use on 1 January 1993 and with respect to professional use (with the exception of tetrachloroethylene which was not included in this ban) from 1 January 1996. The decision to ban was based on the hazards to health posed by these compounds and the fact that they were being used in very large quantities. Factors taken into account when banning trichloroethylene were the volatility of the chemical and the assessment that a limitation or control on trichloroethylene was not enough to ensure people were not exposed. The fact that trichloroethylene use was widespread among small companies, and that knowledge on how to protect people from exposure differed, were factors taken into consideration. In addition, it was considered that a ban would contribute to development of less harmful substances or techniques. The National Chemicals Inspectorate may issue regulations on exemptions and grant exemptions in individual cases, for instance, trichloroethylene may still be used for research and development and analysis purposes. (European Chemical News, 1995; KEMI, 1995; Cederberg, 1996).

Figure 2 - Use of chlorinated solvents in Sweden 1970-1992 (KEMI, 1995)



2.3 Australian perspective

Trichloroethylene was manufactured in Australia for approximately 30 years from the early 1950s to the early 1980s. At present, the Australian market demand for trichloroethylene is entirely met by imports of the chemical. Trichloroethylene is used widely in both large and small industries mainly as a degreasing agent.

It is likely that the use of trichloroethylene in Australia has followed the trend seen in the US and worldwide. Information suggests that several years ago many users changed from using trichloroethylene to 1,1,1-trichloroethane due to the potential carcinogenicity of trichloroethylene. Import data obtained from the ABS show an increase in trichloroethylene imports from 1994 to 1996. This could probably be attributed to the phase out of 1,1,1-trichloroethane and substitution with trichloroethylene. Table 1 shows amounts of trichloroethylene imported from 1988 to 1997.

Table 1 -Trichloroethylene imported into Australia

Year	Amounts (tonnes)
1988	3090
1989	2098
1990	1924
1991	2235
1992	2168
1993	1988
1994	2101
1995	2873
1996	3015
1997	2709

Australia has adopted the Montreal Protocol leading to the phasing out of 1,1,1-trichloroethane. It is therefore likely that trichloroethylene will replace the chemical for some of its uses, resulting in an increase in demand. This may be balanced by increasing trends to recycle trichloroethylene.

3. Applicants

Ajax Chemicals Ltd
9 Short St
Auburn NSW 2128

Albright & Wilson Specialities Pty Ltd
313 Middleborough Road
Box Hill VIC 3128

Beltreco Limited
382 Victoria Road
Malaga WA 6062

Beltreco Pacific Pty Ltd
93 Colebard Street West
Archerfield Qld 4108

Campbell Brothers Ltd
7-11 Burr Court
Laverton Nth VIC 3026

Consolidated Chemical Co.
52-62 Waterview Close
Hampton Park VIC 3176

Dow Chemical (Aust) Ltd
Kororoit Creek Road
Altona VIC 3018

Elf Atochem Australia Pty Ltd
893 Princes Highway
Springvale VIC 3171

Merck Pty Ltd
207 Colchester Road
Kilsyth VIC 3137

Orica Australia Pty Ltd
1 Nicholson St
Melbourne VIC 3000

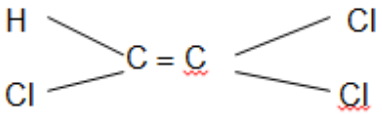
Rema Tip Top Australia Pty Ltd
11/350 Edgar Street
Bankstown NSW 2200

Solvents Australia Pty Ltd
77 Bassett Street
Mona Vale NSW 2103

Specialty Trading Pty Ltd
2 Lanyon Street
Dandenong VIC 3175

4. Chemical Identity

Table 2 - Chemical identity of trichloroethylene

Chemical Name:	Trichloroethylene
Synonyms:	1,1,2-Trichloroethylene 1,1-Dichloro-2-chloroethylene Ethylene trichloride Acetylene trichloride Ethinyl trichloride Trichloroethene
Trade Names:	Altene D6 Altene D1 NEU-TRI* Solvent Specialene Trineu
Molecular Formula:	C_2HCl_3
Structural Formula:	
Chemical Abstracts Service (CAS) Number:	79-01-6
EINECS Number:	2011674

*Trademark of The Dow Chemical Company

5. Physical and Chemical Properties

5.1 Physico-chemical properties

Physico-chemical properties of trichloroethylene are shown in table 3.

Table 3 - Physico-chemical properties of trichloroethylene

Property	Value	Reference
Physical state	clear, colourless or blue mobile liquid	HSDB,1998
Odour	ethereal, chloroform-like	HSDB,1998
Odour threshold	100 ppm	ATSDR, 1993
Molecular weight	131.40	HSDB,1998
Boiling point	86.7°C	ATSDR,1993
Melting point	-86.5°C	UK SIAR,1996
Surface tension	0.0293 N/m	HSDB,1998
Density at 20°C	1.465 g/ml	HSDB,1994
Vapour density	4.53	HSDB,1994
Vapour pressure at 20°C	7.7 kPa	HSDB,1994
Water solubility at 20°C	1.07 g/L	ATSDR,1993
Flash point	None	ATSDR,1993
Autoignition temperature	410°C	UK SIAR, 1996
Flammability limits at 25°C	8.0-10.5% in air	ATSDR,1993
Decomposition temperature	> 125°C	NIOSH,1973
Partition coefficients		
Log K_{ow}	2.42	ATSDR,1993
Log K_{oc}	2.03-2.66	ATSDR,1993
Conversion factors		ATSDR,1993
Air at 20°C	1 mg/m^3 = 0.18 ppm	
	1 ppm = 5.46 mg/m^3	
Water	1 ppm (w/v) = 1 mg/L	
	1 ml/m^3 = 1.465 mg/L	

5.2 Decomposition products

Trichloroethylene decomposes under a number of environmental conditions, including:

- in the presence of oxygen and ultraviolet light it undergoes auto-oxidation with the formation of acidic products such as hydrogen chloride;
- at high temperatures it decomposes to form phosgene and hydrogen chloride; and

- in the presence of moisture, dichloroacetic acid and hydrochloric acid are formed. These products are highly corrosive and react with many metals.

Other decomposition products formed are carbon monoxide, trichloroethylene ozonides and trichloroethylene epoxide.

5.3 Reactivity

In contact with finely divided or hot metals, such as magnesium and aluminium at very high temperatures (300-600°C) it decomposes readily to form phosgene and hydrogen chloride. Such conditions are seen in the vicinity of arc welding and degreasing operations. Aluminium is more reactive than magnesium.

In the presence of strong alkalis such as sodium hydroxide, dichloroacetylene, which is explosive and flammable, is formed.

5.4 Additives and impurities

Trichloroethylene undergoes auto-oxidation in air at higher temperatures and on exposure to ultraviolet radiation. To prevent this, stabilisers and inhibitors are added to the commercial grades. Epichlorohydrin was one of the stabilisers used in the past but its use has been discontinued as it was found to be carcinogenic. Mixed amines are now used as stabilisers. Mixed amines and butylene oxide act as acid acceptors when solvent degradation leads to formation of hydrogen chloride.

Trichloroethylene is available in a variety of commercial grades that are made up of approximately 99% trichloroethylene with impurities and stabilisers forming the remainder.

Additives may include the following:

Butanone

1,2-Butylene oxide

Diisopropylamine

Ethyl acetate

Epoxybutane

Glycidyl ether

Isopropyl acetate

1-Methylpyrrole

2-Methyl-3-butin-2-ol

Thymol

Triethylamine

Trimethyloxirane

2,2,4-trimethylpentene

2,4-di-tertbutylphenol

6. Methods of Detection and Analysis

6.1 Atmospheric monitoring

The most common analytical techniques for trichloroethylene in air are gas chromatography (GC) combined with either flame ionisation detection (FID), electron capture detection (ECD) or Hall's electrolytic conductivity detection (HECD). Gas chromatography with mass spectrometry (MS) is used for identification of the chemical.

Air samples are collected by adsorption on to activated charcoal or Tenax-GC. Trichloroethylene may be extracted either thermally or with a solvent such as carbon disulfide.

In the standard NIOSH method, trichloroethylene is collected by adsorption on activated charcoal. It is then extracted with carbon disulfide and an aliquot is analysed by GC/FID. The estimated limit of detection for this method is 0.01 mg per sample (National Institute for Occupational Safety and Health (NIOSH), 1994).

Table 4 gives details of commonly used analytical methods.

6.2 Biological monitoring

Several methods are available for measuring and testing for trichloroethylene in biological media. Samples may be analysed for the presence of trichloroethylene or its metabolites, trichloroethanol and trichloroacetic acid. Trichloroethylene may be estimated in exhaled air or blood while its metabolites are estimated in blood or urine. The main analytical method used is gas chromatography combined with electron capture detection (ECD).

The headspace gas chromatographic method allows simultaneous measurements of trichloroethylene, trichloroacetic acid and trichloroethanol. In headspace analysis, the gaseous layer above the sample is injected in to a gas chromatograph either directly or following preconcentration prior to injection on to the GC column.

6.2.1 Estimation of trichloroethylene

Reference	NIOSH, 1987	Makide et al, 1979	Krost et al, 1982	Rasmussen et al, 1977	Wallace et al, 1986

Several methods have been described for analysis of trichloroethylene in expired air. Methods used include preconcentration on Tenax-GC cartridges followed by thermal desorption either directly onto the gas chromatograph column for separation and detection or to a cryogenic trap connected to the gas chromatograph.

Results of studies in human volunteers indicate that the concentration of trichloroethylene in expired alveolar air collected during exposure is an indication of current atmospheric concentration, while estimation 16 h after the end of exposure reflects the average airborne exposure during the preceding day (Kimmerle & Eben, 1973; Stewart et al., 1974a; Fernandez et al., 1975; Monster et al., 1979). Measurements of trichloroacetic acid and trichloroethanol are non-specific indicators of exposure to trichloroethylene as they can be metabolites of other chlorine containing hydrocarbons.

American Conference of Governmental Industrial Hygienists (ACGIH) has recommended monitoring of trichloroethylene in end-exhaled air as a confirmatory test when the origin of trichloroacetic acid and trichloroethanol is doubtful.

Blood analyses

The most common method used to analyse trichloroethylene in blood is headspace analysis, followed by GC or GC/MS. Sensitivity is in the low-ppb range (2-20 ppb) (ATSDR, 1993).

6.2.2 Estimation of trichloroacetic acid and trichloroethanol

Urine analyses

Trichloroacetic acid in urine is an indicator of exposure by all routes. Measurements at the end of the shift and at the end of the work week are considered appropriate to measure recent exposure and cumulative effect, respectively. Trichloroethylene is converted to trichloroacetic acid and samples taken at the end of the shift reflect recent exposure. However, trichloroacetic acid is tightly and extensively bound to plasma proteins and has a half-life in blood of 70-100 h. Repeated exposure causes trichloroacetic acid to accumulate in blood with the metabolite being excreted very slowly. Trichloroacetic acid levels are not influenced by timing of exposure and sampling as very little fluctuation in concentration occurs because of the long elimination half-life.

ACGIH recommends a biological exposure index (BEI) of 10 mg/g of creatinine. This provides the same degree of protection as a TLV of 50 ppm. There is a linear correlation between trichloroethylene levels in breathing zone air and urinary levels of the metabolites, total trichloro-compounds, trichloroethanol and trichloroacetic acid in men and women (Inoue et al., 1989). Measurements of trichloroacetic acid in urine may be much higher than indicated by atmospheric monitoring if dermal exposure to liquid trichloroethylene occurs.

There are significant racial and ethnic differences in the production of trichloroacetic acid. Deficiency of alcohol dehydrogenase and aldehyde dehydrogenase is more common in non-Caucasians and can lead to an underestimation of exposure and an increase in risk to workers. Alcohol intake and disulfiram treatment also, partly inhibit production of trichloroacetic acid.

Total trichloro-compounds (TTC) index in urine reflects the sum of trichloroacetic acid (TCA) and free and conjugated trichloroethanol expressed as trichloroacetic acid. Sampling time is critical for this index because of the short elimination half-life of trichloroethanol. ACGIH recommends collection at the end of the shift after 4 consecutive days of exposure. A TTC concentration of 300 mg/g of creatinine in urine provides the same degree of protection as inhalation exposure at the ACGIH TLV of 50 ppm.

Blood analyses

Free trichloroethanol (TCOH) in blood index is an indicator of recent exposure (day of sampling). The sampling time is critical and a method without the hydrolysis of TCOH conjugates must be used as the BEI is for the free form. Hydrolysis would result in conversion of some conjugated trichloroethanol to the free form giving false results. The timing is critical as trichloroethanol in blood rises rapidly during exposure and starts declining shortly after exposure. A BEI of 4 mg/L (27 μmol/L of SI units) of free TCOH is recommended by ACGIH for specimens collected at the end of the shift after at least 2 consecutive days exposure. Alcohol intake may result in lower trichloroethanol levels and lead to an underestimation of exposure. The test is nonspecific as trichloroethanol is a metabolite of other chlorine containing ethanes and ethylenes.

7. Use, Manufacture and Importation

7.1 Manufacture and importation

Trichloroethylene is not manufactured in Australia. Approximately 3000 tonnes of trichloroethylene are imported annually into Australia from France, USA and UK. It is imported in drums and in bulk. Trichloroethylene is also imported as an ingredient in formulated products. From information provided by applicants, it is estimated that approximately 125 tonnes of trichloroethylene is imported in formulated products annually, in a total of 20 products.

Trichloroethylene is recycled in Australia. Recycling occurs by either distillation at the work site or off-site recycling companies. More than 185 tonnes of trichloroethylene is recycled and reused each year.

Data supplied by the Australian Bureau of Statistics indicates a trend towards increasing amounts being imported commencing from 1995 (see Section 2).

7.2 Uses

No published data on the uses of trichloroethylene in Australia were available. Therefore a survey of the industry was conducted in order to identify the uses (the NICNAS industry survey). A total of 310 questionnaires were mailed to companies and organisations selected from customer lists provided by applicants. Users of trichloroethylene were selected on the basis of the industry involved to ensure representation of a wide range of industries using trichloroethylene. The same questionnaire was also sent to applicants and recyclers. The questionnaire comprised of separate sections for formulators, resellers and end users of trichloroethylene and trichloroethylene products (Appendix 3) and also sought information on Material Safety Data Sheets (MSDS) and labels. One hundred and fifteen responses were received, representing a response rate of 37%. The total number of customers identified by applicants was 457, therefore the response represents approximately 25% of the total number of organisations that buy trichloroethylene directly from importers. The information below is based on data gathered from this survey. The data is considered representative but not complete.

7.2.1 Trichloroethylene

The major use for trichloroethylene in Australia is metal cleaning. Metal cleaning occurs during the manufacture, maintenance and repair of articles in a wide range of industries. Trichloroethylene is an effective cleaning agent for many organic materials as it has a low latent heat of vaporisation and is nonflammable.

Industries using trichloroethylene

The NICNAS industry survey identified the following industries using trichloroethylene:

- Metal forming/Machining (50%)
- Powdercoating (10%)
- Automotive (10%)
- Aerospace (6%)
- Electrical (6%)
- Chemical Processing (2%)
- Rubber products manufacture (2%)
- Telecommunications (1%)
- Paint (1%)
- Oil refining (1%)
- Gas production and manufacture (1%)
- Locomotive (1%)
- Lubricants manufacture (1%)
- Manufacture (unspecified) (4%)
- Other (4%)

In the final stages of the assessment NICNAS was advised that trichloroethylene is also used in the Textile Clothing and Footwear Industry as a cleaning agent.

Small amounts of trichloroethylene are also used in the asphalt industry to dissolve bitumen in the laboratory analysis of aggregate in asphalt.

Vapour degreasing

Vapour degreasing was the most common use of trichloroethylene among respondents to the NICNAS survey. Seventy seven percent of respondents (89/115) were end users of trichloroethylene, and of these, 75 percent (67/89) used trichloroethylene for vapour degreasing. Overseas studies have also reported that vapour degreasing is the most common use of trichloroethylene (IPCS, 1985; United Kingdom, 1996).

Vapour degreasing is a process used in many industries to clean metal components. Most commonly it is used to remove oil, grease, and/or metallic swarf from metal components prior to surface coating, assembly or repair operations, machining, inspection, or end use of the component. Vapour degreasing is also used to remove polishing compounds, paints, metallic oxides, and mineral soils.

Vapour degreasing involves the heating of a quantity of solvent in a tank to boiling point. Condensing coils located on the inside perimeter of the tank control the height to which the solvent vapours rise, creating a ‘vapour zone’ into which metal components to be degreased are lowered. Vapour condenses on the cold components, dissolving surface oils and greases. The contaminated condensate drains into the boiling liquid below. This cleaning action continues

until the temperature of the components being degreased reaches the temperature of the vapour, at which point condensation ceases. The components are then lifted above the vapour zone and held in a freeboard area for cooling and evaporation of any remaining solvent, and then removed from the degreaser at a controlled rate to avoid lifting vapour out of the degreaser. Vapour degreasers can incorporate spraying and/or immersion in boiling solvent as part of the cleaning process.

Trichloroethylene is one of several solvents that can be used for vapour degreasing. Other solvents used include tetrachloroethylene, methylene chloride, and 1,1,2-trichloro-1,2,2-trifluoroethane. The manufacture of 1,1,1-trichloroethane, another solvent commonly used in vapour degreasing, ceased in January 1996 in accordance with the Montreal Protocol, and importation of existing stocks is strictly regulated under the Ozone Protection Act 1989. It is possible that the use of trichloroethylene in vapour degreasing may increase due to the phase out of 1,1,1-trichloroethane.

Cold cleaning

Cold cleaning refers to the process of cleaning by dipping or soaking articles in a cleaning liquid, or spraying, brushing, or wiping the cleaner onto articles at temperatures below boiling point. Twenty nine percent of end users (26/89) of trichloroethylene responding to the NICNAS industry survey reported using trichloroethylene in cold cleaning processes. This proportion of use of trichloroethylene in cold cleaning activities is higher than that reported in overseas studies.

Cold cleaning activities mentioned in the NICNAS survey included immersion in tanks, drums, or other containers, ultrasonic cleaning, and spraying, brushing and wiping. In ultrasonic cleaning, a transducer mounted on the bottom or side of a tank containing solvent creates vibrations which cause the rapid expansion and contraction of microscopic bubbles in the solvent, resulting in a scrubbing action on parts that are immersed in the tank. Ultrasonic agitation can be employed in hot or cold immersion cleaning, and is sometimes incorporated into vapour degreasing systems.

7.2.2 Products containing trichloroethylene

Several categories of products containing trichloroethylene have been identified as being in use in Australia from information supplied by applicants and from the NICNAS survey. They are:

- adhesives
- electrical equipment cleaning solvents
- metal degreasing solvents
- waterproofing agents
- paint strippers
- carpet shampoos
- tyre cleaning product

Details on the number of products identified in each product category, the range of concentrations of trichloroethylene within each category, and the total estimated amount of trichloroethylene used in the products are summarised in Table 5.

It is expected that there are more products containing trichloroethylene formulated in Australia which have not been identified. Regarding imported products, it is not possible to identify products containing trichloroethylene from customs data, and so it is possible that more products containing trichloroethylene are being imported.

Table 5 - Trichloroethylene products identified by applicants and notified by respondents to a NICNAS industry survey

Product Type	Number of products	Percentage TCE (range)	Approx. amount TCE used annually (tonnes)
Adhesives – imported	18	20 - >90	105
Adhesives - formulated in Australia	3	10 - 88	6.5
Electrical equipment cleaning solvents	8	13 - >60	93
Metal degreasing solvents	7	<10 - 65	53
Waterproofing agents –imported	1	90	0.2
Waterproofing agents - formulated in Australia	3	60 - 70	5.4
Paint strippers	3	0.05 - 8	1.5
Carpet shampoos	2	3	0.2
Tyre cleaning product - imported	1	>90	18
TOTAL	46	0.05 - >90	282.9

Adhesives

Solvents are used in adhesives to lower the viscosity and increase the wetting of the adherent/substrate. Many industrial adhesives comprise polymer blends, organic compounds and mineral fillers dissolved in solvent (such as trichloroethylene). They are used in bonding natural and synthetic rubber to metal and other rigid substrates, plastics, and fabrics. Other adhesives bond plastics, rubber and fabric, and bond polyurethane coatings to metal or to natural or synthetic rubber. Some are two-part adhesive systems, which are mixed just prior to use. Further dilution of the mixtures with solvents including trichloroethylene may also occur prior to application. Trichloroethylene is often used where a solvent of low flammability with the desired drying time is required.

The majority of the imported adhesives containing trichloroethylene are used for rubber repair and rubber lining in the mining and automotive industries. Uses include the hot or cold vulcanisation of patches to tyres, and sealing tyre inner linings after buffing; and the lining of tanks with rubber and repair of rubber

belting. Two products, used in cold vulcanisation repair of tyres, are available to the public. Approximately 5 tonnes of trichloroethylene per year are used in these two products in total.

7.3 Other information on uses

Trichloroethylene is used overseas as a precursor in the manufacture of CFC alternatives such as HFC-134a or HCFC-123. However, trichloroethylene is not used as a feed stock for other chemicals in Australia.

In the past, trichloroethylene has been used in Australia as an anaesthetic agent, in dry cleaning, in correction fluids and as a solvent in pesticide formulations. These uses apparently no longer occur.

It has come to the attention of NICNAS that trichloroethylene is being considered for use in scouring wool.

8. Occupational Exposure

8.1 Routes of exposure

Occupational exposure to trichloroethylene may occur during transport, storage, formulation or use of the chemical, during the solvent re-cycling process or during disposal (ie of contaminated solvent). Workers may be exposed to trichloroethylene by the inhalation and dermal routes.

Trichloroethylene is a volatile liquid at room temperature. Inhalation of trichloroethylene may occur through exposure to vapour emitted by liquid or mixtures containing trichloroethylene, or by exposure to aerosols. Activities such as heating or agitation of the liquid will increase the emission of vapours and the likelihood of exposure.

Dermal absorption of trichloroethylene may occur through contact with the liquid form. Contact with vapour condensate, or with aerosols from sprayed products or mixtures containing trichloroethylene, are also potential sources of dermal exposure.

8.2 Methodology for estimating exposure

Good quality measured data for various work scenarios is preferable in the assessment of occupational exposure. If monitoring data is limited, then modelling can be used with standard formulae to estimate exposure. In the assessment of trichloroethylene measured data was limited and standard formulae were used to estimate exposure.

The exposure estimates in this assessment are considered to be "feasible" worst case estimates, as they describe high-end or maximum exposures in feasible, not unrealistic situations. The estimates are not intended to be representative of extreme or unusual use scenarios which are unlikely to occur in the workplace. However, it is likely that the majority of occupational exposures will be below these estimates.

The formulae used to calculate exposures are detailed in Appendix 1. The constants in the formulae such as body weight and inhalation rate were those used in international assessments.

Estimates for exposure to vapour did not include dermal uptake of vapour as dermal absorption of vapour is considered to be negligible (see section 9).

8.3 Importation and repacking

8.3.1 Importation of trichloroethylene

Drums

Trichloroethylene is imported in 205 L sealed steel drums and is generally transported to distributors or direct to end-users without being opened. Exposure

during transportation and storage of drums is unlikely except in case of accidents such as leakage from damaged drums.

Bulk storage facilities

Trichloroethylene is also imported in bulk containers to Port Botany in NSW and to Coode Island in Victoria. Bulk trichloroethylene is pumped by shoreline from tanks on board ships to on-shore bulk tanks. From here it is transferred to road tankers and drums (205L) and transported to a warehouse site, where it is stored prior to distribution. Occasionally trichloroethylene is transported directly to the end-user from the bulk storage facility.

Worker activities include connection and disconnection of shore and wharf lines, and a process called 'pigging' in which a polyurethane foam sponge is placed at one end of a line and propelled by nitrogen through the line (for up to one kilometre) in order to clean and dry it. The sponge is collected from the other end of the line by an operator who places it in a bucket of water. Other activities include filling of road tankers and drums, cleaning of bulk storage tanks, and maintenance work on pumps and piping.

A continuously operating automatic carbon absorption vapour extraction system draws air from around hose connections at tanker and drum filling stations, and openings on bulk storage tanks, through piping to a central carbon bed adsorption unit. The air is drawn through the carbon and out an emission stack. The carbon is regularly desorbed of trapped chemical by high pressure steam. Vapour condensate is collected and disposed of through waste collection agencies.

Filling of tankers is controlled by a mass flow meter. Tanker filling station areas have an underground collection area in case of accidental spillage. Drums are filled using a specially designed device that uses a mass flow meter to pre-set the volume. This system involves a moveable filling handle that minimises manual handling of drums. More traditional filling stations employing scales are also used for drum filling. Drums are double capped. Drum filling station areas are bunded. Cloth gloves are supplied for use during filling.

A full face organic canister mask or breathing apparatus is worn in situations where it is believed a potential for high exposure exists, such as during 'pigging' and dipping bulk storage tanks to measure levels. Special work permits issued by management are required before cleaning of bulk storage tanks, and confined space work procedures are followed.

A total of 39 workers are employed at the two sites. Filling and monitoring of bulk tanks typically engages workers for 4-5 hours, 4-6 times a year. Similarly, filling of drums occurs for about 4 hours, 6 times a year. Filling of road tankers is typically undertaken 150 times a year, with filling taking approximately 10-20 minutes.

Due to enclosure of the transfer process and other control measures in place, the potential for inhalation exposure is considered low. The potential for dermal exposure during tanker and drum filling is low due to the use of mass flow meters. Handling of shorelines and the sponges used for cleaning them may pose a potential for dermal exposure through splashes.

In the exceptional circumstance of imported trichloroethylene being contaminated, it is sent to a recycling plant. Information provided suggests this happens rarely.

8.3.2 Repacking

One importer of trichloroethylene and some distributors repack trichloroethylene from drums into smaller containers prior to distribution to end-users. The importer stated that decanting is conducted using a filling hose and controls in place include air extraction systems in the packing area, and the wearing of personal protective equipment. Ten workers are employed on both repacking and formulation tasks for 1 to 4 hours a day, 25 days a year.

The repacking process presents a potential for both inhalational and dermal exposure through vapour emitted during the transfer process and accidental spills and splashes. The extent of exposure will depend on factors such as the method of transfer, amount of time spent on the task, and type of controls in place.

Little information was available to determine whether distributors also repack and if they do, the methods used for repacking. Limited data indicates that repacking generally involves one to two workers, on an intermittent basis.

8.3.3 Importation of products

Products are onsold by importers, and information provided indicates products are not repacked in Australia. Exposure during importation would be expected only in the case of accidental spills/leaks of product.

8.3.4 Monitoring data for bulk storage, transfer and repacking

Atmospheric monitoring results from the Port Botany (3 samples during ship to shore transfer) and Coode Island (60 samples during various activities) bulk storage sites were made available. The results are shown in Table 6. Both area and personal breathing zone sampling were conducted using passive dosimeters over full shift periods. All exposure levels were below 1 ppm with the exception of one sample taken during 'pigging' and connection and disconnection of wharf lines (3.2 ppm) and 3 samples taken during drum filling (2.0 - 2.4 ppm)

No monitoring data were available for worksites engaged in repacking trichloroethylene or handling trichloroethylene products.

Table 6 - Atmospheric monitoring results (TWA) at bulk storage facilities

Activity	Area/Tasks	Type of Monitoring	No. of Samples	Duration of sampling (hours)	TCE (ppm)
Ship to shore transfer	Site boundary	A	15	7.5	0.01 - 0.28
	Top of tank	A	3	9 - 11.5	0.01 - 0.05
	Exchanger pit	A	2	9	0.06 - 0.06
	Pigging & connection lines	P	2	8 - 12	0.8 - 3.2
	Transfer	P	3	10	0.05 - 0.07
	General duties	P	4	8.5 - 10	0.05 - 0.42
Truck Loading	Loading gantry	A	8	7.5 - 8.5	0.01 - 0.26
	"	P	12	"	0.01 - 0.08
	Site boundary	A	4	8	0.01 - 0.01
	Office duties	P	2	8.5	0.06, 0.06
Drum filling	Drum fill building	P	2	7.5 - 11	2.0, 2.4
	"	A	1	"	2.2
General	Site boundary	A	4	7.5	0.27 - 0.31
operations	General duties	P	1	7.5	0.05

TCE = trichloroethylene
A = area monitoring
P = personal monitoring

8.3.5 Summary of exposure during importation and repacking

The potential for exposure to trichloroethylene during importation is likely to be low as transfer and storage of bulk trichloroethylene is an enclosed process, the process occurs intermittently and precautions have been taken to minimise exposure. The atmospheric monitoring data provided indicate low exposure via inhalation with all except four readings being <1 ppm. The maximum TWA reading obtained was 3.2 ppm during pigging and connection and disconnection of wharf lines. Dermal exposure is expected to be minimal if care is taken to avoid splashes during "pigging".

Very little information was provided on repacking. No monitoring appears to have been carried out. However, the limited data indicates that repacking is an infrequent process. Exposure during handling of trichloroethylene products is expected to be very low.

8.4 Formulation

Processes commonly operating in the formulation of products containing trichloroethylene include transferring ingredients to mixing vessels from drums or from bulk storage tanks, cold blending the ingredients in mixing vessels, and filling containers from mixing vessels. Formulation of aerosol products may include production processes such as automated filling of cans with line operators packing cans from the assembly line.

Twenty seven individual products containing trichloroethylene and formulated in Australia by 11 companies, were identified by the NICNAS survey. Information on formulation, including engineering controls and personal protective equipment were provided by nine of the companies. Two formulators use closed pipelines to transfer trichloroethylene from a bulk storage tank to mixing vessels, with metered pumps to control flow rate. One formulator uses a gravity feed hose and a drum trolley to decant trichloroethylene from a drum into 20 L containers containing the other ingredients of the mixture. Closed mixing vessels are used by four formulators while five use open mixing vessels. Two of the formulated products are aerosols.

Approximately 30 workers are involved in formulation of these products. Typically, 1 to 4 process workers are employed on the task for short periods, several times a year. There is a wide variation in the time spent in formulating products ranging from 1-8 hours a day for 4-60 days per year.

Four of the worksites have no mechanical ventilation controls, four have some type of air extraction system in place, one uses a fan. Use of personal protective equipment varies, with all workplaces using gloves and most using safety glasses and overalls. Where specified, gloves are described as impervious, chemical or solvent resistant, or nitrile. A twin cartridge mask is used in one workplace.

Empty drums at the nine sites for which information was provided were disposed of through sale to drum recyclers.

Formulation of trichloroethylene products is conducted at room temperature and is a batch process. There is the potential for inhalation exposure to vapour and incidental dermal exposure through splashes etc. Exposure may occur during transfer to the mixing tank, the mixing process and filling of containers with the product.

The potential exposure of workers to trichloroethylene during formulation is likely to vary as the control measures used by the formulators are variable. When trichloroethylene is added to the mixing tanks through closed pipelines with metered pumps to control flow rate the exposure is likely to be low. However, exposure is likely to be high at worksites having an open mixing process with no mechanical ventilation controls.

There is also the potential for worker exposure during the filling procedure. The frequency and duration of exposure is likely to be greater during the filling procedure when the mixed product is transferred to containers. The NICNAS survey contained an open-ended question asking for a description of the formulation process, however, no information was provided on the filling process. One site visit was made to a formulator of an electrical equipment solvent. After blending, the mixture was decanted into drums and 20 L cans. For filling the cans, an operator stood at a filling and weighing station, with the can on a weigh bench at waist level. A lever was pulled and the mixture flowed from a tap connected to the mixing vessel into the can, from a distance of about 7.5 cms. When the can was full, the lever was lifted, and the can turned around for capping. It was observed that the tap leaked slightly. The worker wore eye goggles. No gloves or other protective clothing was worn.

8.4.1 Atmospheric monitoring and health surveillance

Responses to the NICNAS survey indicated that air monitoring had been conducted at only one of the nine worksites. The results were not provided. Health surveillance in the form of annual liver function tests was performed at one of the worksites, however these results were also not provided.

8.4.2 Summary of exposure during formulation

As no monitoring data from Australian formulators of trichloroethylene products were available, standard formulae were used to estimate exposure (Appendix 1). Inhalation exposure was estimated for three atmospheric levels of trichloroethylene 10, 30 and 50 ppm (the same levels used for vapour degreasing). Duration of exposure was for 4 h a day, 30 days per year.

No dermal exposure data for trichloroethylene were available, hence estimates for exposure to liquid were calculated according to the formula described in Appendix 1. Concentration ranges for the various formulated products were <10%, 10-80%, 10->60%, 60-70%, and 60->90%. The concentration selected for dermal exposure estimate was 90%.

Inhalation exposure was considered to be continuous and dermal exposure incidental (ie 1% of the total time). Estimates for total body burden (mg/kg/day) from inhalation and dermal exposure are provided in Table 7.

Table 7 - Total body burden from inhalation and dermal exposure

	Exposure estimate (mg/kg/day)
Inhalation	
10 ppm (54.6 mg/m^3)	0.26
30 ppm (163.8 mg/m3)	0.76
50 ppm (273 mg/m3)	1.26
Dermal	
90%	0.013

8.5 Vapour degreasing

8.5.1 Numbers of workers potentially exposed

From the survey it is known that there are at least 75 vapour degreaser units involving over 1,000 people in operation in Australia (this figure includes 500 employees of an aerospace company, estimated to be exposed on an intermittent basis). Due to the relatively low response to the survey (37%), it is likely that the number of vapour degreasers in operation and the number of people operating vapour degreasers are much higher.

8.5.2 Potential frequency and duration of exposure

The survey indicated that the majority of workplaces have one vapour degreaser, and employ 1-3 workers on vapour degreasing tasks. Adequate information on the duration and frequency of work on vapour degreasing tasks was provided by 61/67 respondents. Details were provided for a total of 766 workers. Table 8

shows the number of workers involved in vapour degreasing and the duration of exposure. The 500 aerospace workers, employed on vapour degreasing tasks on an "occasional, intermittent" basis, are included in the lowest potential exposure category.

Table 8 - Distribution of potential exposure

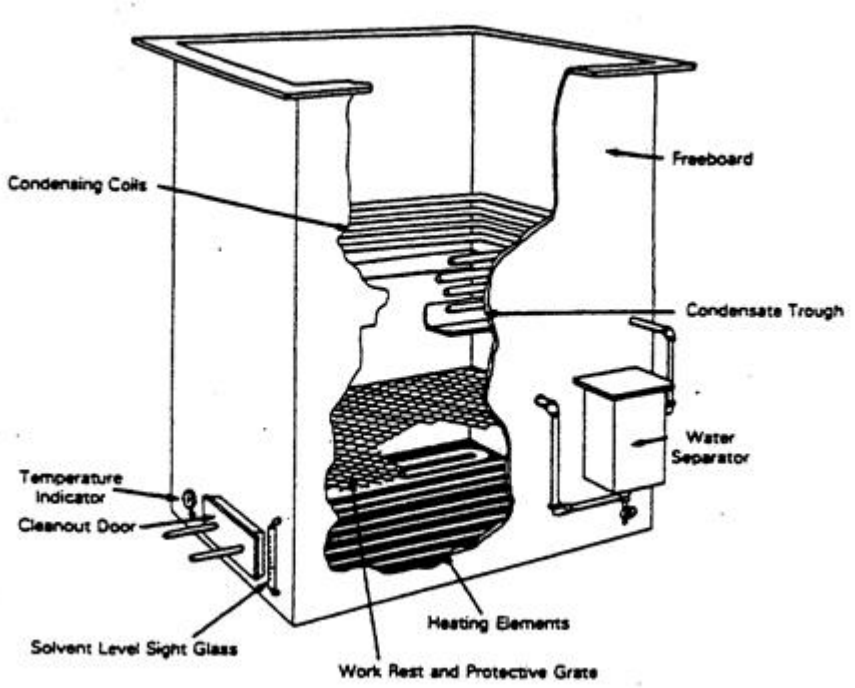
Days per year	Hours per day			
	0.25-2	**>2-4**	**>4-8**	**>8-12**
1-20	509	3	7	
21-50	9		3	
51-100	3	8	1.5	
101-150	15	6	2	
151-200	3	5	2	
201-250	43	8	38	1
>250	35	7.5	51	6

The survey indicates that the most common scenario is working for between 15 minutes to 2 hours, for up to 20 days a year. If the aerospace company employees are excluded, the most common scenario is working > 4-8 hours a day, for more than 200 days a year (33%). The next most common scenario is working for up to 2 hours a day for more than 200 days a year (29%). A small proportion of workers (2%) worked extended shifts for more than 250 days a year.

8.5.3 Types of vapour degreasers

Australian Standard AS 2661 - Vapour Degreasing Plant - Design, Installation and Operation - Safety Requirements (Standards Association of Australia, 1983) describes the requirements for safe design and operation of vapour degreasers. Information from the NICNAS industry survey and site visits (7) carried out in 1995-96 indicated that the types of vapour degreasers in operation in Australia range from small to medium sized manually operated open-topped degreasers to semi-automated plants with platform lifts that lower and raise work containers according to preset cleaning times, to large fully automated end loading degreasers with conveyor monorails that carry the work baskets through the tank. Some vapour degreasers incorporate liquid as well as vapour stages, with components being dipped into boiling solvent and/or sprayed with liquid solvent prior to rinsing and drying through vapour condensation. The length of time of cleaning cycles varies according to the type of degreaser and the articles being degreased, however an average cycle lasts around 30 minutes. Figure 3 illustrates the common features of an open-topped manual vapour degreaser.

Figure 3 - Open-topped manual vapour degreaser



Open-topped top loading degreasers loaded by hoist or manually were the most common type of degreaser described in the survey (49/67). Lids of various types (sliding or lift out/hinged) are sometimes fitted on open-topped top loading degreasers, however information indicated that use of lids appears to be infrequent, and they are sometimes put on only at night or when the degreaser is not in use.

The remainder of the vapour degreasers (18/67) were described as closed or partially closed systems. Some of these incorporated dipping and spraying cycles. One was a 15 station conveyor system with five cycles: hot liquid dip, hot liquid spray, cold liquid, cold liquid spray, vapour rinsing. Three degreasers were operated inside sealed 'clean rooms'. Two very large installations using 11,000 and 12,000L of solvent respectively were also identified.

The survey indicated that addition of trichloroethylene to degreasers is mainly from drums. Only a few respondents (4/67) mentioned addition of trichloroethylene through closed pipelines from bulk storage tanks.

8.5.4 Cleaning and maintenance of vapour degreasers

Vapour degreasers require periodic cleaning to remove sludge and contaminated solvent from the sump area. The frequency of cleaning will vary according to factors such as the volume of work being processed and the nature and amount of contaminants. The boiling point of trichloroethylene rises as it becomes contaminated and so temperature is commonly used to determine the degree of contamination and hence when to clean a degreaser. Another method used to

determine when to clean is the measurement of specific gravity, which falls as the temperature rises.

Information from industries in Australia on clean-out procedures indicated a wide variation in the frequency of cleaning ranging from once a year to twice a week. The cleaning process involves removal of the solvent via distillation or discharge from the sump, usually into drums. Doors usually situated at the bottom of the sump are opened and sludge raked out and transferred to drums. In one case an electric hoist was used to tilt a small degreasing tank to a 45 degree angle in order to allow raking out of the sludge. Raking out is usually done from outside the degreaser, however entry of workers into a degreasing tank sometimes occurs.

Some companies employ contractors to clean degreasing tanks. Information from one contracting company indicated that the usual method employed was to pump out solvent into drums; use high pressure water spray to clean the sides of the tank and scrape solidified material into drums. This company follows confined space procedures when entry into tanks is required. A team of at least 3 and usually 4 workers certified to work in confined spaces work together in cleaning the tanks.

8.5.5 Potential sources of exposure

Routine operation

Routine operation of a vapour degreaser will result in some emission of vapour and consequent potential for exposure. Two main sources of emissions are air/solvent vapour interface losses and workload related losses. Air solvent/vapour interface losses occur by diffusion of solvent vapour from the vapour zone into the air and convection due to heating of the freeboard. Workload losses occur through turbulence and consequent displacement of vapour into the air caused by work routines such as lowering/lifting of baskets, and through dragout of vapour or liquid solvent trapped in work pieces (Radian Corporation, 1990).

During shutdown of the degreaser, vapour can be emitted through evaporation of hot liquid solvent from the sump and its diffusion into the air. After cooling, vapour emissions may continue as a result of evaporation from the liquid surface. During start-up of the degreaser, solvent-laden air can be pushed out of the degreaser as a consequence of the heating of the sump area and creation of a vapour zone.

Filling or topping up the degreasing plant may result in exposure from vapour surges, for instance, as may occur if cold solvent is added to hot solvent or if the solvent is poured in instead of being pumped or fed through gravity feed hoses so that the solvent enters the tank below the existing liquid level in the sump.

Leaks from pipe connections or cracks are another potential source of exposure. Technical service personnel involved in installing, modifying or maintaining plant equipment may be exposed to trichloroethylene when performing these tasks.

Maintenance

During cleanout of degreasers there is high potential for exposure. Draining off solvent into drums, opening sludge doors and raking out sludge into containers and refilling the tank will expose workers to vapour and the possibility of accidental skin splashes. Draining off hot solvent may increase exposure to fumes and may lead to fire. A high potential for exposure is presented by entry into the tank for cleaning and strict procedures for working in confined spaces should be followed (see section 14).

The treatment of plant which has become acidic, as described in Appendix A in the Australian Standard AS 2661 - Vapour Degreasing Plant - Design, Installation and Operation - Safety (Standards Association of Australia, 1983), presents a potential for exposure similar to that involved with clean-out of degreasers.

8.5.6 Atmospheric monitoring

Australian data

WorkCover Authority of NSW

The WorkCover Authority of NSW provided air monitoring data for trichloroethylene from sampling conducted at twelve worksites between 1984 and 1995. The monitoring was carried out by WorkCover inspectors. Requests by the company was the reason for six of the visits, requests by unions were the reason for two visits, and the remainder of the visits were initiated by the WorkCover Authority. A total of 23 samples were taken at or around vapour degreasing tanks. Results ranged from 'not detectable' to 194 ppm. Nine of the 17 personal samples were above 50 ppm, with five over 100 ppm. Seven of the 11 worksites at which personal monitoring was conducted had at least one personal monitoring result above 50 ppm. The duration of monitoring was not specified for 11 samples while the monitoring duration was 4 h or more for the rest of the samples. One of the 6 area samples was greater than 50 ppm. No data was provided on the work practices at the workplaces. The distribution of results in concentration ranges are shown in Table 9.

Table 9 - Results of air sampling of vapour degreasers by WorkCover Authority of NSW: 1984-1995

Concentration ranges (ppm)	Number of samples	
	Personal samples (17)	Area samples (6)
0 - 25	6	4
>25 - 50	2	1
>50 - 100	4	
>100 - 200	5	1

NICNAS survey results

Very little monitoring data for Australian workplaces was provided considering the scale of use of trichloroethylene. A total of 26 organisations out of the 115 respondents to the NICNAS industry survey indicated that air monitoring had been conducted at their workplaces. These 26 organisations were followed up with a further questionnaire aimed at gathering details of their monitoring data.

Thirty-seven samples from 9 worksites were provided. The majority of samples were area sampling around the vapour degreaser while in operation. Samples were taken between 1987 to 1995. All except one sample were below 50 ppm. One result was 145 ppm, taken at 15 cm above the top of a degreaser while the degreaser was at idle (boiling). The range of the other samples was 'not detectable' to 27 ppm. The air monitoring survey indicated that monitoring is generally conducted on an ad hoc basis, not as part of a routine monitoring program. Monitoring was generally conducted on specific occasions such as following modification to a degreaser, following complaints of fumes after installation of a new plant, or as a one-off reading to ensure that standards were being met.

Other monitoring data

Data from air monitoring for trichloroethylene conducted by the School of Public Health and Tropical Medicine of Sydney University at one worksite in 1977 was made available. Eighteen grab samples of up to 20 seconds were taken in the breathing zone of a vapour degreaser operator, around the vapour degreaser, and in a pit under the degreaser. Several high readings (125 ppm to >700 ppm) in the operators breathing zone were obtained when the operator was lowering and pulling up baskets manually, and a reading of >700 ppm was obtained when the operator was spraying objects with his head over the edge of the tank. Removing articles from the tank using a hoist after leaving them suspended to dry also gave high readings (400 ppm to >700 ppm). The lack of rim ventilation and placement of the degreaser in an area exposed to draughts were factors contributing to the high readings, according to the author of the study.

Overseas monitoring data

United Kingdom

Personal sampling at 37 locations was conducted by Shipman and Whim in England in the late 1970s. Of the 306 samples (8 h TWAs), 94% were less than 50 ppm and 96% were less than 100 ppm (Shipman & Whim, 1980). More recent monitoring by HSE inspectors conducted between 1984 and 1994, show that of 25 personal samples (8 h TWAs), 96% were <30 ppm and all were less than 50 ppm (United Kingdom, 1996).

In 1994 a survey of vapour degreasing operations was carried out by the UK Health and Safety Executive (Robinson, updated January 1996). Air sampling using Drager tubes was undertaken at 100 of 120 vapour degreasing plants using trichloroethylene. At most sites, samples were taken at four positions around the degreaser. Of the 120 degreasing plants, 111 were open-topped and manually loaded. Many of these tanks had covers, however it was unclear how many used these covers during degreasing.

A total of 379 grab samples were taken and the results, broken up into 50 ppm ranges, are shown in table 10 below. Of the 379 samples, 155 (41%) were above 50 ppm and 54 (14%) were above 200 ppm. It was also noted that where high results were obtained, generally some obvious deficiency in the maintenance or operating procedures was found which could account for the results. These included draughts, high hoist speeds (ie >3 m/min), blocked rim ventilation, and freeboards less than 75% of the width of the plant.

Table 10 - Results of HSE short-term air sampling of 100 vapour degreasers (Robinson, Updated January 1996)

Concentration ranges (ppm)	No. of samples	No. of sites with at least one reading in the range
0 - 50	224	88
>50 - 100	67	41
>100 - 150	25	18
>150 - 200	9	8
>200	15	13
>250	39	25

Limited data is available from the HSE for air monitoring during the cleaning of degreasing baths where the operator does not enter the degreasing bath. Five samples were taken during 1994/95, with results ranging from 9-350 ppm (2 samples were above 150 ppm). The sampling duration was 18 minutes. (United Kingdom, 1996)

United States

Air monitoring data for trichloroethylene from sampling conducted at four worksites using vapour degreasers are available from reports of investigations carried out by the Hazard Evaluation and Technical Assistance Branch of NIOSH. This Branch is responsible for investigating possible health hazards in the workplace and investigations are carried out following a request from employers or employees.

Exposure data taken at the four manufacturing sites between 1989 -1991 is presented in Table 11. In three cases, health effects were reported in the request to investigate. Effects reported in two cases were headache, dizziness, nausea, sleepiness/fatigue, upper respiratory tract irritation, and skin rash (one site). Effects reported in the third case were cancers, breathing problems, kidney problems and watery eyes. The sites investigated included a large industrial complex with 4 conveyor fed degreasers; a manufacturer operating a conveyor fed liquid-vapour immersion degreaser; a manufacturer operating an open-topped degreaser; and a company operating an open-topped degreaser and an ultrasonic degreaser. At the latter site, a further source of potential trichloroethylene exposure was the use of a spray lacquer containing trichloroethylene. Sampling was done over 8 h obtaining a TWA for the entire shift. (National Institute for Occupational Safety and Health (NIOSH), 1989a; 1989b; 1990; 1991).

The highest readings were three short-term (10-24 minutes) personal samples taken at one worksite while the worker was engaged in servicing a liquid-vapour conveyor-fed degreaser.

Table 11 - Results of air sampling of 4 worksites by NIOSH

Concentration ranges (ppm)	Number of samples			
	Personal samples (37)		Area samples (18)	
	TWA	STEL	TWA	STEL

0 - 25	12		12	
>25 - 50	22		4	
>50 - 100			1	1
>100 - 200		3		

A project, tracking exposure profiles of chlorinated solvents in various industries was conducted as part of the Dow Chemical Company's Product Stewardship Program during 1994 - 1995 in the United States. Personal sampling (61 samples) was carried out using organic vapour monitoring badges. The average concentration of trichloroethylene for all vapour degreasing measurements was 28.4 ppm. The results are shown in Table 12, grouped and analysed according to the different ventilation conditions of the worksites sampled (Skory Consulting Inc. & Skory, 1995)

Table 12 - Trichloroethylene vapour degreasing exposures - Dow Chemical Company (USA)

Ventilation Mode	Average conc. (ppm)	Median	Standard Deviation	Sample Size	Number of Results		
					<50 ppm	50-100 ppm	>100 ppm
Enclosed system	40.2	27.7	40.6	5	3	2	0
Local exhaust	14.8	5.1	23.0	24	23	3	0
General	38.7	17.9	40.9	30	20	6	4
Spray booth	6.0	6.0	2.4	2			

8.5.7 Summary of exposure during vapour degreasing

Inhalation and dermal exposures to trichloroethylene are likely during use of the chemical in vapour degreasing. Emission of vapours from open-topped tanks may lead to inhalation exposure. Inhalation exposure may also occur during manual loading of metal parts to be degreased. Dermal exposure to liquid trichloroethylene may occur during filling of tanks with trichloroethylene or during handling of hollow degreased parts that may contain trapped liquid trichloroethylene or during spills.

A variety of control measures may be incorporated in degreasing tanks to reduce emissions. A survey of degreasing operations carried out by the Health and Safety Executive in U.K.(1996) has shown that emission is likely to be < 30 ppm in tanks fitted with the appropriate control measures such as rim ventilation, adequate freeboard zone, condensing coils etc and where good work practices are followed. Some older tanks do not have all the appropriate controls resulting in high short-term emissions (Robinson, Updated January 1996). According to information obtained from the NICNAS survey most workplaces have open-topped tanks and those equipped with lids are generally only covered at night.

At least 1000 people, excluding aerospace workers, are involved in vapour degreasing in Australia either on a regular or intermittent basis. The most common exposure scenario was 4-8 h a day for more than 200 days a year.

Atmospheric monitoring is not conducted on a regular basis by most users during vapour degreasing in Australia. Very limited atmospheric monitoring data was provided by users with the data relating to grab samples and no time weighted average results being provided. Short-term measurements have been high in some cases especially during manual loading and unloading of parts. The monitoring data provided by WorkCover did not state the time period over which the monitoring was done making it difficult to determine if they were time weighted average or grab samples. Based on the the U.K. data of Shipman and Whim (1980) exposure during vapour degreasing in this assessment were estimated for three scenarios at 10, 30 (results recorded at most workplaces) and 50 ppm.

Dermal exposure to liquid trichloroethylene was assumed to be incidental. The estimates for total body burden (mg/kg/day) from inhalation and dermal exposure were 3.5 mg/kg/day for 10 ppm, 10.2 mg/kg/day for 30 ppm and 16.9 mg/kg/day for 50 ppm. Details of the exposure estimates for vapour degreasing are given in Appendix 1.

8.6 Cold cleaning

Cold cleaning refers to the process of cleaning by dipping or soaking articles in a cleaning liquid, or spraying, brushing, or wiping the cleaning liquid onto articles at temperatures below boiling point. Processes may be manual, such as in wipe cleaning, or semi- or fully automated, such as in some in-line cleaning systems in which parts carried by conveyor lines are dipped into one or more tanks of solvent. Immersion cleaning can involve manual, mechanical or ultrasonic agitation of the solvent in the tank.

The NICNAS industry survey identified 26 companies in Australia using trichloroethylene in various cold cleaning processes. This represented 29% of the total number of respondents who are end users of trichloroethylene. The most common type of cleaning described was immersion in tubs or tanks (15/26 companies). In most cases this was combined with manual scrubbing of the articles using paint brushes and/or some form of agitation of the liquid solvent such as swirling. One respondent used an ultrasonic system. Manual wipe cleaning was the second most common form of cold cleaning (7/26 companies), and spraying was mentioned by one company. One company uses trichloroethylene for regular daily flushing of polyurethane mixing chambers to prevent gelling of mixture in the machine.

Some companies use cold cleaning processes only occasionally, however others use cold cleaning processes on a regular or semi-regular basis, as part of a normal work routine. Details of the industry, type of activity, number of workers, duration and frequency of employment on cold cleaning tasks, and personal protective equipment, where provided by respondents, are given in Table 13. The survey results indicate that there is a great variability in cold cleaning processes.

8.6.1 Potential exposure during cold cleaning

Immersion cleaning

Exposure to trichloroethylene from immersion cleaning processes may occur from inhalation of vapour or skin contact with liquid solvent during the transfer of solvent from bulk storage tanks, drums or other containers into soak tanks, during immersion and washing of the articles, and handling of articles after washing. The use of open containers to transport solvent to soak tanks and agitation of the solvent in the soak tank, via brushing for instance, presents an increased potential for inhalational exposure and for dermal exposure from accidental splashes and spills. The design of immersion tanks will affect the potential for exposure, with open tanks presenting an increased potential for inhalational and dermal exposure compared with closed tanks or enclosed automated systems.

Wipe cleaning

In the case of wipe cleaning, inhalational and dermal exposure may occur during the transfer of solvent from drums or containers onto the cloth and during surface cleaning using the cloth. The use of open containers for dipping cloths increases the potential for inhalational exposure and for dermal exposure from accidental splashes and spills.

Spray cleaning

Spray cleaning using trichloroethylene presents an increased potential for exposure from inhalation of spray mist or vapour and skin contact with spray mist.

Table 14 shows the work activity and control measures obtained from the workplaces as part of a project undertaken by WorkCover for NICNAS.

Table 13 - Details provided to NICNAS industry survey by respondents using cold cleaning processes

Industry	Activity	No. of workers	Duration (h/min per day)	Frequency (days per year)	PPE	Ventilation
Electrical	Immersing and brushing of articles in open 20 L steel pails. Pails are filled by tap from a 2,000 L storage tank.	12	1-2 h	365	Nitrile gloves, face mask with replaceable filters, goggles, protective clothing	Open workplace
Industrial machinery manufacture	Immersion and brushing of wire ropes in an open 44 gallon drum. Drum is partly filled by pumping trichloroethylene from another drum.	2	0.5 h	20	Rubber gloves, protective clothing and footwear, safety glasses, respirator	None specified
Mining/smelting	Parts are soaked in small tin of trichloroethylene and cleaned with brush.	15-20	0.5 - 2 h	not stated	Rubber gloves, half-face respirator, safety glasses	None specified
Manufacturing	Cleaning of brushes used in mould manufacturing process by immersion.	1	10 min.	220	None specified	None specified
Automotive	Electrode assemblies are placed in a basket and immersed in a 20 L tub	4	15-20 min.	235	Nil	Nil
Metal forming/ machining	Tools are soaked in a small covered tank then taken out and hosed.	1	1 h	235	Gloves, glasses	Automatically closed when not in use
Metal heat treatment	Wash parts using brush in open tank	10	variable	variable	Gloves, glasses, fume/smoke mask	None specified
Metal forming/ machining	Immersion of steel strip in tank	8	8 h	200	Gloves	Removable lid on tank
Electrical	Immersion and cleaning of electrical windings and electrical parts with a brush	3	>1 h	>20	Gloves, mask	None specified
Aerospace	Electroplating solvent degreasing bath, sometimes solvent is chilled to lessen evaporation	not stated	not stated	not stated	Full face respirators, viton gloves and coveralls	None specified
Metal forming/ machining	Parts are fed via a conveyor system into an enclosed housing where they are automatically fed through an ultrasonic trichloroethylene bath.	2	8 h	176	Protective breathing masks	Enclosed system with local exhaust ventilation

Table 13 - Details provided to NICNAS industry survey by respondents using cold cleaning processes (cont.)

Light metal products manufacture	Components placed in small open 2 L tank and washed with 1 L trichloroethylene, then removed and air dried.	2	1 h	230	Gloves, face mask	Laboratory style fume cabinet
Lubricants manufacture	Trichloroethylene poured from 5 L containers into dirty lab equipment such as beakers. Used solvent put into vapour degreaser.	5	8 h*	260	Oil impervious gloves, safety glasses, overalls, safety footwear	Fume cupboards
Metal forming/ machining	Small parts washed in container of trichloroethylene, also wipe cleaning	2	1 h	50 #	Gloves and eye protection	None specified
Aerospace	Wipe clean and immersion in small tank with cover	500	variable	variable	Face mask with organic vapour canister is used where necessary with wipe cleaning	Ventilated work area
Electrical	Tipped from 20 L container into 1 L container about half inch full. Small pieces immersed, picked out by hand, dried on rag or air dried. Contaminated solvent is strained through cloth and cloth thrown in garbage. Sludge put on ground as weedkiller.	1	1 h	10	No gloves	Air conditioned office
Electrical	Transformer parts washed in tub. Tubs cleaned out with rag and hand cleaning of parts and equipment with rag.	2	2 h	40	Rubber gloves, overalls, glasses. Breathing apparatus when cleaning out large transformer tanks	Forced ventilation
Metal forming/ machining	Cloth soaked in trichloroethylene, and spray trichloroethylene using adapted oil spray can.	1	rarely	rarely	Gloves, goggles	
Aerospace	Wipe cleaning	1	0.5 h	12	Gloves, several types of filtered breathing masks	None specified
Rubber products manufacture	Trichloroethylene is decanted from drum into smaller containers with lids. When needed it is poured onto cloth and used to wipe steel that has been buffed in preparation for cold bonding with rubber.	12	approx. 5 min	1-3 days a week	Gloves, face mask, cartridge type breathing equipment, safety clothes	Fan
Automotive	Trichloroethylene pumped from drum into 20 L container with lid - cloth dipped in for wipe cleaning.	3	not specified	once a fortnight	Gloves	None specified

* this includes other laboratory cleaning work, including vapour degreasing using trichloroethylene.
\# this includes vapour degreasing as well as cold cleaning using trichloroethylene

Table 14 - Work activity and control measures

Worksite	Work Activity	Duration	TCE conc. TWA (ppm)	Urinary TCA mmol/mol creatinine	PPE	Ventilation
1	Clean wires in a closed trough. Exposure occurring only during transfer of trichloroethylene from a 200 L drum into a stainless steel jug and transporting it to the trough (approx. 10 metres) for topping up and during checking of the wiper system.	2 mins	0.4	1.69	No gloves or respirator	No exhaust ventilation
2	Clean rubber to make glue adhere to the surface more strongly. The job was simulated as there was no current work available. The rubber surfaces were brush and rag wiped with trichloroethylene from a container filled from a tapped 200L drum.	40 mins	0.2	4.90	a single PVC glove on the right hand during rag wiping but not when using the brush.	No exhaust ventilation, only natural ventilation.
3 (4 workers)	Rag wipe to remove oil from filter end caps	not stated	3.8	-	wore latex or vinyl gloves, no respirators	No exhaust ventilation but worked near a open roller door, natural ventilation but also a solar load.
	Rag wipe end caps. TCE used between intermittent warehouse duties. Used a small open glass bowl of TCE before applying a self adhesive foam ring seal to end caps.	not stated	68.3	20.13	No gloves or respirators	No exhaust ventilation
	To clean down urethane rubber dispensing machine's head when it was switched off (2-3 times a day)	not stated	15.1 11.3	9.76 -	"Ansell silver lined industrial gloves", no respirators	
4 (2 workers)	Cold dip degreasing of metal articles prior to their heat treatment in a shallow tray; once the articles were placed in the tray they were rag washed and set aside to dry.	1/2-2 h	0.9 7.5	1.12 1.00	red PVC gloves	No exhaust ventilation, general ventilation, high roof, open area.

8.6.2 Atmospheric monitoring

Australian data (atmospheric and biological monitoring)

No monitoring data were provided by applicants for cold cleaning activities using trichloroethylene.

Atmospheric and biological monitoring was conducted by WorkCover, as part of a project commissioned by NICNAS, at workplaces using trichloroethylene for cold cleaning. The monitoring was carried out on a half shift basis as most of the jobs were continuous throughout the day. At two workplaces trichloroethylene use occurred for only half a day. In these cases the monitoring results were converted to give an eight hour TWA (by halving the results). The cold cleaning activities ranged from dip cleaning to combined dip cleaning and rag wiping to rag wiping alone and are described in Table 14. Atmospheric monitoring was carried out in accordance with Australian Standard AS 2986 "Workplace Atmospheres - Organic Vapour Sampling by Solid Adsorption Techniques". Biological monitoring involved estimation of urinary trichloroacetic acid with urine samples being collected at the end of shift at the end of the work week. Table 15 shows the air monitoring results and the urinary trichloroacetic acid levels obtained during this study.

Overseas data

Some atmospheric monitoring of cold metal cleaning operations using trichloroethylene has been carried out in the United States as part of a larger long-term analysis of exposure profiles for chlorinated hydrocarbons conducted for the Dow Chemical Company Product Stewardship Program (Skory Consulting Inc. & Skory, 1995). Monitoring was carried out using organic vapour monitors attached to the collars of employees during their work day and during the time they are exposed to trichloroethylene. The overall average concentration of 9 samples was 68.4 ppm. Of these, 5/9 were less than 50 ppm, 1/9 was between 50 to 100 ppm and 3/9 were > 100 ppm.

Table 15 - Atmospheric and biological monitoring results during use in cold cleaning

Worksite	Work activity	TCE concentration. TWA	Urinary TCA Concentration (mmol/mol creatinine)
1	Clean wires in a closed trough. Exposure occurring only during transfer of trichloroethylene from a 200 L drum into a stainless steel jug and transporting it to the trough (approx. 10 metres) for topping up and during checking of the wiper system.	0.4 ppm.	1.69
2	Clean rubber to make glue adhere to the surface more strongly. The job was simulated as there was no current work available. The rubber surfaces were brush and rag wiped with trichloroethylene from a container filled from a tapped 200L drum.	0.2 ppm	4.90
3	Rag wipe end caps. TCE used continually between intermittent warehouse duties. Used a small open glass bowl of TCE before applying a self adhesive foam ring seal to end caps.	68.3 ppm	20.13
	Rag wipe to remove oil from filter end caps	3.8 ppm	-
	To clean down urethane rubber dispensing machine's head when it was switched off (2-3 times a day)	15.1 ppm	9.76
	To clean down urethane rubber dispensing machine's head when it was switched off (2-3 times a day)	11.3 ppm	-
4	Cold dip degreasing of metal articles prior to their heat treatment in a shallow tray; once the articles were placed in the tray they were rag washed and set aside to dry.	0.9 ppm	1.12
	Cold dip degreasing of metal articles prior to their heat treatment in a shallow tray; once the articles were placed in the tray they were rag washed and set aside to dry.	7.5 ppm	1.00

2 workers from Worksite 3 did not give urine samples
Worker from Worksite 2 did a simulated job which took 50 mins
TCE=trichloroethylene TCA=trichloroacetic acid

8.6.3 Summary of exposure during cold cleaning

Inhalation and dermal exposure can occur during cold cleaning. Situations in which dermal contact might occur include immersion and brushing of articles in soak tanks, handling of work pieces that are not thoroughly drained of trichloroethylene and handling of cloths and rags used in cold cleaning. There is a potential for accidental splashes during the work process involving trichloroethylene such as transfer of solvent from or to drums or other vessels. Monitoring data from the cold cleaning project was used to estimate exposure. Exposure was estimated for 120 days/yr and 200 days/yr as these were the common scenarios encountered in the workplaces monitored. Inhalation exposure was considered to be continuous and dermal exposure was assumed for 5% of the total time. At two of the workplaces the job was continuous throughout the day while at the other two places exposure was for half a day only. Information obtained from the NICNAS survey indicated that in 3 of 21 workplaces trichloroethylene was used for cold cleaning during the entire shift (8 h). Inhalation exposure was therefore estimated for 8 h/day, 200 days in a year and 120 days in a year. The estimated exposures may be an overestimation for those workplaces involved in this activity for only a few hours of the shift. The temperature during monitoring at the various sites varied from 11.4 °C to 19.5°C. It is expected that in summer with high temperatures exposures are likely to be high. Estimates for the total body burden (mg/kg/day) from inhalation and dermal exposures are provided in Table 16.

Table 16 - Total body burden from inhalation and dermal exposure

	Exposure estimate (mg/kg/day)	
	200 days/yr	**120 days/yr**
Inhalation		
0.4 ppm (2.18 mg/m3)	0.13	0.079
3.8 ppm (20.75 mg/m3)	1.27	0.76
68.3 ppm (372.92 mg/m3)	22.77	13.66
0.9 ppm (4.91 mg/m3)	0.29	0.179
7.5 ppm (40.95 mg/m3)	2.5	1.5
Dermal	1.0	0.60

8.7 Trichloroethylene products

The NICNAS industry survey identified 46 products containing trichloroethylene in use in Australia, including adhesives, electrical equipment cleaning solvents, metal degreasing solvents, waterproofing agents, paintstrippers, and carpet shampoos. Some data on uses of these products were obtained from the NICNAS industry survey and some were obtained from labels and technical bulletins.

8.7.1 Adhesives

Adhesives are applied by brushing, dipping, roller coating or spraying. They may be diluted prior to application with trichloroethylene, xylene, toluene, methyl ethyl ketone, methyl isobutyl ketone, or other solvents, depending on the type of adhesive and processing methods employed by the individual users of the adhesives. Stirring and agitation of adhesive solutions prior to application is

usually done to ensure dispersed solids are uniformly suspended. In some two-part systems, the parts are mixed prior to application. Pre-weighing of ingredients can occur if less than the full amounts are used.

Methods for applying adhesives described in technical bulletins provided by companies for some of the products in use include applying the adhesive to one or both surfaces to be joined, air drying the coated parts at room temperature for 15 minutes to 2 hours, or in hot drying ovens or tunnels (up to 149 °C) for a shorter period, followed by contact bonding and curing.

Six products used for the repair of rubber tyres were identified. They contain <60 to >90% trichloroethylene. They are used variously for hot and cold vulcanisation of patches to tyres, cleaning rubber prior to vulcanisation and for sealing tyre inner linings after buffing. No information was available on methods of application except for the rubber cleaning product, which is rubbed into the surface with a linen cloth prior to repair using adhesive products. This product is comprised of >90% trichloroethylene.

Some information on work scenarios involving the use of adhesives was obtained from the NICNAS industry survey. The scenarios are outlined in Table 17.

Table 17: Work scenarios in adhesive application

Application	Wor-kers	Duration (h/day)	Freq.	Engineering Controls	PPE
Brush paint metal substrates	2	8-10	6 days/week	Extracted spray booth	Rubber gloves, safety glasses, half-face masks (particles and carbon filter), safety boots
Dilute & spray metal surfaces	3	2	10 days/month	Spray booth	Knitted polyester gloves, vapour mask
Apply rubber adhesive by brush or mop onto metal or rubber substrate	20	1-8	250 days/year	Open area Fans in drying tunnel	Gloves, boots, masks, protective clothing
Hand paint metal inserts	15	8	340 days/year	Vented work bench	Gloves, mask, glasses
Mix with curing agent, use in manufacture of automotive trim	1	0.5	218 days/year	Fume extraction system	Gloves, mask, goggles
Glue wood to back of sinks	4	3	240 days/year	Natural ventilation	Gloves

8.7.2 Other products

No end users of other products containing trichloroethylene responded to the industry survey, however some information on possible work scenarios was obtained from labels and technical bulletins, and from information supplied by some formulators of the products (one electrical solvent formulator, one paint stripper formulator and one formulator of waterproofing products) (see table 18).

8.7.3 Atmospheric monitoring during use of products

Australian data

The NICNAS monitoring project referred to earlier in the section also included atmospheric and biological monitoring of workplaces using products containing trichloroethylene. The results are summarised in Table 19.

The results of one personal sample taken by WorkCover in 1984 at a worksite using natural ventilation during adhesive spraying was made available. The result was 1.15 ppm. The monitoring duration was not specified.

Overseas data

Atmospheric monitoring data from a US automotive factory using trichloroethylene containing adhesives in the manufacture of fibrous and non-fibrous glass headliners were available. The adhesives were used in a cold lamination process to bond paper to foam core or fabric to cardboard core. After bonding, the cores were cold rolled, stacked to air dry and cut by a hot wire. Four area samples for trichloroethylene were collected with a sampling time of 5-6 hours. Concentrations ranged from 2.7 to 21.4 ppm, with the highest concentration recorded in the area where adhesive was used to coat paper with fabric.

Table 18 - Use information on products containing trichloroethylene

Product Type	Number of products	Trichloroethylene concentration	Use	Methods Of Application
Electrical equipment cleaning solvents	8	<13 - 60%	Clean grease and oil from electrical motors and equipment. Used in a variety of industries.	Brushing, spraying from a pressure pot, dipping, aerosol can spraying
Metal degreasing solvents	7	<10 - 65%	Clean grease and oil from metallic surfaces. Used in a variety of industries.	Wiping with soaked cloth, dipping
Waterproofing agents	4	60 - 70%	Waterproofing of outdoor and camping equipment (consumer product)	Aerosol spray.
			Fabric protector for use by professionals	Hand-pumped spraying through spray outfit with flat fan jet nozzle
			Masonry protector for use by professionals	as above
			Protection of rubber linings from water and sun	Brush on
Paintstrippers	3	0.05 - 8%	Paintstripping	Brushed on, then scraped off
Carpet shampoos	2	3%	Professional carpet shampooing	Used in professional carpet extraction cleaning machines and in spot cleaning using a spray or a cloth

Table 19 -Atmospheric and biological monitoring data during use of trichloroethylene products

Worksite	Activity	TCE%	TCE concn - TWA (ppm)	Urinary TCA (mmol/mol creatinine	PPE	Ventilation
1	Tyre repair process - abrading the puncture area, applying a sealer and when this dried applying the TCE product	90%	2.5	1.69	No PPE	No exhaust ventilation, work area large and open
2	Press shop: rag wipe areas of a plate about to be placed in a press	20%	57.8 *	1.67	Cotton gloves over red PVC gloves, no respirator	No exhaust ventilation
	Welding shop: rag wipe edges of a small basin in preparation for its seam welding into a basin and board unit.	20%	4.1	2.59	PVC gloves	No exhaust ventilation
	Fabrication section: rag wipe down stainless steel surfaces for welding preparation	20%	3.8	0.70	PVC gloves	No exhaust ventilation
3	Pump components either spray painted, dipped or brush painted with two TCE products	25%	4.8	1.09	Cartridge respirators, cotton gloves, safety glasses and overalls; rarely used spray painting booths	Good natural ventilation
		35%	0.7	0.66		

*this was thought to be a false reading as the levels of trichloroethylene were 10 times higher than the other 2 workers doing similar jobs.

8.7.4 Potential for exposure during use of products

Procedures which present a potential for inhalational exposure include transfer of solutions into containers in preparation for use, including pre-weighing and mixing or dilution of ingredient, and application of the products. Any agitation or heating of solutions, such as may occur in adhesive preparation and in dip cleaning, will increase vapour emission and the potential for exposure. Spraying may increase inhalational exposure through the release of spray mist into the air. Drying of film adhesives, which is accomplished by the evaporation of solvent, and heating processes used for contact bonding and curing, will release solvent into the air, and increase the potential for exposure.

Accidental spills or splashes during transfer or application of the products present a potential for dermal exposure when open containers are used to hold products. Use of brushes to apply products poses a risk of splattering or dripping of the solution onto skin. Cloths used to apply solutions will present a potential for dermal exposure if they come into contact with the skin. Mixing and agitation increase the potential for dermal exposure. In addition, spraying of products containing trichloroethylene presents a potential for dermal absorption of spray droplets.

The total exposure during use of trichloroethylene products was estimated from the monitoring data obtained in the NICNAS project and is shown in Table 20.

Table 20 - Combined inhalational and dermal exposure during use of trichloroethylene products

Concentration - activity		Exposure estimate (mg/kg/day)
ppm	mg/m^3	
35% product - spray painting		
0.7	3.82	0.3
4.8	26.21	1.67
20% product - rag wiping		
3.8	20.75	1.31
4.1	22.38	1.64
90% product - brushing on		
2.5	13.65	1.01

8.8 Recycling

The majority of vapour degreaser users recycle trichloroethylene either through on-site stills or off-site recyclers. From information provided by industry more than 185 tonnes of trichloroethylene in total is recycled each year at three solvent recycling plants. Other companies are known to recycle trichloroethylene, however the amounts recycled are not known. One importer and one major distributor of trichloroethylene provide recycling services to customers. The importer supplies drums to customers to hold drummed off waste. The waste is transported to a recycling plant, and recovered trichloroethylene is bought back from the recycling company. The other company has its own recycling plant and since 1988 has offered a recycling service to its customers as part of its product stewardship, which includes dissemination of literature (company manual on

chlorinated solvents; MSDS; and information on exposure standards, relevant Australian Standards, and a vapour degreasing handbook); analysis of trichloroethylene samples to determine degree of contamination or identify the sources of possible problems with the vapour degreaser; and collection of contaminated trichloroethylene for recycling.

Some vapour degreasers incorporate stills that operate concurrently with the vapour degreaser, collecting waste oils as the contaminated solvent passes through. Twenty-one percent of respondents to the NICNAS industry survey who used trichloroethylene in vapour degreasers indicated that they operated such stills. Waste oil and trichloroethylene mixtures collected in stills is sent to a solvent recycler. Regardless of whether vapour degreasers had stills or not, the majority of respondents sent solvent to recyclers.

8.8.1 Recycling process

Two site visits were made to solvent recycling plants. One plant operates three distillation units 24 hours a day, 5 days a week and recycles trichloroethylene in batches in an enclosed system. Contents of drums are pumped into one of three enclosed distillation stills, and distillate is siphoned into covered, but not fully enclosed 200 L drums. There was no bunding around the distillation units. Distillate is checked for specific gravity, acid acceptance value and clarity. The facility is open roofed providing natural ventilation and ventilation fans run 24 hours a day. Operators wear personal protective equipment consisting of Proban overalls and hood, glasses, gloves and respirator (when cleaning out stills). Stills are cleaned out by opening doors at the bottom of the unit and raking out sludge into containers.

At the other site, the contents of each drum are tested prior to recycling to check the contents. Four 200 L drums are placed on a pallet in front of one of three distillation stills and contents sucked out by vacuum pressure through steel pipes. The distillation units are situated in an open workplace with natural ventilation. Distillate drains from the still into smaller pipes leading to an enclosed vessel. There is no bunding around the stills or collection vessel. Contents of the vessel are analysed and appropriate amounts of stabiliser added. Drums are filled from the vessel. Two operators are employed at the site. Drum filling takes about ten minutes a day and operators wear gloves and organic vapour respirators.

8.8.2 Monitoring during recycling

Air monitoring is conducted at one site, however no test results for trichloroethylene were made available. At another site air monitoring using Drager tubes for grab samples is done occasionally, but not on a regular basis. No results were made available.

No overseas monitoring data during recycling was available.

8.8.3 Potential sources of exposure

During the recycling process, transfer of contaminated solvent from drums into distillation units and of distillate into drums is a potential source of exposure through inhalation of vapour. Cleaning sludge out of stills presents a potential source of high exposure from inhalation of vapour. Accidental spills and splashes present a further potential of inhalation and dermal exposure.

Exposure during recycling is likely to be low as it involves a closed process.

9. Toxicokinetics and Metabolism

Numerous reviews of trichloroethylene that have been conducted include toxicokinetics of the chemical. This section is taken mainly from the UK SIAR and IARC (1995).

9.1 Absorption

Trichloroethylene is a low molecular weight, nonpolar, highly lipophilic compound. It is absorbed readily and rapidly by inhalation, oral and dermal routes in humans and animals. Skin absorption of the vapour is negligible (Lauwerys & Hoet, 1993; Goeptar et al., 1995). In humans, between 28 to 80% of the trichloroethylene in inspired air is taken up by the lungs (Monster et al., 1979) with a high initial rate of uptake. Uptake is dependent on the rate of respiration and the trichloroethylene concentration in the inspired air. Increased workload increases the uptake of trichloroethylene in humans (Monster et al., 1979). After inhalation, 40 to 70% of the absorbed dose is metabolised.

In mice, the dermal absorption rate was reported to be 7.82 μg/cm^2/min on application of 0.5 ml of pure trichloroethylene in a closed cell to the clipped abdominal skin of mice for 15 mins (Tsuruta, 1978). The dermal absorption rate was also investigated in hairless female guinea pigs immersed in low (0.02 - 0.1 ppm) or high (100 ppm) concentrations of trichloroethylene in aqueous solution for 70 mins. The uptake rate was found to be approximately 5.4 μg/cm^2/min for both the high and low concentrations (Bogen et al., 1992).

9.2 Distribution

Absorbed trichloroethylene is distributed rapidly throughout the body and, in humans, the major sites of deposition appear to be body fat and liver (McConnell et al., 1975). It readily crosses the blood:brain and placental barriers. Trichloroethylene was detected in the blood of babies at birth after the mothers had received trichloroethylene anaesthesia (Laham, 1970). The blood:air partition coefficient in humans is 15 (Monster et al., 1979) and the fat:blood partition coefficient is about 700 (Steward et al., 1973; Sherwood, 1976), leading to deposition of trichloroethylene in adipose tissue. Trichloroethylene is stored in the adipose tissue for about 40 h with detectable levels even after 70 h (Fernandez et al., 1977).

9.3 Metabolism

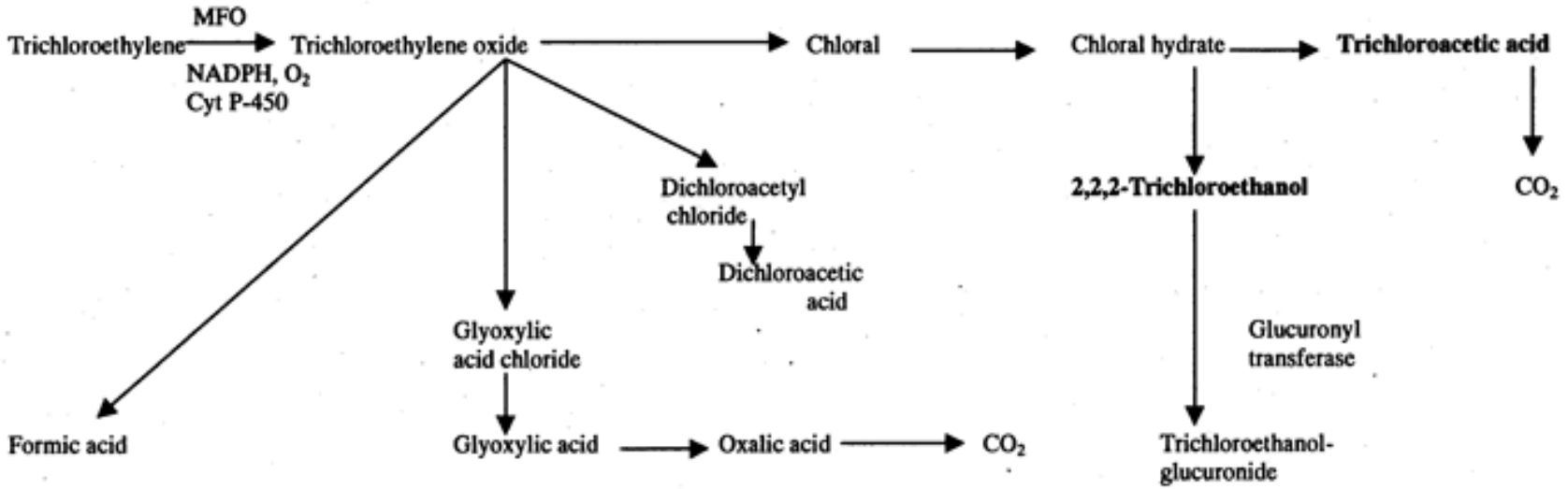
Metabolism of trichloroethylene is rapid with common pathways in animals and humans. Liver is the main site of trichloroethylene metabolism in animals, with lesser metabolism in extra-hepatic organs such as the kidneys and bronchi. Several studies have suggested that the metabolites are responsible for trichloroethylene toxicity (Bruckner et al., 1989; Davidson & Beliles, 1991). The principal metabolites in humans are trichloroethanol, trichloroethanol glucuronide and trichloroacetic acid. Other minor metabolites that have been identified in urine are chloral hydrate, chloroform, monochloroacetic acid, dichloroacetic acid,

N-(hydroxyacetyl)-aminoethanol and N-acetyl dichlorovinyl cysteine following exposure of humans to trichloroethylene. Most of these metabolites have been identified in experimental animals.

In the major metabolic pathways, trichloroethylene is metabolised by cytochrome P-450, possibly P4502E1, to a transient epoxide (trichloroethylene oxide) which may undergo intramolecular rearrangement in two different ways. One pathway leads to chloral which is hydrolysed to chloral hydrate. A recent study (Green et al., 1997) has demonstrated that the specific enzyme responsible for transformation of trichloroethylene to chloral hydrate is cytochrome P4502E1. Chloral hydrate is converted by alcohol dehydrogenase or chloral hydrate dehydrogenase to form trichloroethanol and trichloroacetic acid which are eliminated in the urine. Trichloroethanol is excreted either in the free form or conjugated with glucuronide (Miller & Guengerich, 1983). The other pathway leads to the formation of dichloroacetyl chloride which then forms dichloroacetic acid (Dekant et al., 1984; Green & Prout, 1985) or trichloroethylene oxide may hydrolyse to form formic acid, glyoxylic acid and carbon dioxide (Dekant et al., 1984; Green & Prout, 1985). The main metabolic pathways of trichloroethylene are shown in Figure 4.

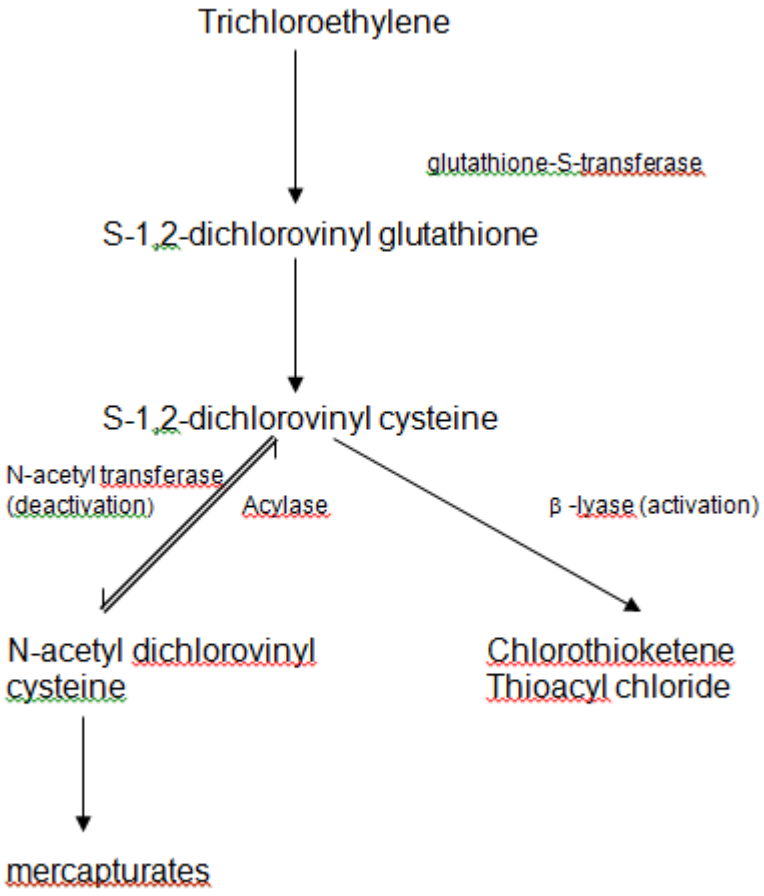
Another minor pathway in rats, mice and humans is conjugation of trichloroethylene in the liver with glutathione by glutathione-S transferase (Figure 5). Both the 1,2-dichloro and the 2,2-dichloro isomers of dichlorovinyl glutathione are found in the liver. The dichlorovinyl glutathione is transported to the kidneys where it is transformed into a cysteine compound, dichlorovinyl cysteine. Dichlorovinyl cysteine is concentrated in the proximal tubule cells. This compound is metabolised either by N-acetyl transferase to the mercapturic acid which is excreted in the urine or by β-lyase to form a thiol. The thiol is an unstable, highly reactive intermediate forming a thioketene which can react with cellular nucleophiles. Both the isomers 1,2-dichlorovinylcysteine and to a lesser extent 2,2-dichlorovinylcysteine are substrates for β-lyase. The glutathione metabolites were detected in the urine of volunteers exposed to 40, 80 and 160 ppm for 6 h. These metabolites were excreted slowly with considerable amounts detected in the urine 48 h after the end of exposure (Bernauer et al., 1996). The ratio of the two isomers of N-acetyl-S-(dichlorovinyl)-L-cysteine,1,2- and 2,2- excreted in urine is different in rats and humans (Bernauer et al., 1996). The proportion of the two isomers are similar in human urine while rats excrete more of the 2,2- isomer. The 1,2- dichlorovinylcysteine is a better substrate for renal β- lyase than the 2,2- isomer. Bioactivation of the 1,2- isomer may lead to the formation of chlorothioketene and the 2,2- isomer to the less cytotoxic thioaldehyde (Commandeur et al., 1991).

Figure 4 - Metabolic pathways of trichloroethylene (Adapted from ATSDR (1993))



MFO = Mixed Function Oxidase
Cyt P-450 = Cytochrome P450

Figure 5- Metabolism of trichlorethylene via glutathione conjugation (From: (United Kingdom, 1996))



Trichloroethylene metabolism has been shown to be saturable at lower doses in rats than in mice. In rats, metabolic saturation occurs after administration of 200-500 mg/kg trichloroethylene orally while in mice saturation is only seen at 2000 mg/kg of oral trichloroethylene or at inhalation doses of 2000 ppm (Stott et al., 1982; Buben & O'Flaherty, 1985; Prout et al., 1985). After administration of 2000 mg/kg, 78% of the dose in rats was exhaled as unchanged trichloroethylene but only 14% in mice (Prout et al., 1985). There is no evidence that the metabolic pathway is saturable in humans, however, the exposure levels used in human studies were considerably lower (maximum 380 ppm) than those used in animal studies. Saturation of metabolism in humans has been predicted at relatively high concentrations (2000 ppm) by mathematical models (Feingold & Holaday, 1977).

The rate of biotransformation of trichloroethylene in mice is much higher than in rats and blood levels of trichloroethanol and trichloroacetic acid were 4 and 6 times higher than those in rats (Fisher et al., 1991).

A number of commonly used drugs or chemicals are able to modify the metabolism of trichloroethylene. Phenobarbitone is an inducer of some forms of cytochrome P-450 and has been shown to stimulate the metabolism and binding of trichloroethylene. Ethanol has a dual effect on the metabolism of trichloroethylene in rats. At low doses it inhibits the metabolism of trichloroethylene giving rise to high blood levels (Jakobson et al., 1986). High doses of ethanol, however, enhance the metabolism of trichloroethylene to trichloroacetic acid (Kaneko et al., 1994). Other substances competitively inhibiting the metabolism of trichloroethylene are 1,1,1-trichloroethane (Savolainen, 1981), tetrachloroethylene, isopropanol, pyrazole and tetraethylthiuram disulfide (Jakobson et al., 1986).

9.4 Excretion

Trichloroethylene, following oral or inhalation exposure, is mainly excreted in the urine as trichloroethanol and trichloroacetic acid in animals and humans. In humans, about 48 to 85% of inhaled trichloroethylene is excreted as metabolites by urinary excretion and approximately 8% in the faeces. About 10 to 28% of trichloroethylene is exhaled unchanged in the breath. Small amounts of trichloroethanol are also excreted in the breath while trichloroacetic acid has been identified in bile.

The elimination kinetics of trichloroethanol and trichloroacetic acid differ in humans. Studies in volunteers have shown that during inhalation exposure to trichloroethylene, trichloroethanol levels in blood rise steadily with no plateau being reached within a 6 h exposure period. Trichloroethanol is excreted rapidly once exposure to trichloroethylene stops and most of the trichloroethanol is excreted in the urine within 24 h. Some accumulation of trichloroethanol occurs with repeated exposure but elimination is rapid once exposure ceases. The half-life of trichloroethanol in human blood is approximately 10-12 h (Ertle et al., 1972; Muller et al., 1972; Muller et al., 1974).

Trichloroacetic acid is tightly and extensively bound to plasma proteins in humans and has a half-life in blood of 70-100 h. Repeated exposure causes trichloroacetic acid to accumulate in blood with the metabolite being excreted very slowly once exposure has ceased.

The levels of trichloroethylene and its metabolites trichloroacetic acid and trichloroethanol were measured in blood and urine of a worker following acute poisoning, to investigate the kinetics of trichloroethylene (Yoshida et al, 1996). Accidental ingestion of trichloroethylene had occurred as a result of a fall into a reservoir bath during maintenance. The worker had been in the bath for 3 to 5 mins and was in deep coma with chemical burns and pneumonia on admission. Trichloroethylene was detected in urine for the first two days (43.4 mg/day on the first day and 13.3 mg/day on the second day) suggesting that it may be directly excreted in urine prior to metabolism. Trichloroethylene levels in blood fell rapidly and biphasically. Trichloroethanol levels however, increased for up to 4 days after ingestion and then decreased biphasically with a half life of 53 h in the rapid phase and 269 h in the slow phase. This elimination pattern and the half-life of trichloroethanol observed in blood, differed from previous studies in volunteers following inhalation exposure (Nomiyama, 1971; Monster et al., 1976). In these studies, inhalation of trichloroethylene resulted in maximum trichloroethanol concentration in blood immediately after inhalation followed by an exponential decrease with a half-life of 10 to 15 h. The difference in the study by Yoshida et al (1996) is attributed by the authors to delayed formation of trichloroethanol from trichloroethylene stored in adipose tissue.

Yoshida et al (1996) also observed that trichloroethanol and trichloroacetic acid were excreted in urine bi-phasically with the amount of trichloroethanol excreted being twice that of trichloroacetic acid for the first two days. Subsequently the ratio of trichloroethanol to trichloroacetic acid excretion became approximately 1:2. The excretion of trichloroacetic acid is slow in humans because of protein binding.

Some studies have reported sex differences in the urinary excretion of trichloroethylene metabolites. The urinary levels of trichloro compounds and trichloroethanol were significantly higher in men than in women workers exposed to trichloroethylene while the urinary levels of trichloroacetic acid did not differ between the two sexes (Inoue et al., 1989). However, one study reported that urinary trichloroacetic acid levels were greater in women than in men within 24 h of exposure (Nomiyama & Nomiyama, 1971).

Physiologically based pharmacokinetic (PBPK) models predict that humans have a lower rate of metabolism than mice but higher than rats (Allen & Fisher, 1993). A PBPK model used to predict the differences in body weight, fat content and sex found that women and obese people would be expected to have lower concentrations but longer residence times of blood trichloroethylene because of their higher fat content.

10. Effects on Experimental Animals and *in vitro* Test Systems

Numerous reviews of the health effects of trichloroethylene have been conducted. No additional toxicity data was provided by applicants. For the genotoxicity and carcinogenicity endpoints a different approach was taken acknowledging the contentious interpretation of many of the available studies. For these endpoints individual studies which were in contention were reviewed together with views of other authorities.

10.1 Acute toxicity

Trichloroethylene has low acute toxicity by all routes of exposure. The LC_{50} and LD_{50} values in various animals are shown in Table 21. The lowest LC_{50} in rats is 4800 ppm for 4 h and 5857ppm in mice following 6 h exposure.

Table 21- LC_{50} and LD_{50} values for trichloroethylene

Route	Species	LC_{50}\LD_{50}	Reference
Inhalation	rat	26000 ppm (1 h)	(Vernot et al., 1977)
Inhalation	rat	4800 ppm (4 h)	(Adams et al., 1951)
Inhalation	rat	12000 ppm (4 h)	(Siegal et al., 1971)
Inhalation	rat	5918 ppm (6 h)	(Bonnet et al., 1980)
Inhalation	mouse	8450 ppm (4 h)	(Friberg et al., 1953)
Inhalation	mouse	5857 ppm (6 h)	(Gradiski et al., 1978)
Oral	rat	5400-7200 mg/kg (in water)	(Smyth et al., 1969)
Oral	mouse	2900 mg/kg b.w (in water)	(Aviado et al., 1976)
Oral	rat	5600 mg/kg b.w (in corn oil)	(National Cancer Institute (NCI), 1976)
Oral	mouse	10000 mg/kg b.w. (in corn oil)	(National Cancer Institute (NCI), 1976)
Dermal	rabbits	29000 mg/kg b.w. (occluded)	(Smyth et al., 1962) (Smyth et al., 1969)
Dermal	rabbits	> 20000 mg/kg b.w. (semi-occlusive)	(Kinkead & Wolfe, 1980)

The major acute toxic effects in animals are consistent with the findings in humans. The main signs of acute toxicity in rats and mice were those of CNS depression such as stupor and poor coordination and respiratory failure. Irritation of the eyes and respiratory tract were also reported. Effects on the liver, indicated by transient increases in serum ALT and AST, were reported following oral administration.

Species specific toxicity has been noted since pulmonary toxicity has been observed in mice but not in rats. A dose dependent increase in the number of vacuolated Clara cells was seen in mice following single inhalation exposures between 20 and 2000 ppm of trichloroethylene for 6 h. At higher dose levels pyknosis and focal loss of bronchiolar epithelium were observed. Other cell types were not affected (Odum et al., 1992).

10.2 Irritation and corrosivity

10.2.1 Skin

Several studies in animals, guinea pigs and rabbits, using occluded and non occluded dressing indicate that trichloroethylene is irritating to the skin. (Smyth et al., 1969; Duprat et al., 1976; Wahlberg, 1984; Anderson et al., 1986).

10.2.2 Eye

Animal studies provide limited information on eye irritation. No animal tests complying with standard protocols for detecting eye effects of trichloroethylene have been reported. Two studies reported corneal abrasions and necrosis of the cornea following instillation of trichloroethylene into rabbit eyes (Smyth et al., 1969; Duprat et al., 1976).

10.3 Sensitisation

No skin or respiratory sensitisation studies have been conducted in animals.

10.4 Repeated dose toxicity

Many repeated dose studies (inhalation and oral) have been conducted in a range of species. The results of the major studies are summarised in Table 22.

The main toxic effects following repeated exposure of animals by the inhalation and oral route are on the liver and kidneys. Adverse effects were also seen on hearing, the lungs and the nervous system following inhalation exposure. Studies reported animals surviving repeated inhalation exposure to between 1000 and 7000 ppm for 90 days.

No Observed Adverse Effect Levels (NOAEL) have been identified for effects of trichloroethylene on the various systems in animals. The kidneys appear to be the most sensitive organs in animals. Kidney effects were observed in male rats following inhalation, and in both rats and mice in both sexes after oral exposure. In a 2-year inhalation study using rats, meganucleocytosis of the renal tubules was reported at 300 ppm (LOAEL) in male rats with no effects being seen at 100 ppm (0.55mg/L) (NOAEL) (Maltoni et al., 1988). Meganucleocytosis was also reported in an oral study at 250 mg/kg bw/day in rats with a NOAEL of 50 mg/kg bw/day (Maltoni et al., 1986). In mice, renal cytomegaly was observed in both sexes following oral administration of 1000 mg/kg bw/day for 2 years (US National Toxicology Program NTP, 1990)

Trichloroethylene-induced liver effects have been reported in mice and rats, with mice being more sensitive than rats. Increased liver weight, AST and ALT levels and cytochrome P-450 activities have been noted. At very high doses centrilobular cell enlargement and necrosis have been observed following inhalation and oral exposure. Peroxisome proliferation has been observed in the mouse liver but not in rats. NOAELs identified for liver effects are 200 ppm (inhalation) in both rats and rabbits (Adams et al., 1951) and 375 mg/kg/day and 500 mg/kg/day (oral) for mice and rats respectively.

Evidence of neurotoxicity, such as increased activity and ototoxicity was also reported in animals. Simultaneous exposure to two solvents, styrene and trichloroethylene did not produce a greater hearing loss than from exposure to either solvent alone (Rebert et al., 1993).

Pulmonary toxicity was reported in mice following repeated inhalation exposure to 450 ppm trichloroethylene for two weeks. Vacuolation of Clara cells was observed following exposure on the first day, however the lungs returned to normal after 4 or 5 consecutive exposures. The Clara cell lesions were observed again after a 2-day break from exposure to trichloroethylene. It is likely that restoration of the non-ciliated cells occurs (Odum et al, 1992).

Table 22 - Repeated dose toxicity

Species	Exposure	NOAEL	LOAEL	Results	Reference
Inhalation exposure					
Rats (Wistar, 15 males, 15 females in each exposure group)	0, 200, 400 ppm; 7 h/day, 5 days/wk for 8 months	200 ppm	400 ppm	Increase in relative liver and kidney weights	(Adams et al., 1951)
Rabbits, guinea pigs	0, 200, 400 ppm; 7 h/day, 5 days/wk for 8 months	200 ppm	400 ppm	Increase in relative liver weights	(Adams et al., 1951)
Rats	372 ppm, 30 mins/day for 120 days			Increased liver amino transferases; hyperaemia and degenerative changes in hepatocytes.	(Fonzi et al., 1967)
Rats (Fischer, 12 in exposed group and 4 controls	Continuous exposure for 12 wks. 400 ppm for 2 wks 1500 ppm next 3 wks 600 ppm between weeks 6 & 8. 500 ppm 9th to 12th wk. Average exposure 800 ppm for 12 wks.			Dose reduced because of death of animals. Weight gain reduced in the rats that died. Liver: Increased relative liver weights, centrilobular liver cell enlargement, clumping of Kupffer cells and liver cell necrosis; decreased total plasma cholesterol and triglyceride concentrations; plasma albumin and albumin/globulin ratios slightly increased. Kidney: Relative kidney weights increased; no evidence of gross or microscopic damage; changes in serum urea nitrogen, creatinine and urinary amino acids but not statistically significant; urinary glucose excretion was markedly increased;	(Arai et al., 1988)

Table 22 - Repeated dose toxicity (cont.)

Species	Exposure	NOAEL	LOAEL	Results	Reference
Mice (NMRI), Rats (Sprague-Dawley), Mongolian gerbils	Continuous exposure to 0 or 150 ppm for 30 days.			Liver weights increased in all species with increase in mice more marked.	(Kjellstrand et al., 1981)
Mice(seven strains: wild, C57BL, DBA, B6CBA, A/sn, NZB, NMRI)	Continuous exposure to 0 or 150 ppm for 30 days.			Liver weights increased in all strains with NZB mice the most sensitive.	(Kjellstrand et al., 1983a)
Mice (NMRI, 20/ group)	Exposed intermittently or continuously to between 37 and 3600 ppm for 30 or 120 days	37 ppm for 30 days - no changes in kidney weights		Liver increased in both sexes along with increase in the size of hepatocytes and increased vacuolation of the cytoplasm with variations in the size and shape of nuclei. Kidney weight increased in males exposed to 75 ppm or more and in both sexes exposed to 150 ppm or more for 30 days. Liver and kidney weight changes were reversed following a recovery period of 30 days.	(Kjellstrand et al., 1983b)
Rabbits (8 in group)	2800 ppm; 4 h/day 5 days/wk for up to 50 wks			Degenerative changes in hepatocytes including necrosis noted at necropsy. Some changes also seen in the lung, spleen, brain and occasionally the kidney. No signs of CNS depression, no histopathological changes in heart, adrenals or spinal cord	(Pennarola et al., 1966)
Rats (Sprague-Dawley)	7 h/day, 5 days/wk for 78 wks	100 ppm	300 ppm	Kidney tubule meganucleocytosis in males.	(Maltoni et al., 1986)
Rats (Fischer, 12 males and 12 females/group)	0, 250, 800 and 2500 ppm; 7 h/day, 5 days/wk for 13 wks	250 ppm	800 ppm	Mild neurotoxicity	(Dow Chemical Company, 1993)
		800 ppm	2500 ppm	Evidence of ototoxicity such as elevated auditory brainstem response thresholds and focal loss of hair cells in the cochlea.	

Table 22 - Repeated dose toxicity (cont.)

Species	Exposure	NOAEL	LOAEL	Results	Reference
Guinea pigs, dogs and squirrel monkeys	700 ppm; 8 h/day, 5 days/wk for 6 wks	700 ppm		No clinical chemistry or histopathological changes in the heart, lung, liver, spleen or kidneys.	(Prendergast et al., 1967)
Mice (Female CD-1)	450 ppm, 6 h/day, 5 days/wk for 2 weeks			Marked vacuolation of Clara cells after first exposure; lungs appeared morphologically normal after 4 or 5 exposures, however the Clara cell lesions were observed again when exposure resumed.	(Odum et al., 1992)
Oral exposure					
Rats (F344, 10 of each sex)	males:0, 125, 250, 500 and 1000 mg/kg/day females: 0, 6.25, 125, 250, 500 and 1000 mg/kg/day 5 days/wk for 13 wks	500 mg/kg	1000 mg/kg	Pulmonary vasculitis in 6 males and 6 females and minimal /mild renal tubule cytomegaly and karyomegaly in 5 females and 8 males.	(US National Toxicology Program NTP, 1990)
Mice (B6C3F1)	0, 375, 750, 1500, 3000 and 6000 mg/kg/day 5 days/wk for 13 wks	375 mg/kg	750 mg/kg	Male bodyweight gain reduced and dose- related increase in liver weight.	
Rats (30 of each sex)	0, 50, 250 mg/kg/day for 4 or 5 days/wk for 52 wks	50 mg/kg	250 mg/kg	Kidney tubule meganucleocytosis in males; females not affected.	(Maltoni et al., 1986)
Rats (Male, Alderly Park and Osborne-Mendel). Mice (B6C3F1 and Alderley Park)	TCE in corn oil at 500, 1000 and 1500 mg/kg daily for 10 days.			Increase in liver weights in mice and rats with smaller increases in rats; hepatic DNA concentration was reduced in mice and to a lesser extent in rats; marked increase in DNA synthesis in mice but not in rats; the changes occurred at all dose levels and no dose response relationship was evident. Increased hepatic peroxisomal enzyme activity was noted in mice.	(Elcombe et al., 1985)
Rats (F344 10 males/group)	2000 mg/kg in corn oil once daily for 6 wks; control animals received corn oil only.			Relative kidney and liver weights increased; plasma ALP levels were increased; urinary volume and urinary protein, glucose, ALP and NAG all increased; histopathology showed liver hypertrophy but no changes in the kidneys.	(Green et al., 1990)

10.5 Immunotoxicity

Immunotoxic effects of trichloroethylene have been assessed in mice. Impairment of the cell mediated immune response to sheep erythrocytes was reported in mice given doses of 24 or 240 mg/kg by gavage daily for 14 days. No effects were observed on the humoral immune response (Tucker et al., 1982). Mice exposed to trichloroethylene in drinking water at doses of 18 - 800 mg/kg for 6 months have exhibited depressed cell and humoral mediated immune response. In mice exposed by gavage to 24 or 240 mg/kg for 14 days, a significant inhibition of cell mediated immunity was noted in males (Sanders et al., 1982).

10.6 Reproductive toxicity

10.6.1 Fertility

Short-term inhalation exposure of mice resulted in sperm abnormalities with no effects being seen in rats. Sperm morphology was affected in mice at 2000 ppm in short-term studies with a NOAEL of 200 ppm (Land et al., 1981). These findings are not consistent with the results of long-term oral exposure. Long term oral exposure studies indicate that effects on fertility (reduced sperm motility) are seen in animals only at doses that produce general toxicity. The LOAEL for fertility effects was 750 mg/kg/day in mice and 150 mg/kg/day in rats while the NOAEL for fertility effects was 350 mg/kg/day in mice and 75 mg/kg/day in rats (US National Toxicology Program, 1990).

Table 23 summarises the studies carried out to assess effects on fertility and developmental toxicity of trichloroethylene.

10.6.2 Developmental toxicity

Several developmental studies have been conducted according to conventional test guidelines. No clear evidence of developmental toxicity was reported in any of these studies. The UK SIAR has described three studies from the same laboratory that suggest maternal exposure to trichloroethylene in drinking water in rats at doses ranging from 28-110 mg/kg/day produce increased locomotor activity, a decrease in the 2-deoxyglucose uptake by the brain and a decrease in the number of myelinated fibres in one region of the brain (Taylor et al., 1985; Noland-Gerbac et al., 1986; Isaacson & Taylor, 1989). The significance of these findings is not clear but they are of concern as the findings indicate a potential for trichloroethylene to induce developmental neurotoxicity.

Table 23 - Effects on fertility and development in animals

Species	Exposure	NOAEL	LOAEL	Results	Reference
Fertility					
Inhalation exposure					
Mice	0, 200, 2000 ppm, 4 h/day for 5 days	200 ppm	2000 ppm	Abnormal sperm	(Land et al., 1981)
Rats (Sprague-Dawley, 12/group) Mice (CD-1, 12/group)	0, 100 or 500 ppm, 7 h/day for 5 days. Animals killed at 1, 4 or 10 wks after dosing.		100 ppm	No effect on sperm in rats; however no effect seen in positive controls (TEM i.p.). Statistically significant increase in the frequency of abnormal sperm in mice at the highest dose at week 1 and 4 and in week 4 at the lowest dose. The background incidence of sperm abnormalities was variable.	(National Institute for Occupational Safety and Health (NIOSH), 1980)
Oral Exposure					
Mice (CD-1, 20 males and females/group control group of 40 animals/sex.)	Task 1: preliminary 14 day feeding study. Task 2: 14 wk co-habiting phase when reproductive performance monitored. Continuously exposed to concentrations of 0.15, 0.3 or 0.6% (approx. 187, 350 or 750 mg/kg/day) in the diet during a 1 wk premating period and 17 wk mating trial (Task 2). Task 3: "cross-over" mating trial; control males with high dose females and vice versa. Not conducted. Task 4: reproductive - 20 males and 20 females (F_0 generation). 40 animals of each sex included in the control group. 20 male and 20 female F_1 generation offspring from control and high dose groups were retained for assessment of reproductive capacity. After sexual maturity, each F_1 female was paired with a F_1 male for 7 days.	350 mg/kg/day	750 mg/kg/ day	Significant reduction in body weight at dietary TCE concentrations = 1.2%. No clinical signs of toxicity or adverse effects on bodyweight gain among F_0 generation. No effect on fertility. Number of litters produced and litter sizes similar for treated and control group. Fertility of reared F_1 generation not affected by treatment. At necropsy, in the Fo and F_1 at the highest dose level relative liver weights for both sexes were increased by 30-40% relative to controls and the proportion of motile sperms was 43% compared with 78% in controls. Hypertrophy of the centrilobular liver cells and renal tubular degeneration and karyomegaly of the tubular cells observed.	(US National Toxicology Program (NTP), 1986)

Table 23 - Effects on fertility and development in animals (cont.)

Species	Exposure	NOAEL	LOAEL	Results	Reference
Rats (F344)	75, 150, 300 mg/kg/day; same protocol as previous study except that task 3 was conducted. Task 4 the reproductive capacity from all 4 groups was assessed and the F_1 generation was evaluated at 21 and 45 days of age.	75 mg/kg/day	150 mg/kg/ day	A dose related reduction in body weight in both sexes in F_1 generation; at the high dose a slight but statistically significant reduction in the number of litters produced by F_0 pairs; at the middle and high dose, a decrease in litter size was observed. No effects on fertility in the F_0 generation cross-over mating trial. At necropsy, relative liver weight was increased in both sexes in the high dose group and combined left testis/epididymis mean weight was increased in the high dose group. In the F1 generation relative liver weight was increased in males at all doses and in females at the middle and high doses.	(US National Toxicology Program (NTP), 1986)
Rats (Long-Evans hooded, 23 females/group)	Gavage doses of 0, 10, 100 and 1000 mg/kg/day for 5 days/wk 2 wks prior to mating and during mating and 7 days/wk throughout pregnancy.	100 mg/kg/day	1000 mg/kg/day	Maternal body weight gain was significantly reduced at the highest dose during premating period and pregnancy; pup survival to weaning was also significantly reduced at the highest dose.	(Manson et al., 1984)
Rats (Long-Evans, 10 males/group)	0, 10, 100, 1000 mg/kg/day 5 days/wk for 6 wks followed by 4 wks recovery period			Reduced bodyweight gain and increased liver weight at 1000 mg/kg/day; males neglected females for prolonged periods and there were numerous instances of incomplete genital contact; sperm parameters and testosterone levels not affected at any dose.	(Zenick et al., 1984)
Rats	1000 mg/kg			Increased ejaculation latency which was blocked by naltrexone.	(Nelson & Zenick, 1986)
Developmental toxicity					
Inhalation exposure					
Rats (Sprague-Dawley, female Rabbits (New Zealand White)	0, 500 ppm for 7h/day during pregnancy; for rats exposure periods were from days 0-18 or 6-18 of pregnancy; for rabbits exposure was from days 0-21 or 7-21; some groups were exposed to 500 ppm for 3 wks prior to mating.			No clear evidence of maternal or developmental toxicity in either species. Four rabbit foetuses from the group exposed during pregnancy from days 0-21 had hydrocephalus.	(National Institute for Occupational Safety and Health (NIOSH), 1980)

Table 23 - Effects on fertility and development in animals (cont.)

Species	Exposure	NOAEL	LOAEL	Results	Reference
Rats (Long-Evans hooded, 30 females/group)	1800 ppm either for 2 wks prior to mating and throughout pregnancy or prior to mating alone or during pregnancy alone; half of the mothers in each group were killed on day 21 of pregnancy			No evidence of maternal toxicity. Slight increase in the incidence of visceral and skeletal abnormalities in the group with exposure during pregnancy alone.	(Dorfmueller et al., 1979)
Mice (female Swiss-Webster); 12 treated and 26 controls. Rats (Sprague-Dawley), 18 treated and 30 controls	0 or 300 ppm for 7 h/day from day 6 to 15 of pregnancy.			No evidence of maternal or developmental toxicity.	(Schwetz et al., 1975)
Rats (Wistar, 32 treated females and 31 controls)	100 ppm for 4 h/day from days 8 to 21 of pregnancy.			No information on maternal toxicity. Increased total litter loss in the exposed group.	Healy et al, 1982
Oral Exposure					
Rats (Female Sprague-Dawley rats)	Exposed to 0, 312, 625 or 1250 mg/l via drinking water for 2 wks prior to mating, during pregnancy and lactation until weaning of offspring on day 21. Dosages were estimated to be 35, 60 and 110 mg/kg/day			No data presented on maternal toxicity. Increased exploratory activity of offspring from all the exposed groups at 60 days of age. At 90 days of age, exploratory activity was significantly increased in the offspring from the highest exposure group	(Taylor et al., 1985)
Rats (Female Sprague-Dawley)	0 or 312 mg/l in drinking water with an estimated daily intake of 45 mg/ kg/day. Same schedule as previous study. Two male pups from each litter killed at 7, 11, 16 and 21 days and uptake of 2-deoxy-glucose in the hippocampus, cerebellum and total brain was determined.			Uptake of 2-deoxyglucose by brain tissue was depressed at all sampling times.	(Noland-Gerbac et al., 1986)
Rats (Sprague-Dawley, 6 females/group)	0, 312 or 625 mg/l in drinking water with the estimated daily dose being 0, 28 and 56 mg/kg/day.			Decrease in the number of myelinated fibres in the hippocampal region.	(Isaacson & Taylor, 1989)

10.7 Genotoxicity

Trichloroethylene has been investigated in a number of *in vitro* and *in vivo* test systems. The genotoxicity of trichloroethylene has been reviewed extensively by IARC (1995); Fahrig et al (1995) and by the UK in the UK SIAR (1996). The description below is based mainly on the UK SIAR. Data on the genotoxic effects of trichloroethylene metabolites are from IARC (1995). Three published studies (Fahrig, 1977 ; Duprat & Gradiski, 1980; Kligerman et al., 1994) have been assessed in this report as the interpretation of the results of these three studies differed in the above reviews. Two published articles describing tests conducted in mice and indicative of point mutation were reviewed during this assessment: a mouse spot test and mouse pink-eyed unstable mutation.

10.7.1 *In vitro* tests

Genotoxicity studies for trichloroethylene are summarised in Table 24. Briefly reported studies are not included in the table.

Bacterial tests

Trichloroethylene used industrially is stabilised to prevent auto-oxidation. Epichlorohydrin was one of the stabilisers used but its use has been discontinued as it was found to be carcinogenic. Mixed amines are now used as stabilisers. Early mutagenicity studies using trichloroethylene stabilised by epichlorohydrin and 1,2-epoxybutane reported positive results in *S. typhimurium* assays either with or without an exogenous metabolising system. These epoxide stabilisers in vapour form, when tested alone, in *S. typhimurium* strains TA1535 and TA100 were also found to be mutagenic in low concentrations (McGregor et al., 1989). It is therefore difficult to interpret genotoxicity studies with trichloroethylene containing these stabilisers.

Epoxide-free trichloroethylene vapour in three studies did not induce mutations in various strains of *S. typhimurium* in the presence or absence of an exogenous metabolising system. Three studies reported positive results in the presence of a metabolising system. In a further three briefly reported studies trichloroethylene produced positive responses according to the authors (Riccio et al., 1983; Milman et al., 1988; Warner et al., 1988). The study by Crebelli et al (1982) reported a small dose-related statistically significant increase in the number of revertants per plate that was reproducible in nine experiments. There was no increase in the number of revertants in the absence of metabolic activation.

Trichloroethylene liquid (purity >99.9%) was not mutagenic in various strains of *S. typhimurium* in the presence or absence of an exogenous metabolising system with toxicity seen at the highest concentration tested (Henschler et al., 1977; Mortelmans et al., 1986).

Analytical grade trichloroethylene induced arg^+ reverse mutations but not forward mutations or gal^+ or nad^+ reversions in *E. coli* (Greim et al., 1975).

Fungal tests

Epoxide-free trichloroethylene was tested in *Schizosaccharomyces pombe* and various strains of *Saccharomyces cerevisiae* either in the presence or absence of an exogenous metabolising system. In most of these assays, trichloroethylene tested positive. Of the positive studies, the increase in colonies of *Saccharomyces cerevisiae* strain D61.M in one study was thought to be due to "respiratory deficiency" (Whittaker et al., 1990) in the UK SIAR, and a dose-related increase in the number of colonies seen with strain D61.M in the second (Koch et al., 1988) was considered by the authors to indicate aneuploidy. In two other studies positive results were only seen at concentrations toxic to the cells (Shahin & Von Borstel, 1977; Callen et al., 1980). No information on the presence or absence of stabilisers was provided in any of the studies.

Mammalian cells

Three mouse lymphoma L5178Y/TK$^{+/-}$ mutation tests reported positive results in the presence of metabolic activation provided by rat liver S9 fraction. Of these, two (Caspary et al., 1988; Myhr & Caspary, 1991) are reported to be further reports of the experiment described by NTP (1988). Another positive experiment was only available as an abstract (Rudd et al., 1983). The assays were negative in the absence of S9.

Trichloroethylene tested negative in two *in vitro* chromosomal aberration tests and in a sister chromatid exchange (SCE) assay whilst the results were equivocal in another SCE assay. Trichloroethylene did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes as assessed by autoradiography. Assays using scintillation counting techniques have reported positive results (Table 24). One SCE test was considered equivocal as the frequencies in the exposed cells were within the background range of negative controls.

10.7.2 *In vivo* tests

In vivo assays conducted to assess genotoxicity of trichloroethylene are summarised in Table 25.

Host-mediated assays

A host-mediated assay using mice (National Institute for Occupational Safety and Health (NIOSH), 1980) did not provide any conclusive evidence of the mutagenic activity of trichloroethylene (purity >99.9%) in *S. typhimurium* strain TA98, as an appropriate response was not observed in the positive control group.

A host-mediated assay was conducted by Bronzetti et al (1978) and showed an increased number of mutants in cultures from the liver and kidneys but not from the lungs. Groups of 3 to 4 mice were treated with an oral dose of 400 mg/kg of trichloroethylene followed by instillation of yeast cultures. Some groups received additional oral exposure to 150 mg/kg/day prior to instillation. The animals received 22 administrations of trichloroethylene over a 4 week period. The purity of trichloroethylene was not specified in either of these studies.

Micronucleus tests

Four micronucleus tests were reported in the U.K. SIAR. Of these, one was reported to be negative (Shelby et al., 1993) and a positive study (Sbrana et al., 1985) was only reported to be available as an abstract. The other two studies (Duprat & Gradiski, 1980; Kligerman et al., 1994) have been reviewed as part of this assessment.

Kligerman et al (1994) exposed rats and mice to a single 6 h exposure by inhalation of 0, 5, 50, 500 or 5000 ppm of reagent grade trichloroethylene. The only significant effect seen was a dose-related increase in micronuclei in rat bone marrow polychromatic erythrocytes (PCEs). At 5000 ppm the increase was approximately four-fold and was reproducible. Animals in the 5000 ppm group displayed signs of toxicity such as tremors and paralysis. Evidence of cytotoxicity was also observed at this level with a significant reduction in the percentage of PCEs in bone marrow. The authors state that their findings of micronucleus induction without the presence of chromosomal aberrations and the large size of the micronuclei may be indicative of spindle effects such as aneuploidy. No statistically significant cytogenetic changes were seen in mice similarly exposed. Groups of rats were also exposed for 6 h/day for 4 days to 0, 5, 50 or 500 ppm of trichloroethylene. The number of micronuclei in bone marrow PCEs was comparable to the 1-day study. However, the number of micronuclei in the concurrent control in the 4-day study was unusually high and hence the results were not statistically different from the control. There was no increase in micronucleated peripheral blood leukocytes (PBL) with single or repeated exposures.

A dose-related increase in the number of micronucleated PCEs in mice was also reported by Duprat and Gradiski (1980) with analytical grade trichloroethylene. Groups of 10 CD1 strain mice were treated orally with trichloroethylene dispersed in a vehicle at doses of 3000, 2250, 1500, 1125, 750 and 375 mg/kg. The study also included an untreated control group (20 animals), a vehicle group (0.5 ml/20 gms of a 10% gum arabic solution) and a positive control group (100 mg/kg of cyclophosphamide). The mice were treated with two single doses separated by 24 h and were killed 16 h later and bone marrow smears examined. However the significance of this study is limited by the uncertainties of the scoring method used (micronuclei, including microbodies appearing to be of nuclear origin) and the unusually high frequency of micronucleated PCEs in the control group. The micronucleus frequency in the untreated and vehicle control groups also differed significantly from each other.

Chromosomal aberrations and sister chromatid exchange

According to the UK SIAR, trichloroethylene did not induce chromosomal aberrations or sister chromatid exchange in 2 assays each.

Tests for UDS, DNA binding and damage

Induction of unscheduled DNA synthesis was also reported to be negative in two assays. The SIAR also reported 6 tests investigating DNA interaction in rats and mice. Of these, 3 were positive and 3 negative.

DNA interactions

Trichloroethylene induced DNA single strand breaks in two studies. DNA binding could not be demonstrated *in vivo* in the tissues of mice in one study or in the liver of rats in another study. However, a low level of interaction with DNA of rat and mouse liver, kidney, lungs and stomach was reported by Mazullo et al (1992).

Germ cell assays

Trichloroethylene did not increase the frequency of micronuclei in spermatids in mice following inhalation exposure nor induce dominant lethal mutations in mice or in rats.

Mouse spot test

In a mouse spot test the number of offspring with spots presumed to result from somatic mutation were 2 of 145 at 140 mg/kg and 2 of 51 at 350 mg/kg after a single intra-peritoneal dose of trichloroethylene (99.5%). In the pooled negative control group 1 of 794 had genetically relevant spots (Fahrig, 1977). The survival of offspring in the treated groups was low compared with the control. The results are considered to be equivocal because of the unusually low frequency of spots in the control group.

Mouse pink-eyed unstable mutation

Highest purity grade trichloroethylene in corn oil was administered intra-peritoneally to mice homozygous for pink eyed dilution (C57BL/6J pun/pun) at a dose of 200 mg/kg, 10.5 days postconception. The mice were observed for the frequency of spontaneous and chemical-induced spots. A positive response was noted. Spontaneous frequency varied between 4 and 11 %. Control animals injected with corn oil alone had a spotting frequency of 3.9% while trichloroethylene caused 32% spotting. Trichloroethylene caused sedation in the female adult mice because of its anaesthetic effect. The litter size was also reduced in the trichloroethylene treated group. The pun mutation causes a dilution of the pigment in coat colour and eye colour and reversion of the pun mutation is scorable as black spots on the dilute coat (Schiestl et al., 1997). A positive response was noted in this preliminary study.

Table 24 - Genotoxicity of trichloroethylene *in vitro*

Species (Test system)	End Point	Results		Comments	Reference
		With Activation	Without Activation		
Prokaryotic organisms					
Trichloroethylene vapour					
S. typhimurium TA100	gene mutation	+	-	Reproducible, dose related, statistically significant increase in the number of revertants/plate.	(Crebelli et al., 1982)
S. typhimurium TA98, TA100	gene mutation	-	-	Non-toxic concentrations of up to 20% used.	(McGregor et al., 1989)
S. typhimurium TA100, TA1535	gene mutation	-	-	Toxicity seen at the highest concentration tested. Results not confirmed by independent study.	(Shimada et al., 1985)
S.typhimurium TA100, TA1535	gene mutation	-	-	No effects seen at concentrations up to 10%.	(Waskell, 1978)
S. typhimurium TA100	gene mutation	+	-	Mean 135 revertants/plate at a concentrations of 5%, 75/plate in unexposed plates. Reproducibility not investigated.	(Bartsch et al., 1979)
S. typhimurium TA 100	gene mutation	+	-	Statistically significant and reproducible increase at concentrations of 1 and 3%. Increase was not dose dependent and about 30% above background rate.	(Baden et al., 1979)
Trichloroethylene liquid					
S. typhimurium TA98, TA100, TA1535, TA1537	gene mutation	-	-	Toxicity seen at the highest concentration tested.	(Mortelmans et al., 1986)
S. typhimurium, TA100	gene mutation	-	-	Not clear if toxic concentrations included in the assay.	(Henschler et al., 1977)
E. coli	gene mutation	+	-	Non-standard test system used.	(Greim et al., 1975)

Table 24 - Genotoxicity of trichloroethylene *in vitro* (cont.)

Species (Test system)	End Point	Results		Comments	Reference
		With Activation	Without Activation		
Eukaryotic cells					
Fungal tests					
S. pombe	gene mutation	-	-	Up to toxic concentrations used	(Rossi et al., 1983)
S. *cerevisiae*, D61.M	gene mutation	+		Increased number of colonies may have been due to "respiratory deficiency" and not due to chromosome loss. No indication if testing done with or without S9.	(Whittaker et al., 1990)
S. *cerevisiae*, D7	gene mutation	-	-	Moderately toxic concentrations used; a dose related response considered by authors to be due to induction of aneuploidy.	(Koch et al., 1988)
D61.M		+	+		
S. *cerevisiae* D7	gene mutation	not tested	+	Concentration used produced moderate cytotoxicity.	(Callen et al., 1980)
S. *cerevisiae* D4, D7	gene mutation	+	-	Toxic levels included in concentrations tested; 50% survival at the highest concentration.	(Bronzetti et al., 1978)
S. *cerevisiae* XV 185-14C	gene mutation	+	-	Response only at concentrations toxic to the yeast cells.	(Shahin & Von Borstel, 1977)
Aspergillus nidulans 35, 35x17	gene mutation		+	Not internationally validated.	(Crebelli et al., 1985)
Mammalian cells					
Mouse lymphoma L5178Y/tk	gene mutation	+	-	Reproducible doubling compared to control at the highest concentration	(US National Toxicology Program NTP, 1988)
		+	-	Probably further reports of the NTP experiment.	(Caspary et al., 1988); (Myhr & Caspary, 1991)
		+	-		
Chinese hamster ovary (CHO) cells	chromosomal aberration	-	-	14.9 mg/L was the highest concentration used.	(US National Toxicology Program NTP, 1988); (Galloway et al., 1987)
		-	-		

Table 24 - Genotoxicity of trichloroethylene *in vitro* (cont.)

Species (Test system)	End Point	Results		Comments	Reference
		With Activation	Without Activation		
Chinese hamster ovary (CHO) cells	sister chromatid exchange	-	-	Toxic levels not used limiting the value of the test	(White et al., 1979)
Chinese hamster ovary (CHO) cells	sister chromatid exchange	(+)	(+)	Frequencies of SCEs in the exposed cells were within the background range of negative controls.	(Galloway et al., 1987)
Rat hepatocytes	unscheduled DNA synthesis	-	-	Cytotoxic concentrations used. Autoradiography used to assess UDS.	(Shimada et al., 1985)
Human WI-38 cells	unscheduled DNA synthesis	+	+	Dose response relationship not evident. An appropriate response not observed in positive controls.	(National Institute for Occupational Safety and Health (NIOSH), 1980)
Rat hepatocytes treated with phenobarbital	unscheduled DNA synthesis	+		Not clear if adequate number of replicates used.	(Costa & Ivanetich, 1984)
Human lymphocytes	unscheduled DNA synthesis	+			(Perocco & Prodi, 1981)

\+ positive - negative (+) equivocal

Table 25 - Genotoxicity of trichloroethylene *in vivo*

Species	Endpoint	Method	Results	Reference
Host mediated assay				
S. typhimurium TA98 recovered from mouse	gene mutation	Groups of 5 mice of both sexes exposed (inhalation) to 100 or 500 ppm of TCE. 10^{10} bacterial cells was injected i.p. and cells recovered 3 h later in i.p. fluid. Negative and positive controls included.	No clear evidence in TCE treated group. Appropriate response not obtained in the positive control.	(National Institute for Occupational Safety and Health (NIOSH), 1980)
S.cerevisiae D4 recovered from mouse liver, lungs and kidneys; D7 recovered from liver, lungs and kidneys.	gene mutation	Mice (3-4/grp) treated with a single oral dose of TCE at 400 mg/kg.	+	(Bronzetti et al., 1978)
		Further groups received repeated oral exposure of 150 mg/kg/day (22 over 4 wks).The animals also had intrasanguinous instillation of yeast cultures ($2x10^9$).	+	(Bronzetti et al., 1978)
Drosophila melanogaster	sex-linked recessive lethal test	Not clear if exposure included toxicity levels. Result not confirmed in a separate experiment.	-	(National Institute for Occupational Safety and Health (NIOSH), 1980)
Micronucleus tests Mouse polychromatic erythrocytes	micronucleus test	B6C3F1 strain (4-6 males/grp) received 3 daily injections of 0, 500, 1000 and 2000 mg/kg and killed 24 h after last injection. Test was repeated at 1, 2000 and 2500 mg/kg.	- Mortality noted at 2000 and 2500 mg/kg	(Shelby et al., 1993)
Bone marrow erythrocytes in rats	micronucleus test	Single 6 h exposure by inhalation of 0, 5, 50, 500 and 5000 ppm. Tremors and paralysis in the 5000 ppm group.	+ (single dose) Authors believe may be due to aneuploidy.	(Kligerman et al., 1994)
Bone marrow erythrocytes in mice	micronucleus test		-	(Kligerman et al., 1994)
Peripheral blood leukocytes (PBL) in rats and splenocytes in mice	chromosomal aberrations		-	(Kligerman et al., 1994)
	sister chromatid exchange;		-	
	micro-nuclei induction		-	

Table 25 - Genotoxicity of trichloroethylene *in vivo* (cont.)

Species	Endpoint	Method	Results	Reference
Bone marrow erythrocytes in rats		Groups of rats exposed to 0, 5, 50 or 500 ppm 6 h/day for 4 days.	-	(Kligerman et al., 1994)
Polychromatic erythrocytes in CD1 mice	micronucleus test	Oral doses of 0, 375, 750, 1125, 2250 and 3000 mg/kg given to 10 CD-1 mice. Two single doses separated by 24 h were given and the animals killed 16 h later.	+ Frequency of micronucleated PCEs in the control groups was unusually high. Uncertainty regarding the counting method used	(Duprat & Gradiski, 1980)
Polychromatic erythrocytes	Micronucleus	Single oral dose of 1200 mg/kg to mice. Only abstract available	+	(Sbrana et al., 1985)
Chromosomal Aberrations & Sister Chromatid Exchange				
Rat bone marrow cells	chromosomal aberrations	Sprague-Dawley rats, 10 males and females/group given either a single 7 h exposure or 5 daily 7 h exposures at 0, 100 or 500 ppm. Bone marrow cells sampled at 6, 24 or 48 h after single exposure. For repeated exposures 6 h after the last exposure.	- (inhalation)	(National Institute for Occupational Safety and Health (NIOSH), 1980)
	Chromosomal aberrations sister chromatid exchange	Briefly reported studies.	- (oral)	(Loprieno & Abbondandolo, 1980)
			- (intraperitoneal)	(Cerna & Kypenova, 1977)
UDS Assays				
Rat and mice hepatocytes	Unscheduled DNA synthesis	Fischer 344 rats and B6C3F1 mice (3/group) received oral doses of 50, 200 and 1000 mg/kg. Animals killed 2 or 12 h after treatment and primary hepatocyte cultures prepared.	- Evidence of hepatocellular proliferation, more marked in males.	(Mirsalis et al., 1989)
Transgenic muta mouse				
Mouse	Transgenic muta mouse	Groups of mice exposed to 0, 200, 1000 and 2000 ppm, 6 h/day for 12 days. Highest dose was the maximum tolearted dose..	-	(Douglas & et al., 1995)

Table 25 - Genotoxicity of trichloroethylene *in vivo* (cont.)

Species	Endpoint	Method	Results	Reference
Mouse Spot test				
Mouse	Spot test	Single dose given by i.p. at 140 or 350 mg/kg on day 11 of pregnancy.	(+)	(Fahrig, 1977)
Pink eyed unstable mutation				
Mouse	Pink-eyed unstable mutation	C57BL/6J pun/pun mice were given 200 mg/kg TCE i.p. 10.5 days postconception. Matings were set up between pun mice, p[-] mice or between pun and p[-] mice	+	(Schiestl et al., 1997)
Tests for DNA interaction				
Rat and mouse liver, kidneys, lungs and stomach	DNA interaction		(+)	(Mazzullo et al., 1992)
Mouse liver, oral, i.p.	DNA alkylation	Single oral dose of 1200 mg/kg of TCE to a group of 4 mice. Animals killed 5 h after dose.	-	(Stott et al., 1982)
Mouse liver, i.p.	DNA strand breaks	Single i.p. doses of between 10 and 1000 mg/kg	-	(Parchman & Magee, 1982)
Rat and mouse liver	DNA single strand breaks	Oral administration of 3 to 4 mg/kg to TCE to male Sprague-Dawley rats and 1.5 mg/kg to male B6C3F1 mice..	+	(Nelson & Bull, 1988)
Mouse liver and kidneys	DNA single strand breaks (SSB)	I.P. administration of TCE	+	(Walles, 1986)
Mouse lung	DNA SSB	I.P. administration of TCE	-	(Walles, 1986)
Gem Cell Assays				
Mice	Dominant lethal mutations	50 male mice exposed to a single 24 h inhalation to TCE at 0, 50, 200, and 450 ppm. Toxic concentrations of TCE not used.	-	(Slacik-Erben et al., 1980)
Rats	Dominant lethal mutations	High frequencies of dead implantations in the negative control group.	-	(National Institute for Occupational Safety and Health (NIOSH), 1980)
Mouse spermatids	Micronuclei frequency	C57B1/6J mice (6/group)exposed by inhalation to 0, 5, 50 or 500 ppm for 6 h/day for 5 days. No data provided on general toxicity.	-	Allen et al, 1994

10.7.3 Trichloroethylene metabolites

Trichloroethylene metabolites may be responsible for cytotoxicity in the liver and extrahepatic organs and therefore the mutagenic effects of these metabolites need to be considered. Data on trichloroethylene metabolites in this report were obtained from IARC (1995) and the original studies and articles have not been sighted. Data reported for dichlorovinyl cysteine is a summary of data reported in the Documentation for the MAK evaluation of trichloroethylene.

Chloral hydrate

Chloral hydrate is mutagenic only in *S. typhimurium* strains TA100 (Haworth et al., 1983) and TA 104 (Ni et al., 1994). It did not induce reverse mutations in *S. cerevisiae*. However, induction of gene conversion in the absence of metabolic activation was observed (Bronzetti et al., 1984). Chloral hydrate induced somatic mutations in *Drosophila melanogaster* in a wing-spot test (Zordan et al., 1994). Chloral hydrate did not induce single strand breaks in rat hepatocytes *in vitro*. Frequency of micronuclei was increased in Chinese hamster cell lines. In mammalian cell cultures chloral hydrate induced genetic effects such as chromosomal aberrations (Degrassi & Tanzarella, 1988; Furnus & et al., 1990), aneuploidy (Furnus & et al., 1990; Vagnarelli et al., 1990; Natarajan, 1993; Sbrana et al., 1993) and micronuclei (Degrassi & Tanzarella, 1988; Migliore & Nieri, 1991; Bonatti & et al., 1992; Lynch & Parry, 1993).

Chloral hydrate did not induce chromosomal aberrations *in vivo* in rat (Leuschner & Leuschner, 1991) or mouse (Xu & Adler, 1990) bone marrow cells or in mouse spermatocytes (Russo & Levis, 1992a.). Conflicting results were observed in micronucleus tests using mouse bone marrow cells. Weakly positive results were obtained in some experiments (Gudi & et al., 1992; Russo & Levis, 1992a.; Russo & Levis, 1992b.; Leopardi & et al., 1993) while negative results were reported by others (Bruce & Heddle, 1979; Adler & et al., 1991; Leuschner & Leuschner, 1991).

Chloral hydrate induced aneuploidies in mouse spermatocytes (Russo et al., 1984; Liang & Pacchierotti, 1988; Miller & Adler, 1992) but not in mouse oocytes (Mailhes & et al., 1988.; Mailhes et al., 1993).

Trichloroacetic acid

Trichloroacetic acid is not mutagenic to *S. typhimurium* strains in the presence or absence of metabolic activation (Shirasu et al., 1976; Waskell, 1978; Nestmann et al., 1980; Rapson et al., 1980, Moriya, 1983; Moriya et al., 1983; DeMarini et al., 1994). It did not induce DNA strand breaks in mammalian cells *in vitro*. DNA strand breaks were not observed in the livers of rats or mice (Chang et al., 1992). Chromosomal aberrations were not induced in human lymphocytes *in vitro* (Mackay et al., 1995). Trichloroacetic acid induced micronuclei and chromosomal aberrations in bone marrow cells and abnormal sperm morphology in Swiss mice *in vivo* (Bhunya & Behera, 1987). However, no micronucleus induction was observed in another study when a 10-fold higher dose was used in a different strain of mouse (Mackay et al., 1995).

Dichloroacetic acid

Dichloroacetic acid was mutagenic to *S. typhimurium* TA98 (Herbert et al., 1980) and TA100 (DeMarini et al., 1994) while other studies have reported negative results with TA1535, TA1537, TA1538 and TA100 (Herbert et al., 1980). Dichloroacetic acid did not induce single strand breaks in mammalian cells *in vitro* in the absence of an activating system (Chang et al., 1992). The *in vivo* results were conflicting with DNA strand breaks observed in mouse and rat hepatic cells pretreated with dichloroacetate but no effects after a single dose of 500 mg/kg and after repeated dosing (Nelson & Bull, 1988). No effects on DNA were observed in mouse hepatocytes, splenocytes, epithelial cells from stomach and duodenum and in rat hepatic cells following repeated dosing (Chang et al., 1992).

Dichlorovinyl cysteine

Dichlorovinyl cysteine was mutagenic in *S. typhimurium* in the presence of rat kidney S9 (Dekant et al., 1986). The 1,2-isomer and its mercapturic acid were more potent mutagens than 2,2-dichlorovinyl cysteine and its mercapturic acid (Commandeur et al., 1991). The mutagenic activity of 1,2-dichlorovinyl cysteine was inhibited by inhibition of β-lyase activity (Vamvakas et al., 1988a). 1,2-dichlorovinyl cysteine induced an increase in DNA repair in cultured kidney cells (Vamvakas et al., 1989b).

10.8 Carcinogenicity

A number of long term animal studies (in hamsters and various strains of rats and mice) by the oral and inhalation routes have demonstrated that trichloroethylene is carcinogenic in rats and mice. Details of the carcinogenicity studies in animals are shown in Table 26.

Table 26 -Carcinogenicity studies in animals

Trichloroethylene grade	Dose & Duration	Species	Results	References
Inhalation Exposure				
Epoxide-free, stabilised with 0.0015% triethanolamine	0, 100 or 500 ppm 6h/day, 5 days/week for 18 months and observed until 30 (mice, hamsters) and 35 (rats) months.	Wistar rat, NMRI mice, Syrian hamster. Thirty animals per sex in each group	Rats and hamsters: incidence of tumours similar to controls. Mice: In females statistically significant increase in animals with malignant lymphomas at 100 and 500 ppm. High incidence among control females and NMRI mice are known to have a high spontaneous incidence of lymphomas.	(Henschler et al., 1980)
Purified, epoxide-free	0, 100, 300 or 600 ppm, 7 h/day, 5 days/week. Mice exposed for 8 or 78 wks, rats for 8 or 104 wks. Animals observed for life.	Sprague-Dawley rats B6C3F1, Swiss strains of mice. Ninety animals of each sex.	Rats: No tumours after 8 wks exposure. General toxicity limited to kidney tubule meganucleocytosis following long term exposure to 300 and 600 ppm. Kidney tubular adenocarcinoma in 4 males and cortical adenocarcinoma in 1 female at 600 ppm. Dose-related statistically significant increase in the incidence of Leydig cell tumours. Swiss mice: In male mice lung adenomas were significantly increased at 100 and 300 ppm and incidence of hepatocellular adenomas and carcinomas was significantly greater than controls at 600 ppm. B6C3F1 mice: In females there was a dose-related increase in lung adenomas at 600 ppm. There was an increase in hepatomas in both sexes.	(Maltoni et al., 1986)
Reagent grade, 99.82% pure with 0.019% impurities including epichlorohydrin.	0, 50, 150 and 450 ppm, 7h/day, 5 days/wk for 2 yrs and an observation period of 3 wks.	Female ICR mice and female Sprague-Dawley rats, 50 animals in each group	No evidence of general toxicity and in survival rates. Mice: the incidence of lung adenocarcinomas was significantly greater than controls at 150 ppm and 450 ppm. Rats: No evidence of tumours.	(Fukuda et al., 1983)

Table 26 -Carcinogenicity studies in animals (cont.)

Trichloroethylene grade	Dose & Duration	Species	Results	References
Oral Exposure				
Epoxide-stabilised, purity 99%, with 0.2% 1,2 epoxybutane and 0.19% epichlorohydrin.	Rats: approx 1097 mg/kg/day and 549 mg/kg/day. Mice: approx 2339 and 1169 and 1739 and 869 mg/kg/day for males and females respectively. Administered by gavage, vehicle control group of 20 animals/sex included. Animals dosed for 78 wks 5 days a wk. Study terminated at 90 wks for mice and 110 wks for rats.	Osborne-Mendel rats and B6C3F1 mice. Fifty animals of each sex per group. .	Rats: Low survival rate in treated and control animals. No evidence of carcinogenicity. Mice: Increased incidence of hepatocellular carcinomas in low and high dose groups of males and females.	(National Cancer Institute (NCI), 1976)
Epoxide-free, "Hi-Tri" grade, >99.9% with 8 ppm amine stabiliser.	Rats: 500 or 1000 mg/kg/day. Mice: 1000 mg/kg/day, 5 days/wk for 103 wks. Gavage administration. Vehicle (corn oil) and untreated control groups included.	F344/N rats and B6C3F1 mice. Fifty animals of each sex per group.	Rats: male survival rate significantly reduced in treated group compared to controls. Female survival not affected. Renal cytomegaly was observed in most treated animals of both sexes. A low but statistically significant incidence of renal tubular cell adenomas and adenocarcinomas in males in the treated groups. Adenomas in 2 animals of the low dose group. No tumours in females. Mice: Male survival rate and body weight were reduced. Renal cytomegaly was seen in treated groups in both sexes. Increased incidence of hepatocellular carcinomas and adenomas in the treated animals.	(US National Toxicology Program NTP, 1990)
Epoxide-free, "Hi-Tri" grade, >99.9% with 8 ppm amine stabiliser	Rats: Gavage doses of 500 or 1000 mg/kg/day, 5 days/wk, for 103 wks. Vehicle and untreated control groups included.	ACI, August, Marshall and Osborne-Mendel rats. Groups of 50 animals of each strain and sex per group.	Low survival in many of the treated groups. Low incidence of kidney tubular cell carcinomas and adenomas in the treated groups. Severe kidney toxicity with kidney tubular cell cytomegaly and nephrosis in all treated groups. Increased incidence of testicular interstitial cell tumours in high dose Marshall rats however, high incidence noted in the control groups.	(US National Toxicology Program NTP, 1988)

Table 26 -Carcinogenicity studies in animals (cont.)

Trichloroethylene grade	Dose & Duration	Species	Results	References
Epoxide-free, purified	Rats: Gavage doses of 0, 50 or 250 mg/kg/day, 4 or 5 days/wk for 52 wks, observed until death.	Sprague-Dawley rats. Thirty rats of each sex per group.	Kidney tubule meganucleocytosis at 250 mg/kg/day. Dose-related though not statistically significant increase in the incidence of leukaemias.	(Maltoni et al., 1986)
Highly purified, with 0.0015% triethanol-amine. . Industrial grade, 99.4% pure, with 0.11% epichlorohydrin and 0.2% 1,2-epoxybutane. . with added 0.8% epichlorohydrin. . with added 0.8% 1,2-epoxybutane. . with both 0.25% epichloro-hydrin and 0.25% 1,2- epoxybutane.	Mice: Gavage doses of 2400 mg/kg/day for males and 1800 mg/kg/day for females daily for 18 months. Dosing was interrupted for several weeks and reduced to half the initial dose from week 40 due to severe toxicity. Study was terminated 2 yrs after start of treatment.	Groups of fifty male and female Ha:ICR Swiss mice. Vehicle (corn oil) control group included.	Severe toxicity such as mortality, retarded body weight gain and enlarged liver with initial dose. Statistically significant increases in fore-stomach tumours in mice treated with epoxide-stabilised trichloroethylene. No tumours seen with epoxide-free trichloroethylene. No treatment-related changes in incidence of tumours at other sites.	(Henschler et al., 1984)
Dermal Exposure				
Purified	Thrice weekly dermal application of 1 mg (in acetone) trichloroethylene until death.	Ha:ICR Swiss mice, group of thirty.	No skin tumours and no signs of toxicity observed.	(Van Duuren et al., 1979)
	Initiation-promotion study Single dermal application of 1 mg trichloroethylene followed by thrice-weekly application of phorbol myristate acetate for life		No evidence of initiating properties	

10.8.1 Hepatic tumours

In the mouse, trichloroethylene induced hepatocellular tumours by oral and inhalation routes in Swiss and B6C3F1 strains (Maltoni et al., 1986) but not in NMRI or Ha:ICR strains (Henschler et al., 1984). The tumours were observed at oral doses of 1000 mg/kg and above and by inhalation at 600 ppm but not at 300 ppm (Maltoni et al., 1986). HA:ICR strains were also tested dermally for tumour initiating properties with negative results.

Trichloroethylene has been shown to induce peroxisome proliferation in mice but not in rats (Elcombe, 1985 and Goldsworthy, 1987). Hepatic peroxisome proliferation has therefore been proposed as the primary mechanism for eliciting hepatocellular tumours. Peroxisomal proliferation has also been proposed as a mechanism for hepatic tumours for several other chemicals eg tetrachloroethylene (Ashby et al., 1994) and HCFC-123 (National Industrial Chemicals Notification and Assessment Scheme (NICNAS), 1996)

There is growing evidence, as shown below, indicating that liver tumours in mice are due to the major metabolite, trichloroacetic acid. Evidence indicates that:

- Oral administration of trichloroacetic acid produced similar levels of peroxisome proliferation in mice and rats (Elcombe, 1985 ; Goldsworthy & Popp, 1987; Watson et al., 1993).
- The inability of trichloroethylene to induce peroxisomal proliferation in rats is believed to be related to saturation of metabolism of trichloroethylene to trichloroacetic acid. Saturation of metabolism occurs at much lower levels in rats than in mice (Prout et al., 1985). Hence greater amounts of the metabolites trichloroacetic acid and dichloroacetic acid are produced in mice as compared to rats. It has been postulated that a threshold exists for peroxisome proliferation and mice produce sufficient trichloroacetic acid to exceed this threshold but rats do not. Oxidative stress associated with peroxisome proliferation in mice may be responsible for development of hepatic tumours (Reddy & Rao, 1992).

Trichloroethylene metabolites, trichloroacetic acid and dichloroacetic acid, have been demonstrated to be tumourigenic in certain strains of mice (Herren-Freund et al., 1987; Bull et al., 1990). Limited data suggest that mice are more sensitive to the effects of dichloroacetic acid than rats.

Peroxisomal proliferation is considered to be species specific (ECETOC, 1992; Purchase et al., 1994) with humans being relatively insensitive. Human hepatocytes metabolise trichloroethylene to trichloroacetic acid at a slower rate than rats and a much slower rate than mice (Elcombe, 1985; Knadle et al., 1990). *In vitro* studies have shown that trichloroacetic acid does not induce peroxisome proliferation in human hepatocytes (Elcombe, 1985).

The other potential mechanism for carcinogenicity of trichloroethylene investigated in rats and mice include effects on hepatic DNA synthesis and mitosis. There may be some species differences in DNA synthesis and cell division between rats and mice (Stott et al., 1982; Elcombe, 1985; Mirsalis et al., 1985; Dees & Travis, 1993). The extent to which DNA synthesis is increased in rats given trichloroethylene is conflicting. There are also some indications of species differences in the extent to which mice and rats undergo DNA synthesis in response to trichloroacetic acid (Sanchez & Bull, 1990; Watson et al., 1993).

The effects of the other metabolites of trichloroethylene have been investigated in an attempt to clarify their role in carcinogenicity. There is some evidence to indicate that dichloroacetic acid may have a different mechanism of action compared to trichloroacetic acid. Dichloroacetic acid induces peroxisome proliferation in mice but at doses much higher than those inducing liver tumours (DeAngelo et al., 1989; Daniel et al., 1992). Administration of dichloroacetic acid in drinking water to male B6C3F1 mice for 52 weeks produced severe cytomegaly and glycogen accumulation throughout the liver (Bull et al., 1990). In rats hepatocyte enlargement was less marked with localised glycogen accumulation.

Conflicting data are available on the levels of dichloroacetic acid produced following trichloroethylene administration. One study has shown that mice metabolise trichloroethylene to dichloroacetic acid to a greater extent than rats (Larson & Bull, 1992) while others have shown that mice and rats produce similar amounts of dichloroacetic acid (Dekant et al., 1984); (Green & Prout, 1985).

The effects of dichloroacetic acid on human liver are not known. Formation of dichloroacetic acid is probably a minor pathway in humans as in rats.

Chloral hydrate and monochloroacetic acid, other metabolites of trichloroethylene, have not been adequately investigated for their liver effects in experimental animals. There are limited data in animals regarding liver carcinogenicity of chloral hydrate. Chloral hydrate administered to B6C3F1 mice (1g/L, 166 mg/kg) for 104 weeks resulted in hepatocellular carcinomas in 2/5 animals killed at 60 weeks. No carcinomas were detected in the control group. Of those killed at 104 weeks, 11/24 treated and 2/20 controls had hepatocellular carcinomas. Hepatocellular adenomas were seen in 7/24 treated mice and 3/20 controls. Non-neoplastic changes were also reported in the animals (Daniel et al., 1992).

The role of these metabolites in the tumourigenic effect of trichloroethylene is unclear based on the limited data available.

10.8.2 Lung tumours

Pulmonary toxicity specific to the Clara cells was observed in mice given single or repeated doses of trichloroethylene by the inhalation or intra-peritoneal route. No effects were seen in rats (Forkert et al., 1985; Forkert & Birch, 1989; Villaschi et al., 1991; Odum et al., 1992). Lung tumours were seen in some strains only, with female Ha:ICR mice, male Swiss mice and female B6C3F1 mice of both sexes being affected, while no tumours were seen in female Swiss mice, NMRI mice of either sex or in hamsters. Lung tumours occurred at exposure levels of 150 ppm and above of trichloroethylene (Fukuda et al., 1983).

In vitro studies on Clara cells from mice have shown that the major metabolite formed in these cells is chloral hydrate (Odum et al., 1992). The Clara cells are unable to metabolise chloral hydrate further leading to accumulation of the metabolite within these cells. Inhalation exposure of female CD-1 mice to 100 ppm of chloral hydrate produces lung toxicity.

It is thought that chloral hydrate is responsible for the pulmonary toxicity though the exact mechanism is not yet known. Regeneration and repair of the damaged Clara cells occurs (Villaschi et al., 1991). Lung tumours may result from repeated damage and regeneration. Chloral hydrate has also been shown to be mutagenic and other mechanisms may also be involved.

Inhalation exposure to a single dose of 100 ppm trichloroethanol for 6 h or 500 ppm for 2 h or 200 or 500 mg/kg trichloroacetic acid administered intraperitoneally failed to produce any lung toxicity. Oral administration of trichloroethylene or chloral hydrate does not result in lung tumours as the compounds would undergo metabolism before reaching the Clara cells. Inhalation exposure results in direct contact of Clara cells with trichloroethylene with metabolism of the chemical to chloral hydrate by the cytochrome P-450 in the cells.

Changes in the Clara cells of mice exposed to chloral hydrate by inhalation were more severe, with alveolar necrosis and epithelial desquamation. In addition, in trichloroethanol treated mice only few animals were affected at 100 or 500 ppm with minimal lesions and no vacuolation. The metabolite chloral hydrate has been implicated in lung toxicity as Clara cells are able to metabolise trichloroethylene to chloral hydrate but have a low ability to metabolise chloral hydrate to trichloroethanol. Cytochrome P-450 activities were found to be reduced in a dose dependent manner in Clara cells from lungs of trichloroethylene exposed mice. The activities of glutathione S-transferases were not affected. The lowest observable adverse effect level was 20 ppm for 6 h.

Metabolism of trichloroethylene has also been investigated in isolated rat and guinea pig lungs (Dalbey & Bingham, 1978). Trichloroethanol and trichloroacetic acid were detected in the perfusate in both species but not chloral hydrate. This suggests that rat and guinea pig lungs are able to further metabolise the chloral hydrate formed to trichloroethanol and trichloroacetic acid (United Kingdom, 1996)

Human lung tissue is capable of xenobiotic metabolism (Benford & Bridges, 1986) but very few studies have been conducted using human lung tissue. The Clara cells found in human lung tissue are few in number and lack smooth endoplasmic reticulum suggesting less cytochrome P450 activity. The Clara cells in humans are localised in specific regions of the airways. It is not clear which cells in human lungs are capable of metabolising chemicals and the extent to which trichloroethylene is metabolised in human lung.

A recent study has investigated the metabolic processes for trichloroethylene in rat and human lungs. Green et al (1997b) measured the formation of chloral hydtrate from trichloroethylene in liver and lung microsomal fractions from mice, rats and humans. The liver samples in these three species were found to metabolise trichloroethylene to significant extents. The chloral levels however, were twenty times higher in mouse lung microsomal incubations than in rat lung microsomes and could not be detected in human lung incubations. Rat lung cytosol was found to be most active in metabolising chloral to trichloroethanol in this study, followed by mouse lung and then human lung. Conjugation of trichloroethanol with glucuronic acid catalysed by UDP-glucuronosyl-transferase was low in mouse lung (rate 0.03 nmol/min/ mg protein) and was not detectable in human lung. Immunolocalisation showed that mouse lung contains high levels of cytochrome P4502E1 heavily localised in the Clara cells. The number of Clara cells in the rat lung was smaller and the concentration of P452E1 was less than the mouse lung. Cytochrome P4502E1 could not be detected in sections of the human lung. Enzyme protein levels were quantified and were found to be consistent with the results of immunolocalisation.

10.8.3 Kidney tumours

Kidney tubular adenomas along with meganucleocytosis were seen in rats exposed to 600 ppm by inhalation but not at 300 ppm (Maltoni et al., 1986). No increases in any tumour types were reported in inhalational rat studies by Henschler et al (1980) and Fukuda et al (1983). Kidney tubule meganucleocytosis was observed in rats following administration of 250 mg/kg/day orally (Maltoni et al., 1986). Oral exposure of rats at 500 mg/kg/day and 1000 mg/kg/day produced kidney tumours (US National Toxicology Program (NTP), 1988). Kidney tumours were also observed in male rats in a subsequent NTP study at 500 and 1000 mg/kg/day (US National Toxicology Program (NTP), 1990). The US NTP considered these studies as inadequate due to insufficient survival and significant non-tumour pathology. Despite this conclusion the findings of the two studies are consistent with each other (UK Report, 1996) and with studies conducted by Maltoni et al (1986) following oral administration and inhalation exposure.

Some chemically-induced renal tumours in rats have been attributed to binding of the chemical or its metabolite to α-2μ-globulin. In this mechanism, binding of the chemical to the male rat-specific protein α-2μ-globulin, results in accumulation in the form of protein hyaline droplets in kidney tubule cells. Overload of the chemically associated protein in the cells results in increased cell death and increased regenerative cell replication. Studies have shown that hyaline droplet accumulation is unlikely to be responsible for kidney toxicity with trichloroethylene in rats (Goldsworthy & Popp, 1987 ; Green et al., 1990).

Renal cytotoxicity was observed in rodent studies with trichloroethylene at concentrations or doses that did not cause renal tumours. Renal tumours were observed in rats, only in the presence of cytotoxicity at very high concentrations of trichloroethylene. It has been proposed that a likely mechanism of renal tumours seen in rats exposed to trichloroethylene is repeated cytotoxicity and regeneration (United Kingdom, 1996).

The mechanism by which trichloroethylene causes rat kidney cytotoxicity is still unclear. It has been postulated that cytotoxicity could be due to formation of the metabolite dichlorovinyl cysteine (Henschler 1995). Dichlorovinyl cysteine has been identified in the urine of workers exposed to 50 ppm of trichloroethylene. Renal tumours have been reported in one two studies in workers exposed occupationally to high levels of trichloroethylene. However, three other well conducted epidemiological studies failed to show an association between occupational exposure to trichloroethylene and renal cancer under the conditions of exposure in these studies. These are discussed in detail in section 11.7.

A recent study by Green et al (1997a) has assessed quantitatively the metabolic pathway leading to the formation of dichlorovinyl cysteine in rats *in vivo* and in rats, mice and humans *in vitro (*Green et al, 1997a). The *in vitro* studies have shown that the rate of conjugation of trichloroethylene with glutathione is higher in the mouse (2.5 pmol/min/mg protein) than in the rat (1.6 pmol/min/mg protein) and is very low in human liver (0.02-0.37 pmol/min/mg protein). The β lyase activity in rat kidney was found to be ten-fold greater than in the mouse and the metabolic clearance through this pathway was found to be greater in rat kidney than in human kidney. *In vivo* studies have shown that the mouse is more sensitive to the nephrotoxic effects of DCVC than rats.

Green (1997) have postulated an alternative mechanism for the renal toxicity of trichloroethylene. Rats administered trichloroethylene, trichloroethanol and trichloroacetic acid excreted high levels of formic acid. This was also observed in mice exposed to trichloroethylene, though the amount of formic acid was lower than in rats. The authors have postulated that formic acid excretion may be responsible for renal toxicity. Formic acid is not a metabolite of trichloroethylene and the source of formic acid needs to be studied further.

The mechanism of renal toxicity is being investigated further by several workers. Renal toxicity in rats is considered to be of concern to human health until the mechanism is elucidated.

10.8.4 Testicular tumours

A dose related and significant increase in the incidence of Leydig cell tumours was reported in Sprague Dawley rats following inhalation exposure to trichloroethylene for 8 weeks to 0, 100, 300 or 600 ppm (Maltoni et al., 1986). The number of affected animals ranged from 4% in controls to 24% in the 600 ppm group (Maltoni et al., 1986).

Following gavage administration of trichloroethylene to four strains of rats, ACI, August, Marshall and Osborne-Mendel strains, an increased incidence of Leydig cell tumours was observed in Marshall rats receiving 1000 mg/kg/day (67%) as compared to control (35%) and vehicle control (37%) (US National Toxicology Program NTP, 1988). An increased incidence was not seen in the other strains. The Leydig cell tumours were not considered to be associated with trichloroethylene because of the high incidence seen in controls and the absence of tumour induction in the other strains.

Benign Leydig cell tumours are common in aging rats and are associated with senile endocrine disturbances. The spontaneous incidence varies in the different strains. The spontaneous incidence rate for testicular tumours, at NCI, in Sprague Dawley rats is 4.2%. No historical control data were available for Marshall rats. However, Leydig cell tumours are rare in men and constitute <3% of all testicular neoplasms (Mostofi & Price, 1973). Leydig cell tumours are often associated with peroxisome proliferators and therefore their relevance to humans is questionable.

11. Human Health Effects

A number of reviews have been published on the health effects of trichloroethylene. This section summarises data from the published reviews and is based mainly on the UK SIAR (United Kingdom, 1996). Articles published recently, that is, since completion of the SIDS report, have been assessed. No unpublished studies were provided for assessment.

11.1 Acute toxicity

Data are available from studies in volunteers, accident reports and from use as an anaesthetic.

11.1.1 Inhalation

The predominant effect of acute inhalation exposure of humans to trichloroethylene is CNS depression. At very high doses trichloroethylene causes narcosis and has been used as an anaesthetic for short operations at concentrations of 5000 to 10,000 ppm. Generally, there were no adverse effects after the patients had recovered from anaesthesia. Cardiac arrhythmias have been reported during use as an anaesthetic. Cranial neuropathies specially involving the trigeminal nerve have also been observed. The trigeminal palsies were believed to be due to dichloroacetylene, a decomposition product of trichloroethylene.

Death has been reported following accidental exposure to high levels of trichloroethylene at work. Death was thought to be due to ventricular fibrillation resulting from sensitisation of the heart by trichloroethylene to endogenous catecholamines. Loss of sensation in the trunk and lower extremities and extensive sensory loss over face with numbness have been reported following accidental exposure to high concentrations of trichloroethylene. Loss of consciousness for varying periods has been observed in workers with exposure to high levels (2800 ppm). Workers have also reported symptoms of CNS depression such as dizziness, lethargy, headache and vertigo. Other effects seen following accidental exposure to high levels were raised serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, hypercalcaemia and hyperglobulinaemia. Kidney damage was reported in one worker with acute renal failure following exposure (David et al., 1989).

Several studies in volunteers under controlled conditions have reported acute effects of trichloroethylene on CNS functions at 500 ppm and above. Dizziness, lethargy and lightheadedness have been noted by volunteers. Exposure to 1000 ppm for 2 h resulted in marked changes in performance of a range of tests. These changes were potentiated with exposure to alcohol. No significant signs of CNS depression have been noted at 300 ppm. Some subjective effects such as dizziness and lethargy were reported at lower doses (27 ppm) by volunteers in one study (Nomiyama & Nomiyama, 1971). No significant changes were seen in flicker fusion frequency and two-point discrimination. “Irritant effects” have been reported in this study at 27 ppm, however these effects were not reported in other studies following higher exposures. The results of this study were not considered for NOAEL as only three subjects were involved and the symptoms reported were subjective. Another study (Salvini et al., 1971) indicated that impairment of performance can be induced by exposures to 130 ppm of trichloroethylene. This is in contrast to the effects seen in

other studies. However the UK SIAR states that actual data was not given and only a statistical analysis of the results was given. This study involved six subjects and was not included when considering a NOAEL for acute effects.

From case reports, the no effect level for single inhalation exposure of humans to trichloroethylene is around 300 ppm and is similar to that in animals.

Acute effects of trichloroethylene following accidental exposure and in volunteers under controlled conditions are summarised in Table 27.

11.1.2 Oral

CNS effects are the main effects observed following acute oral ingestion of trichloroethylene. Ingestion of <20 ml (450 mg/kg) has reportedly caused headache and slight confusion, while with doses of >50 ml (1100 mg/kg) CNS and cardiac effects (tachycardia and ventricular systoles) have been reported. Death due to ventricular fibrillation after ingestion of 50 ml has been reported, but recovery has been observed even after ingestion of up to 200 ml of trichloroethylene (around 4500 mg/kg body weight).

Two recently published articles reporting accidental and suicidal ingestion respectively of high doses of trichloroethylene have been reviewed during this assessment. No new data on low dose ingestion was available.

Accidental oral ingestion of approximately 29 gms of trichloroethylene by a 58 year old man following a fall into a reservoir bath resulted in disturbed consciousness and markedly oedematous pharynx and larynx. Laboratory examinations showed slightly elevated serum AST and ALT levels but kidney functions were normal. The man also developed respiratory insufficiency, chemical pneumonia and chemical burns to 30% of his body surface. The CNS functions returned to normal by 5 weeks and the man was discharged after 44 days (Yoshida et al., 1996).

Ingestion of 70 ml trichloroethylene by a 17 yr old male in a suicide attempt resulted in tremor, general motor restlessness and sinus tachycardia. The person lost consciousness 5 h after poisoning. The highest concentration of trichloroethylene in blood was 4 mg/L and was detected 13 h after ingestion. The metabolites by the oxidative and glutathione pathways were quantified in urine. N-acetyl-S-1,2-dichlorovinyl-L-cysteine excretion increased continuously with a maximum (1.25 nmol/mg creatinine) seen 5 days after poisoning. Several low molecular weight proteins were also detected in the urine 5 days after poisoning indicating renal tubular damage (Bruning et al., 1996a).

Table 27 - Acute inhalation toxicity of trichloroethylene

Exposure conditions	Exposure concentration	Duration	Effects	Reference
Accident reports				
Three male workers entered a tank containing an unknown amount of trichloroethylene.	2800 ppm (estimated)	20, 25 or 30 mins.	Loss of consciousness within 5 mins. of entering the tank. Two fully recovered consciousness within 4 h and the other man was only partly conscious after 4 h. The 2 men who recovered complained of headache, vertigo and burning /tearing eyes. Serum AST and ALT levels were raised up to 3 days after exposure	(Kostrzewski et al., 1993)
Ten male workers exposed due to accidental spillage of trichloroethylene.	Not estimated		Most of the men were unconscious for a short period. The men complained of cramps, diarrhoea, headaches and lower back pain which persisted for up to 1 mth. Hypercalcaemia and hyperglobulinaemia were noted and one man had haematuria 1 wk after exposure.	(Cotter, 1950)
A 34 yr old man was exposed while cleaning computer ribbons for recycling. He wore gloves, no respirator and worked in a poorly ventilated 800 m^3 room containing a 7.5L vessel of trichloroethylene.	not estimated	8 h	Drowsiness and distaste for alcohol and nicotine the next day. Developed symptoms of acute renal failure and admitted to hospital 3 wks after exposure. Needle biopsy of kidney showed interstitial nephritis with secondary tubular necrosis and tubular obstruction by intraluminal casts.	(David et al., 1989)
Four men exposed during operation of a degreasing tank.	200 to 8000 ppm in the working area of one individual. No details for other workers.		Drowsiness, dizziness and vomiting but continued working. All workers died within several h of leaving work. Suggested cause of death was ventricular fibrillation due to sensitisation of heart to endogenous catecholamines by trichloroethylene.	(Keinfeld & Tabershaw, 1954)
A young woman accidentally exposed	several 1000 ppm	unknown period	Unconscious for 2 h; complete loss of sensation in the trunk and lower extremities, disturbance of vision; effects were thought to be due to lesions in the spinal cord. Sensory loss was persistent with only slight recovery over a nine month period. Milder effects noted in a second woman who was unconscious only for 1 h.	(Sagawa et al., 1973)

Table 27 - Acute inhalation toxicity of trichloroethylene (cont.)

Exposure conditions	Exposure concentration	Duration	Effects	Reference
Accidental exposure during investigation of a leak in a degreasing machine	high concentrations	few mins.	Nausea, vomiting and giddiness but not anaesthesia; extensive sensory loss over face with numbness also in the mouth and pharynx, blurred vision. Complete numbness over a large area of the face for about 3 mths with hyperanalgesia in some areas of the face for over a year; complete recovery after 80 wks.	(Feldman, 1970)
Studies in volunteers				
Nine subjects, each given a comprehensive medical examination prior to the first exposure and following the last exposure.	50, 110 ppm	2 4-h periods with 1.5 h break	No significant reduction in performance noted in a range of behavioural tests.	(Stewart et al., 1974a)
Twelve students in groups of 3	0, 27, 81 or 201 ppm	4 h	Noticed smell of TCE at 27 ppm but after 3 h had lost sensitivity to smell even at 201 ppm; irritation of mucous membrane and eyes and drowsiness at 27 ppm and above, headaches after 2 h exposure to 81 ppm; dizziness and skin irritation after 4 h at 201 ppm.	(Nomiyama & Nomiyama, 1977)
Eight male volunteers were subjected to a range of psychomotor tests.	0, 100, 300 or 1000 ppm	2 h through a breathing tube	Dizziness, light-headedness and lethargy at 1000 ppm and at 300 ppm in one individual; no symptoms at 100 ppm. Significant effects on performance at 1000 ppm in a perception test and test for steadiness; no effects on performance of any of the tests at 300 ppm.	(Vernon & Ferguson, 1969)
Six young adult males not normally exposed to TCE underwent a series of tests to evaluate psychophysiological efficiency.	110 ppm; measured concentrations ranged from 90-130 ppm.	2 4-h periods with 1.5 h interval.	Dizziness and transient eye irritation when exposures were at the top range; no clinical disturbances in motor function, co-ordination, equilibrium or behaviour patterns; statistically significant decreases in performance ability in all tests particularly complex tasks.	(Salvini et al., 1971)
One subject	0, 100, 200, 300 or 500 ppm	2.75 h	"mild irritation" to the upper respiratory tract, a dull and wooly-headed feeling and somnolence at 500 ppm with the effects being reversed 15 mins after leaving the exposure chamber; slight tendency to somnolence at lower concentrations;no effects noted on behavioural tests at 100 ppm; changes seen at 300 ppm and above.	(Stopps & McLaughlin, 1967)

Table 27 - Acute inhalation toxicity of trichloroethylene (cont.)

Exposure conditions	Exposure concentration	Duration	Effects	Reference
Forty-seven young adult males aged between 19-27 yrs were randomly divided into 3 groups of 15 or 16 individuals. During exposure they were subjected to a range of behavioural tests.	0, 150 or 300 ppm	2.30 h	No signs of toxicity; no significant differences in performance of a range of behavioural tests.	(Ettema & Zielhuis, 1975)
A group of 24 students aged 19-26 yrs were subdivided into 4 groups of six. Alcohol was given as a 35% solution at a dose of 350 mg/kg, 50 mins prior to end of exposure.	One control group, one group exposed to alcohol alone, one to 200 ppm of TCE and one to 200 ppm of TCE and alcohol.	2.30 h	Blood alcohol levels in those exposed to TCE were the same as those given alcohol alone. However blood levels of TCE were higher in those co-exposed to alcohol than in those exposed to TCE alone. No significant impairment in performance of the tests.	(Windemuller & Ettema, 1978)
In a second experiment 15 male volunteers were used each being his own control. Alcohol was given 10 mins prior to the end of the 2.30 hour period.	Exposure to TCE similar to above with a 2 wk break between exposures; alcohol given 10 mins prior to end of exposure.		Blood alcohol levels were not different in the two groups; no impairment in performance of the binary choice test; a decrease in performance of the pursuit rotor test was noted in subjects with blood alcohol levels above 45 mg/ 100 ml following alcohol alone; no difference in heart or breathing rates. Metabolism of TCE was inhibited by administration of alcohol.	
Twenty healthy male volunteers , average age 27 yrs; ECG monitored continuously	95 ppm	4 h	Ventricular extra-systoles noted in one individual after 15 mins of exposure and lasted for 1 h after which ECG was normal. No changes in the absence of TCE.	(Konietzko et al., 1975).
Twelve volunteers	1000 ppm	2 h	Slight changes on optokinetic nystagmus indicating some effects on the CNS.	(Kylin et al., 1967)
Twenty healthy volunteers	95 ppm	4 h	No effects on serum liver enzymes were seen at 0, 4 and 20 h post-exposure.	(Konietzko & Reill, 1980)

Irritation and corrosivity

11.2.1 Skin

In humans, trichloroethylene is irritating to the skin after both single and repeated exposures. Studies in volunteers and case reports of workers exposed to the chemical have described erythema, burning sensation of the skin (Sato & Nakajima, 1978), rashes and dermatitis. Repeated dermal contact with trichloroethylene causes defatting of the skin with roughening and erythema (Irish, 1963). Chemical burns to about 30% of the total body surface was reported in a man who had accidentally fallen into a reservoir bath during a degreasing operation (Yoshida et al., 1996).

11.2.2 Eye

Limited human data are available on the eye irritant effects of trichloroethylene. Ophthalmodynia (pain in the eyes) was reported in a worker following an accident that resulted in his face, shoulders and chest being bathed in trichloroethylene (Nakajima et al., 1987). Direct eye contact with the chemical has been reported to cause burning and irritation of the corneal epithelium. Burning and tearing of the eyes has been reported following acute occupational exposure to trichloroethylene (Kostrzewski et al., 1993). Studies carried out in volunteers to investigate performance in behavioural tests have also reported irritation of eyes (Salvini et al., 1971; Nomiyama & Nomiyama, 1977).

11.3 Sensitisation

There have been a few reports of apparent skin sensitisation in humans. In one case report, a male worker developed severe dermal effects including skin lesions, erythroderma with oedematous face and eyes due to delayed hypersensitivity to trichloroethylene. Hypersensitivity in this worker was also detected to the metabolite trichloroethanol but not to trichloroacetic acid (Nakayama et al., 1988). In another report, similar reactions were described in a female worker who developed erythematous lesions when challenged twice with trichloroethylene during asymptomatic periods (Conde-Salazar et al., 1983). These cases are thought to be idiosyncratic reactions to trichloroethylene as the number of cases is very small for such a widely used chemical.

There have been no reports of respiratory sensitisation in humans.

11.4 Repeated dose toxicity

This section is based primarily on the UK SIAR. Numerous repeated dose toxicity studies in volunteers and occupationally exposed individuals have been published. A number of health surveys have been carried out in occupationally exposed workers but they have several limitations. These studies have little information on the atmospheric concentrations of trichloroethylene, concomitant exposure to other chemicals and some do not have a control group for comparison or have not taken confounding factors into account. Toxicity of trichloroethylene following repeated exposures is summarised in Table 28.

Table 28 - Repeated dose toxicity in humans

Subjects	Exposure concentration	Duration	Effects	Reference
Volunteers				
Three groups of 3-4 men aged from 19 to 46 yrs; pulmonary function tests prior to and at end of exposure; EEG recorded at hrly intervals during exposure; blood collected for haematology and clinical chemistry.	20 ppm TCE for 1st wk, 100 ppm for 2nd and 3rd wks and 200 ppm for 4th wk for 5 days a wk.	1, 3 or 7.5 h	No symptoms of toxicity; no effects on pulmonary function tests reported; "minimal changes" were noted at 200 ppm; no impairment in performance of behavioural tests; no abnormalities in EEG after exposure to 200 ppm for 7.5 h a day.	(Stewart et al., 1974a)
Small amounts of alcohol, 0.5 ml/kg administered during exposure	200 ppm		Marked vasodilatation of the superficial skin vessels of the face, shoulders and trunk; onset 20 mins after drinking alcohol, maximum effects 30 mins later and fading completely after 60 mins.	(Stewart et al., 1974b)
Twenty healthy male subjects, average age 27 yrs; EEG recorded every hr.	95 ppm	4 h	No EEG changes under control conditions; a slight increase in the duration of alpha activity was noted during first 2 h of exposure; no effects noted on the frequency or amplitude of these waves.	(Konietzko et al., 1975)
4 subjects; each performed a range of tests during and after exposure; subjects acted as controls.	100 ppm	6 h/day on 4 successive days with a 1 h break after 3 h	No significant impairment in performance of the tests	(Nakaaki et al., 1973)
3 male and 4 female students aged 19-28 yrs; a range of behavioural tests were performed during exposure; control group "exposed" to a "placebo" atmosphere produced by a mixture of hair lotion and disinfectant.	100 ppm	6 h/day for 5 successive days	No significant difference in the performance of the tests between the exposed and control groups.	(Triebig et al., 1977a)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
Occupational Exposure				
Cross-sectional study of 240 metal degreasers in Denmark; of these 99 had used TCE or CFC 113 for degreasing; age range was 19-68 yrs; no history of liver or kidney disease; confounding factors were age and alcohol abuse; assessment of degree of neurosis or "psycho-organic" syndrome was based on medical history of symptoms of mental impairment, clinical signs of dementia and performance in various tests.	In the highest exposure group, the mean urinary TCA concentration was 7.7 mg/l	Period of work in full time degreasing ranged from 1 mth to 36 yrs; four groups were identified: group 1: reference group with < 1 yr full time exposure; group 2: 1 to 2.8 yrs; group 3: 2.9 to 6.7 yrs and group 4: 6.8 to 35.6 yrs.	Statistically significant exposure-response relationships for raised concentrations of γ-GT and urinary NAG; relationship was not statistically significant when confounding factors were taken into account; no changes in serum levels of AST, alkaline phosphatase, bilirubin and protein and plasma prothrombin. Increased risk of developing "psycho-organic syndrome" was seen only for those in the highest exposure group after adjustment for potential confounders (OR=11.2). Thirty-one of the workers diagnosed with "psycho-organic syndrome" were predominantly exposed to TCE while 7 were exclusively exposed to TCE	(Rasmussen et al., 1993)
Seventy-five people occupationally exposed to TCE, 12 at dry-cleaning establishments and 55 during use as a degreasing agent; no controls included	Dry-cleaning exposure: 30-632 ppm; degreasing shops: 5-154 ppm	Workers were subdivided into 4 groups based on their duration of exposure as <1 yr, 1-2 yrs, 2-9 yrs and > 10 yrs	Effects related to length of exposure were skin and eye irritation, sleep disturbances, giddiness, tremors, intolerance to alcohol, bradycardia and "severe neurasthenia syndrome with anxiety state.	(Bardodej & Vyskocil, 1956)
One hundred and four workers, 87 males and 17 females, using TCE for degreasing, from dry cleaning establishments and the rubber industry; no control group; ECG recorded in 77 workers.	No data on the atmospheric levels of TCE but urinary TCA levels were measured.	About half of the workers had been exposed to TCE for 2 yrs or more at the start of the experiment	CNS effects such as headache, dizziness, vertigo, fatigue, nausea, vomiting, tremors, sleepiness; most individuals with urinary TCA levels > 75 mg/l showed some symptoms; mild symptoms were noted in the group with the lowest urinary TCA levels. An isolated case of transient numbness in the area of the 5th cranial nerve and paraesthesia and tremors of the fingers in a few cases; no abnormalities in haematology or clinical chemistry and liver function tests; symptoms disappeared 4-5 mths after cessation of exposure to TCE; abnormal ECG tracings were noted in 1/3 of those studied with ectopic auricular rhythm, shifting pacemaker and perisinus rhythm.	(Anderson, 1957)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
8 male Japanese workers exposed to TCE during use in vapour degreasing; TCE used in an open tank heated to 50°C, with no ventilation.	230 to 380 ppm in the breathing zone of workers using the tank; single level in the centre of the room was 115 ppm.		Severe fatigue, muscular pains, nausea and vomiting; increase in plasma gamma-globulin and a decrease in albumin; most workers had abnormal values in cephalin cholesterol flocculation test; increase in urinary albumin and urobilinogen. No abnormalities were detected when these tests were repeated 10 days later after cessation of exposure.	(Nomura, 1962)
Fifty employees working in the degreasing area and adjacent room	Degreasing room: 100-600 ppm; adjacent room:50 -100 ppm	Employed for 2.5 yrs	Vertigo, fatigue, headaches, sleeplessness, visual disturbances such as diplopia; increase in serum gamma-globulin and a decrease in serum albumin levels; albumin and urobilinogen in urine.	(Takamatsu, 1962)
A second survey was carried out 10 mths later with 3 groups; 8 from the degreasing room, 14 from part of the assembly room adjacent to the degreasing area and 16 workers from the other end of the assembly room	Degreasing room: 150-250 ppm, urinary TCA 311 ± 119 mg/l; assembly room adjacent to the degreasing room: 50-100 ppm, urinary TCA 141 ± 53 mg/l. The other end of assembly room:< 50 ppm, urinary TCA 50 ± 24 mg/l		More than 50% of the workers from the high exposure group complained of dizziness, giddiness, headache, feelings of drunkenness, flushing of the face, burning in the throat, skin effects and fatigue; marked decrease in serum albumin and increase in serum gamma-globulin levels. Fewer symptoms were experienced by >50% of workers in the intermediate group and consisted of headache, burning sensation in the eyes, flushing of the face and fatigue. Some workers were affected in the lowest group but the frequency of symptoms was unclear.	(Takamatsu, 1962)
Seventy young workers at a Romanian semi-conductor plant, mainly women, mostly below 30 yrs; control group not available for comparison.	40% of determinations above 9 ppm, 12% above 37 ppm.	Most had been employed for < 2 yrs, maximum duration 6 yrs.	Most of the workers complained of dizziness, headache, nausea, euphoria, sleepiness at end of shift, palpitations and visual disturbances; nine workers had periods of inebriation and had to go outdoors; one had loss of consciousness for a short period; other symptoms that occurred after exposure for months to 2 yrs included irritability, loss of appetite, excessive sweating and alcohol intolerance. Physical examination revealed tremors, hyperactive tendon reflexes and nystagmus in some workers.	(Lilis et al., 1969)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
130 workers from several factories in the U.K. No control group.	61% of workers had urinary TCA<20 mg/l, 21% had 20-60 mg/l and 18% had > 60 mg/l		Symptoms included fatigue, dizziness, gastro-intestinal disturbances, headache and effects on the autonomic nervous system.	(Smith, 1970)
22 female and 28 male Polish workers from various small factories and dry cleaning establishment varying in age from 21-55 yrs; no control group	No data	Exposed from between 1 and 23 yrs	Most frequent symptoms were somnolence, loss of appetite and nausea, intolerance to alcohol and headaches; impairment of sensation in the face was noted in 6 workers, weakness of the optic reflex in 4 and sensory disorders in the wrist and fore-arm in 9 workers	(Szulc-Kuberska, 1972)
140 Polish female workers at 3 workshops, average age 37 yrs; control group of 44 women of comparable age and training	Mean level was 37 ppm	Length of exposure was 9.2 yrs	Symptoms noted were drowsiness, general malaise, intolerance to alcohol, reduced appetite and muscle pains; no difference in serum proteins or bilirubin levels, no significant effects noted on haematology	(Zielinski, 1973)
Thirty male workers from an Egyptian printing factory where TCE was used for cleaning plates used in rotogravure printing; all but 2 were below 50 yrs; control group of 30 workers of comparable age and social class	41-163 ppm in the breathing zone at different parts of the plant	Most employed for > 3 yrs	Headache, dizziness, sleepiness, nausea and vomiting., lachrymation, reduced libido, skin rashes and itching and fatigue; haematological and liver function tests were normal; no abnormalities in the ECG recordings.	(El Ghawabi et al., 1973)
24/30 workers from a tannery with an average age of 40.5 yrs, no control group;	Urinary TCA 24 h post-shift was in the range of 50 to 100 mg/l.	Mean length of exposure to TCE was 16.5 yrs	Vertigo, irritability, drowsiness, weakness, dyspeptic disorders, headache, eye irritation, irritation of throat, sweating, alcohol intolerance and pruritis; hepatomegaly(5/24) and hyperbilirubinaemia (9/24); no effects on serum aminotransferase, total serum proteins or cholesterol levels; no evidence of peripheral neurotoxicity or effects on renal function; auditory function impairment noted in 6 workers was thought to be due to noise; vestibular abnormalities such as symmetrical bilateral vestibular hyper-reflexia was noted in 11 workers, this was reduced when examined 2 mths later.	(De Rosa et al., 1971)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
Group of 12 women workers from a factory where TCE was used as an adhesive to join rubber strips; it was applied to one side of the strip and allowed to evaporate partially before the strips were joined.	Urinary TCA values ranged from 44 to 80 mg/l.	Employed in the factory for 2-3 yrs	Headache, dizziness, feeling of elation, dyspepsia; enlarged tender liver (6/12), raised serum gamma globulin levels (6/12) and increased serum bilirubin (2/12); serum total protein, albumin, cholesterol, and alkaline phosphatase levels were normal.	(Capellini & Grisler, 1958)
70 workers (43 females) using TCE for degreasing and cleaning textiles	Degreasing: 93 to 743 ppm; Cleaning textiles: 279-1078 ppm	1 to >10 yrs exposure	Slight liver enlargement (14/70), abnormalities in liver function tests (23/70); effects were related to length of exposure (2/19 with < 1 yr and 9/19 with > 10 yrs of exposure); mild changes in thymol turbidity test, decrease in serum albumin levels.	(Graovac-Leposavic et al., 1964)
Group of 12 workers involved in degreasing operations at a factory in Paris. Tests carried out were flocculation test, prothrombin levels and electrophoretic pattern of serum proteins.	167 to 558 ppm; mean urinary TCA measured over a 5 yr period ranged from 219 mg/l to 505 mg/l.	not stated	Repeated complaints of subjective CNS-related symptoms; no abnormalities in the tests performed and physical examination showed no signs of liver damage.	(Tolot et al., 1964)
Worker selection based on personal samples; controls matched for age, sex and race; 9 workers and 9 controls	8-h TWA : from 22-66 ppm (mean 38 ppm); short term peaks from 77-370 ppm; the 8-h TWA for other workers ranged from 0.1 to 23 ppm. Pre-shift total TCE metabolites in urine was 297.5 mg/l and post shift was 479.9 mg/l; trichloroethanol concentrations rose from 97.9 to 155.2 mg/l; no increase in urinary TCA over the shift. Second investigation: 8-h TWA for "exposed" group from 6.9-26 ppm and short term peak mean value of 74 ppm	Mean duration of employment were 4.4 and 9.4 yrs	Fatigue, light headedness, sleepiness, eye irritation, shortness of breath, dyspnoea on exertion, nausea, skin irritation, cough and headache reported (7/9); no symptoms in controls. Second investigation done 3 mths after the first; exposure levels were markedly reduced; number of workers reporting symptoms and number of symptoms reported were markedly reduced.	(Landrigan & Kominsky, 1987)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
31 male printing workers and 28 non-exposed workers from the same printing works; workers with risk factors for neuropathy and those consuming >50 glasses of alcohol a wk were excluded; control group matched with cases for physical job activity, education, nationality and age.	At the time of the study exposure levels were estimated to be about 17 ppm, 3 yrs previously for about 8 yrs it was 35 ppm after installation of local ventilation; prior to that exposures were 70 ppm	6 yrs exposure to TCE	Slight reduction in the sural nerve conduction velocity and a 0.4 millisecond prolongation in the sural nerve refractory period; masseter reflex (trigeminal nerve function measure) was increased by 0.4 msbut no prolongation of blink reflex (another indicator of trigeminal nerve function); no impairment of motor functions of peripheral nerves or of autonomic nerve function.	(Ruijten et al., 1991)
2 women and 5 men aged between 19 to 32 yrs; control group consisted of 4 women and 9 men of comparable age to exposed group.	20 to 40 ppm	Ranged between 6 mths to 9 yrs	No signs of neurological illness; no difference in conduction velocity between exposed and controls.	(Triebig et al., 1978)
31 employees (26 men and 5 women) of 3 firms aged between 16 and 56 yrs; 24 sex and age-matched controls with no history of risk factors for neuropathy.	5 to 70 ppm	Exposed from 1 mth to 35 yrs	No significant differences in the peripheral nerve function between exposed and controls.	(Triebig et al., 1982)
4 workers each at 2 separate Australian factories; control group comprised of 4 women workers from other areas of the factory; each worker performed a complex reaction time test prior to and at the end of the morning shift (4 h) and at the beginning and end of the afternoon shift.	148 to 418 ppm (mean 245 ppm) at one site and 3 to 87 ppm (mean 27 ppm) at the other site.	Not stated	Exposure to mean levels of about 250 ppm resulted in a reduction in performance in reaction time tests; symptoms of marked CNS disturbances had been noted in these workers.	(Gun et al., 1978)
Small group of 20 women workers at a factory in Sofia; age range of subjects varied from 34 to 47 yrs; control group consisted of 58 healthy individuals of about the same age and similar work histories. Cardiac effects measured included ECG, carotid sphygmogram and phonocardiogram; phase analysis of the left ventricular systole was carried out using polycardiographic indices.	No data on atmospheric levels; mean urinary TCA were 40.71 mg/l in the exposed group and 1.58 in the controls; mean urinary TCE were determined in 11 workers and was 45.70 mg/l; control workers urinary TCE was 28.45 mg/l.	Between 7 mths and 4 yrs	Polycardiograpic indices that were affected include a shortening of the cardiac cycle, prolongation of the isometric period and the tension phase and a decrease of the intrasystolic index; results suggest some impairment of cardiac function due to a prolongation of the ineffective phase of systole	(Dimitrova et al., 1974)

Table 28 - Repeated dose toxicity in humans (cont.)

Subjects	Exposure concentration	Duration	Effects	Reference
75 workers involved in degreasing operations using TCE in a West German factory; average age of workers was 43 yrs; workers subjected to medical examination and ECG.	Limited data suggest that TCE levels were about 100 ppm in the vicinity of the degreasing tank.	Duration of employment from 2 mths to 20 yrs	Abnormal ECGs noted in 3 workers; one had right-heart block which had existed for some years prior to working at the factory; the second case was a 29 yr old worker who had been employed for 6 mths and had ventricular extrasystoles; the third was a 50 yr old man employed for 20 yrs, ECG was normal during first examination but 2 yrs later signs of first degree AV heart block noted.	(Konietzko et al., 1975)
ECG recordings of 6 workers using a degreasing tank were continually monitored by telemetry during one workshift; results were compared to those obtained in the same individual the next day when not exposed.	87 ppm		Repeated ventricular extrasystoles noted in a 34 yr old man during exposure, no abnormalities when not exposed. No ECG abnormalities in a further group of six workers.	(Konietzko et al., 1975)
44 yr old male worker involved in using rapidly setting adhesives in shoemaking, working in a poorly ventilated room; he did not smoke or drink alcohol or suffer from known heart disease		10 h/day	He had suffered episodes of amnesia and confusion, a burning sensation in the pharynx and eczema of the hands, underarms and head; he collapsed while mowing the lawn and suffered frequent polytopic ventricular extrasystoles and tachycardia; serum enzyme analysis revealed some signs of liver injury but heart and kidney-specific enzymes were normal; urinary TCA levels 14 days after last day at work was 2 mg/24 h.	(Wernisch et al., 1991)
40 workers exposed in various factories in Poland, age ranged from 25 to 50 yrs	Urinary TCA of at least 40 mg/l with some as high as 200 mg/l		Hearing defects in 26 of the workers consisting of perceptive impairment at frequencies in range 2-3 kHz; frequency depended on the length of exposure with 13/22 employed for 4-10 yrs and 10/11 employed for >10 yrs; balance disturbance noted in 19 workers; all these workers also had hearing disorders.	(Szulc-Kuberska, 1972)

Subjective symptoms of CNS disturbances have been reported in most of these studies. Most common symptoms include fatigue, dizziness, vertigo, headaches and memory loss and impaired ability to concentrate. Skin and eye irritation have also been reported. A high incidence of CNS effects and hearing defects were noted in some workers.

Some studies have mainly investigated the liver effects of trichloroethylene. Evidence of liver damage has been reported in some studies while liver changes were not seen in other studies Workers exposed to trichloroethylene developed hepatomegaly, changes in serum hepatic enzyme levels (ALT, AST and aldolase) and abnormalities in liver function tests such as thymol turbidity and cephalin-cholesterol tests. Raised serum bilirubin levels and gamma globulins were noted in one study. Increased serum beta- and gamma- globulins and some abnormalities in the cephalin flocculation test were reported in workers regularly exposed to trichloroethylene (Guyotjeannin & Van Steenkiste, 1958). The hepatic effects seen in all these studies could not be definitively attributed to trichloroethylene as trichloroethylene exposure levels were not noted and similar changes are associated with alcohol ingestion.

In a recent correspondence to the editors of a journal, Bruning et al (1996b) has reported renal tubular damage in patients who had been diagnosed with renal cell carcinoma and had undergone nephrectomy. Seventeen patients had been exposed to high concentrations of trichloroethylene over many years and were later diagnosed with renal cell cancer. All these patients reported that prenarcotic symptoms such as feeling of drunkenness, dizziness, headache and drowsiness had occurred frequently during occupational exposure to trichloroethylene. Duration of exposure was 15 years with a mean latency period of 30.4 years. The frequency of pathologic protein excretion patterns in these patients were compared with 35 renal cell cancer patients (controls) from a large urological clinic. SDS PAGE (SDS polyacrylamide gradient electrophoresis) was used to separate and differentiate between different pathological protein patterns in the excreted urine. This method allows a high-resolution separation between 20 different urinary proteins according to molecular size and thus helps to differentiate between different pathological protein patterns excreted in urine indicating tubular, glomerular or mixed renal damage. Protein excretion patterns indicating tubular damage in the remaining kidney was identified in all the 17 exposed patients (6 severe tubular damage, 6 moderate damage, 2 minor and 3 mixed glomerular/tubular damage). Of the control patients 18 of the 35 showed normal protein excretion patterns with 12 controls showing tubular damage, 4 mixed glomerular/tubular damage and 1 with glomerular damage. One of these controls had been occupationally exposed to tetrachloroethylene. The others had no history of being occupationally exposed to potentially nephrotoxic substances. A lower prevalence of tubular damage was found among the non-exposed group of renal cell cancer patients than patients who had been occupationally exposed to trichloroethylene. This data, though limited, cannot be dismissed especially in the light of renal toxicity findings in rodents.

Alcohol intolerance has been reported in some workers who consumed alcohol during exposure to trichloroethylene and in single and repeated dose volunteer studies. This presented as transient flushing of the face, shoulders and neck due to vasodilatation of the superficial vessels. This condition is commonly known as “degreasers’ flush”. Competitive inhibition of acetaldehyde dehydrogenase resulting in accumulation of acetaldehyde in blood is thought to be the underlying mechanism.

Effects of trichloroethylene on the cardiovascular system have been investigated in a number of studies. Abnormalities in cardiac rhythm such as ventricular extra-systoles and tachycardia, have been reported.

The UK SIAR has described reports of other effects of trichloroethylene. Stevens-Johnson syndrome, an autoimmune disease, has been reported in some workers exposed to trichloroethylene by inhalation and also the dermal route (Phoon et al., 1984). Scleroderma has also been observed in some workers exposed to trichloroethylene (Flindt-Hansen & Isager, 1987). Stevens-Johnson syndrome and scleroderma may be idiosyncratic reactions to trichloroethylene, however more evidence is needed before any conclusions can be drawn.

11.4.1 Oral

The UK SIAR includes two studies on the effects of trichloroethylene following oral exposure. In the first study the effects of trichloroethylene were evaluated four months after contamination of drinking water by a spill from a trichloroethylene plant placing thirteen residents potentially at high risk. The concentration of trichloroethylene in the water consumed by the residents was not known, but concentrations in drinking water wells ranged up to 1000 ppb. No symptoms of toxicity were reported by any of the residents. Measurable levels of trichloroethylene metabolites were detected in the urine of two residents but one used trichloroethylene at work and the other had not consumed the contaminated well water and did not work with trichloroethylene (Landrigan & Kominsky, 1987). This study did not provide any useful data as exposure levels could not be determined.

In the second study the residual neurological effects following past exposure to trichloroethylene in drinking water (up to 256 ppb) have been studied (Feldman et al., 1994). Blink reflex latency and neurological assessments were carried out in a group of 28 people. A significant difference in conduction latency was seen between control and exposed groups indicating subclinical changes in the 5th cranial nerve. However, other chlorinated solvents were also detected in the contaminated water indicating simultaneous exposure to other chemicals.

11.5 Reproductive toxicity

11.5.1 Fertility

The UK SIAR indicated that fertility effects of trichloroethylene have not been investigated in humans. The report cited isolated cases of reduced potency and decreased libido among male workers (Bardodej & Vyskocil, 1956; El Ghawabi et al., 1973) and increased incidence of menstrual disorders in exposed females (Bardodej & Vyskocil, 1956; Zielinski, 1973)

11.5.2 Developmental toxicity

According to the UK SIAR few studies have investigated possible links between effects on pregnancy and exposure to trichloroethylene. The report states that the studies in humans are of limited use as exposure data were not quantified. An association between trichloroethylene exposure and abortions or congenital malformations has not been reported in any of the studies (Tola et al., 1980; Taskinen et al., 1989; Goldberg et al., 1990; Lindbohm et al., 1990).

11.6 Genotoxicity

A recently published article by Bruning et al (1997) analysed tumour tissues for somatic mutations within the von Hippel-Lindau (VHL) gene, from 23 patients with renal cell cancer and prolonged occupational exposures to high levels of trichloroethylene. The VHL gene was reported to be a specific target in trichloroethylene induced renal cell cancer with a high mutation frequency (100%) at the VHL gene in the trichloroethylene exposed cases. In the trichloroethylene unexposed group the mutation frequency for renal cell cancers was 33-55% (Bruning et al., 1997). The VHL gene has been isolated and found to be a tumour suppressor gene (Latif et al., 1993). Renal cell cancers may develop as a result of somatic mutation in the VHL tumour suppressor gene. The findings of this report are preliminary as all the VHL genes had not been confirmed by sequencing. Limitations of this study include exposure not being determined precisely for each individual, cases not selected from a well-defined study base and controls were not selected from the same base. Further work is underway in Europe to confirm the effects of trichloroethylene on the VHL gene.

The UK SIAR states that several other studies conducted in occupationally exposed groups are considered to be inconclusive. Sister chromatid exchange (SCE) in peripheral blood lymphocytes was investigated in workers exposed to trichloroethylene. Frequency of SCE was found to be slightly increased in the exposed group in one study (Gu et al., 1981). However this study did not account for potential confounding factors, had a small group size and exposure was not stated adequately. Nagaya et al (1989) did not observe any difference in the frequency of SCE between trichloroethylene exposed (average concentration 30 ppm) and control groups.

The frequency of SCE in a group of workers exposed to trichloroethylene (Seiji et al., 1990) was investigated by taking gender and smoking habits into account. Breathing zone concentrations were between 10 and 50 ppm. The frequency of SCE was statistically significantly greater in male exposed smokers than in age-matched controls. No differences were seen between the control and exposed groups among females and male non smokers. The group sizes were small in this study and no conclusions can be drawn.

In a chromosomal aberration study in lymphocytes of a group of 15 trichloroethylene exposed workers, the number of metaphases with gaps was significantly greater when compared with 669 (unmatched) controls (Rasmussen et al., 1988). The increases were primarily in three workers who had the highest exposures as determined from urinary trichloroethylene levels. The urinary trichloroacetate values were not stated. Potential confounders such as smoking were not considered. In the same study, sperm counts and the frequencies of sperm with two fluorescent Y bodies - indicating presence of two Y-chromosomes - were not significantly different in the control and exposed groups.

11.7 Carcinogenicity

A number of cohort and case-control studies have been conducted in occupationally exposed populations to investigate the carcinogenicity of trichloroethylene. This report only includes a discussion of the most relevant studies. Other studies have not been described here because of a number of limitations such as small numbers of subjects, short follow-up periods, exposure to more than one chemical and lack of characterisation of exposures. Readers are referred to IARC (1995) for a detailed description of the other studies.

11.7.1 Cohort studies

The major cohort studies are those by Axelson et al (1994), Spirtas et al (1991) updated by Blair et al (1998), and Antilla et al (1995). These are detailed further in Table 29. The study by Henschler et al (1995) reported as a retrospective cohort has been included in table 29 as it is a recent study and provides limited data of an association between trichloroethylene exposure and human renal cancer. The study by Garabrant et al (1988) has not been included as a number of chemicals were used at the company with only 37% of the workers being exposed to trichloroethylene. The follow-up period was only 15.8 years and it is unlikely that cancers with a long latency period would have been detected in this study.

In the cohort investigated by Axelson et al (1994) no significant increases in cancer mortality or morbidity were observed. Mortality was analysed in worker subgroups categorised according to urinary trichloroacetic acid levels (<49, 50 to 99 or >100 mg/L) and exposure time (< or > 2 years). The two lowest exposure groups had low cancer mortality.

However in the > 100 mg/L group, the standardised mortality ratio (SMR) for cancer was slightly increased. In males, some excess of cancers of the liver, larynx, prostate and of non-Hodgkins lymphoma were observed but the excess of liver and prostate cancers and lymphomas were in the low exposure group. A statistically significant increase was seen for malignant skin tumours in men (standardised incidence ratio SIR 2.36, 95% confidence interval 1.02 - 4.65). This increase, however, was in the low exposure group. The overall female cancer morbidity was slightly higher than expected (SIR 1.32, CI 0.53 - 3.79) among women with < 2 years exposure. Half of these cases had tumours of the breast or genital organs and the other cancers were in the gastrointestinal tract. There were no cases of skin or liver cancers, lymphoma or leukaemia among women.

Table 29 - Characteristics of major cohort studies of people occupationally exposed to trichloroethylene (Adopted from Weiss (1996))

	Axelson et al (1994)	Spirtas et al (1991)	Antilla et al (1995)	Henschler et al (1995)
Cohort characteristics				
Location	Sweden	Utah, USA	Finland	Germany
Exposed group	All workers who had urine tested for TCA between 1955 and 1975.	White persons who had been employed for >1 yr between 1951 and 1956.	All workers who had urine tested for TCA between 1965 and 1982 and workers who had TCE poisoning.	Persons in a cardboard factory exposed for at least 1 year to TCE between 1956 and 1975.
Number of members included in analysis	1670 workers, 1421 men and 249 women.	7000	1698 male and 1391 female workers	169 males
Follow up of members				
Nature of outcome	Mortality and incidence	Mortality	Incidence of cancer	Mortality and incidence
Vital status	100%	97%	100%	92%
Exposure	Based on mean urinary TCA for all samples. 81% of cases had low exposure with TCA levels <50 mg/L. Exposure time was taken as time interval from first urine sample until end of employment or 1979.	Combination of job and organisation was used to determine if a job had frequent or infrequent peak exposures or continuous or intermittent low level exposure to TCE.	Based on mean level of the concentration of TCA in the urine. Time elapsed from the first personal measurement.	Exposure evaluated by walk-through surveys and interviewing long-term employees. 3 areas identified: cardboard-machine area - high exposure; locksmith's area and electrical workshop lower exposure.
Control group	General population, Swedish national rates.	Utah white population adjusted for sex, age and calendar period	Finnish national register and general population.	190 male workers from the same factory matched for age and physical activity. Incidence also compared with cancer registries of Denmark and German Democratic Republic

TCE trichloroethylene
TCA trichloroacetic acid

An epidemiological study was conducted in a group of workers at an aircraft maintenance facility in Utah (Spirtas et al., 1991). A number of chemicals were used at the facility, such as chlorinated hydrocarbons (including trichloroethylene), aromatic hydrocarbons (such as toluene and xylene) and some alcohols. Exposure indices were calculated based on job, frequency of exposure, frequency of peak exposure and duration of exposure. Mortality from all causes was significantly less than expected for both men and women. There were no statistically significant excesses for cancer deaths in general or for specific kinds of cancer.

Blair et al (1998) followed up the cohort of 14457 aircraft maintenance workers previously reported by Spirtas et al (1991). Workers exposed to trichloroethylene showed non-significant excesses for Hodgkin's lymphoma (RR 2.0), cancers of the oesophagus (RR 5.6), colon (RR 1.4), primary liver (RR 1.7), breast (RR 1.8), cervix (RR 1.8), kidney (RR 1.6) and bone (RR 2.1). The findings in this study did not show a strong association between trichloroethylene exposure and any cancers. The associations were not significant or dose related and not consistent between men and women. This study included a large cohort of workers with a follow up period of about 40 years enabling detection of cancers with a long latency period. However workers were exposed to a number of chemicals and it was not possible to evaluate risks from individual chemicals.

Antilla et al (1995) divided the total cohort into sub-groups, on the basis of the observation period, into 0-9, 10-19 or more than 20 years. The average urinary trichloroacetic acid levels were 8.3 mg/L in women and 6.3 mg/L in men. The mean latency period was 18 years. Risk of cervical cancer was significantly increased for the study cohort , with higher numbers in the shortest follow-up group (0-9 yrs). There was a significantly increased incidence of cancer in general (SIR 2.98 95% CI 1.20 - 6.13) in the group with the follow-up of > 20 yrs. There was a significant increase in the incidence of tumours of the liver (SIR 6.1; 95% CI 1.3 - 18), prostate (SIR 3.56; 95% CI 1.5 - 7.0), stomach (SIR 3.0; 95% CI 1.2 - 6.1) and lymphohaematopoietic system (SIR 3.0; 95% CI 1.2 - 6.1) in the group with a follow up of > 20 yrs.

Henschler et al (1995) reported a study of renal cancer in workers exposed to trichloroethylene at a cardboard manufacturing factory. Physical examination of the workers included abdominal sonography and causes of death were obtained from hospital records. Tumour diagnosis date was the date of surgery and renal tumours were verified by histopathological examination. Air concentrations of trichloroethylene or metabolites in urine were not available. Information indicates that the workers in the cohort were exposed to high concentrations of trichloroethylene over long periods of time. The average period of exposure was 18 years and the average observation period was 30 years. The incidence of renal cancer in the cohort was compared directly with the incidence in the control group and with data of the cancer registries of Denmark and German Democratic Republic.

Five cases of renal cancer were diagnosed by the close of the study and two additional cases were diagnosed later giving a total of seven cases in the cohort. No renal cancer was observed in the control group. A statistically significant increase in incidence of renal cancer was obtained compared with cancer registry of Denmark (SIR of 7.97; 95% CI 2.6 - 19) and German Democratic Republic (SIR of 9.66; 95% CI 3.1 - 23). This study has been criticised for a number of reasons. IARC (1995) have noted that the study may have been initiated after observing a cluster of cancer cases. Others have also noted that the study was a cluster study and that physician and hospital records should not be compared with general population mortality rates (Bloemen & Tomenson, 1995; Swaen, 1995). Though this study appears to be a

cluster investigation rather than a retrospective cohort the findings of this study raise concern of an association between high trichloroethylene exposure and renal cancer.

Mortality at a plant in the US using trichloroethylene as a degreasing agent was investigated in a study by Shindell and Ulrich (1985). Persons working for more than three months from 1957 to 1983 were included in the study. No data on exposure levels were available. Overall mortality (SMR for white males 0.79) and cancer mortality (SMR for white males 0.62) were found to be less than expected.

11.7.2 Case-control studies

Several case-control studies have been conducted, however many are of limited use. Studies which provide useful information are discussed below.

A case-control study including 59 nephrectomised patients has been described by Vamvakas et al (cited in Deutsche Forschungsgemeinschaft, 1996). The study included all patients who had been diagnosed with renal cell tumours at histopathology after nephrectomy between December 1987 and May 1992. The control group included 84 traffic accident patients treated in the same clinic. Abdominal ultrasonography was used to exclude renal tumours in the control group. Exposure evaluation was carried out by questionnaires and personal interviews. Information was also obtained from physicians and occupational hygienists. Of the nephrectomy cases, 20 had been exposed to trichloroethylene and none to tetrachloroethylene. Five from the control group had been exposed to trichloroethylene and 2 to tetrachloroethylene. The average exposure period for the cases was 19 years. A highly significant odds ratio of 13.42 (95% CI 3.50 - 51.39) was obtained for the combined exposure to trichloroethylene and tetrachloroethylene. However, no exposure to tetrachloroethylene had been reported in the nephrectomised patients. Factors such as age, sex, smoking habits, blood pressure and consumption of diuretics were allowed for by logistic regression. The significant odds ratio is suggestive of an association between trichloroethylene exposure and renal cell carcinomas. The nephrectomised patients were classified into high, medium or low level exposures on the basis of duration, frequency of exposure and the workplace description. Eight patients with renal tumours were in the high exposure group, 10 in the medium and 2 in the low. Of the controls, 2 were in the high exposure group, 3 in the medium and 2 in the low exposure group. Only a summary of this study was available during the Priority Existing Chemical assessment. The data are therefore limited and do not allow an in depth assessment of the quality of the study.

Several other case-control studies have investigated the carcinogenic effects of trichloroethylene. Trichloroethylene exposure was not found to be a risk factor for astrocytic brain tumours (Heineman & et al., 1994). The incidence of liver cancer was investigated in people exposed to trichloroethylene in separate studies (Novotna et al., 1979; Paddle, 1983). None of the liver cancer cases identified were found to be occupationally exposed to trichloroethylene. These two studies only looked at one type of cancer and included limited numbers. A high odds ratio (7.4) was found for dry cleaners exposed to trichloroethylene in a case-control study investigating risk factors for colon cancer (Fredrickson et al., 1989). The odds ratios were not significantly increased for all dry cleaners or for all exposed to trichloroethylene. This study does not provide sufficient evidence of a causal association between trichloroethylene and colon cancer in dry cleaners because of the small number of exposed people.

12. Hazard Classification

Data on physicochemical hazards, toxicokinetics and health hazards in humans and animals are integrated in this chapter. The potential hazards to human health from exposure to trichloroethylene can then be characterised and the appropriate classification determined.

Workplace substances are classified as hazardous to health if they meet the NOHSC *Approved Criteria for Classifying Hazardous Substances* (the Approved Criteria) (National Occupational Health and Safety Commission (NOHSC), 1994) and hazardous in terms of physicochemical properties if they satisfy the definitions in the *Australian Code for the Transport of Dangerous Goods by Road and Rail* (ADG Code) (Federal Office of Road Safety, 1998)

Trichloroethylene is currently included in the *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994) as a carcinogen category 3.

For transport by road and rail, substances are classified as dangerous goods according to the criteria in the ADG Code, for example the criteria for corrosivity, acute toxicity and physicochemical properties such as flammability.

12.1 Physicochemical hazards

Trichloroethylene is non-flammable and non-explosive under normal conditions of use. It is moderately volatile with a vapour pressure of 7.7 kPa. It is relatively stable but at high temperatures, as seen in the vicinity of arc welding and degreasing operations, it may decompose to hydrochloric acid, phosgene and other compounds. In contact with hot metals, such as magnesium and aluminium at very high temperatures (300-600°C) it decomposes readily to form phosgene and hydrogen chloride.

Classification

Trichloroethylene does not meet the ADG Code criteria for any classes pertaining to physicochemical properties.

12.2 Kinetics and metabolism

In humans, trichloroethylene is absorbed via inhalational, dermal and oral routes, with the most significant uptake being through inhalation of the vapour. Dermal absorption of the vapour is negligible, however, some absorption of liquid occurs through the skin. Absorbed trichloroethylene is distributed throughout the body and is deposited mainly in adipose tissue and liver. Metabolism of trichloroethylene is mainly via the oxidative pathway with the major metabolites being trichlorethanol, trichloroacetic acid and trichloroethanol glucuronide. A minor metabolite, N-acetyl dichlorovinyl cysteine, has been identified in animal and human urine and is formed via conjugation with glutathione.

The metabolism and excretion of trichloroethylene in animals is similar to humans, however there are some species differences in the metabolism of trichloroethylene. The rate of metabolism of trichloroethylene to trichloroacetic acid in mice is more rapid than in rats. Saturation of the oxidative pathway has also been reported in rats

at 200 to 500 mg/kg while in mice saturation is only seen at 2000 mg/kg. Saturation in humans has not been seen at doses up to 380 ppm and has been predicted by PBPK models to occur at 2000 mg/kg.

12.3 Health hazards

12.3.1 Acute effects

Trichloroethylene has low acute toxicity by all routes of exposure. In acute studies, the oral LD_{50} in rats ranged from 5400 to 7200 mg/kg, inhalational LC_{50} (4h) in rats was 4800 ppm (4 h) and dermal LD_{50} in rabbits was > 20000 mg/kg.

The acute effects of trichloroethylene reported in animals are consistent with the findings in humans. The predominant effect of acute exposure of humans to trichloroethylene is CNS depression. At very high doses trichloroethylene causes narcosis. Other symptoms of CNS depression such as dizziness, light headedness and lethargy have also been reported in volunteers. Changes in ECG were reported in one study at 100 ppm. However this was seen in only one subject and the ECG returned to normal after some time. The NOAEL for acute CNS effects in humans is 300 ppm.

Several deaths have been reported in workers following occupational exposure to very high levels of trichloroethylene. Ventricular fibrillation, due to sensitisation of the heart to endogenous catecholamines, has been reported as the cause of death in some of these cases.

The acute toxicity in animals is generally similar to humans. An exception is the acute pulmonary toxicity seen as vacuolation of Clara cells in mice at exposures of 20 ppm. This is related to the metabolism of trichloroethylene in mice.

Classification

Trichloroethylene does not meet the Approved Criteria (National Occupational Health and Safety Commission (NOHSC), 1994) for classification on the basis of acute lethal effects by oral, dermal or inhalation exposure. The ADG Code lists trichloroethylene as Class 6.1. The LD_{50} for the oral and dermal routes and the LC_{50} for the inhalation route for trichloroethylene were below the cut-off for classification as 'harmful' under the ADG Code. It is therefore likely that trichloroethylene was classified as acutely toxic based on human experience.

12.3.2 Irritant effects

Studies in human volunteers and reports of workers exposed to trichloroethylene have indicated that trichloroethylene caused burning sensation of the skin, erythema, rashes and dermatitis. Prolonged contact can cause defatting of the skin. Studies in guinea pigs and rabbits also indicate that trichloroethylene is a skin irritant.

Direct eye contact with the chemical in humans has been reported to cause burning and irritation of the corneal epithelium. Volunteers have reported irritation of eyes during investigation of behavioural performance following exposure to trichloroethylene. Two studies in rabbits reported conjunctivitis, corneal abrasions and necrosis after instillation of trichloroethylene into the eyes.

Classification

From human evidence and results of the animal studies, trichloroethylene meets the Approved Criteria for classification as a skin irritant (R38 - Irritating to skin) and an eye irritant (R36 - Irritating to eye).

12.3.3 Sensitisation

A small number of cases of apparent skin sensitisation have been reported in humans. Due to the small number of cases for such a widely used chemical, it is thought that these were idiosyncratic reactions and not due to sensitisation. No skin sensitisation studies have been conducted in animals. No studies have investigated the potential of trichloroethylene as a respiratory sensitiser.

Classification

Trichloroethylene does not meet the Approved Criteria for classification as a sensitiser.

12.3.4 Effects after repeated or prolonged exposure

Several health surveys have been carried out in workers occupationally exposed to trichloroethylene. These surveys are however limited due to lack of information on atmospheric trichloroethylene levels, exposure to other chemicals and potential confounding factors. Most of the studies reported CNS effects such as dizziness, headaches, memory loss, inability to concentrate and skin and eye irritation. Liver effects of trichloroethylene have been investigated in some studies. No consistent evidence of liver damage is available as some studies reported hepatomegaly and changes in blood chemistry while no effects were reported in other studies. A limited number of studies included tests for the potential neurotoxicity of trichloroethylene in occupational cohorts. These studies provided no evidence of significant effects on EEG patterns or nerve conduction velocity. ECG was affected in one out of ten subjects in one study. However, the ECG returned to normal after a few days. Data on renal effects of trichloroethylene in humans is limited. Severe renal tubular damage and tubular-glomerular damage have been reported in workers with long-term occupational exposure to high levels of trichloroethylene.

The toxic effects identified from repeated inhalational exposure to trichloroethylene in animal studies were liver, kidneys, CNS, lungs and hearing effects. The kidneys appear to be the most sensitive organs in animals. Kidney effects were observed in rats following inhalation and oral exposure and in mice following oral exposure. In a 2-year inhalation study using rats, meganucleocytosis of the renal tubules was reported at 300 ppm (LOAEL) with no effects being seen at 100 ppm (0.55mg/L) (NOAEL). Meganucleocytosis was also reported in an oral study at 250 mg/kg/day in rats with a NOAEL of 50 mg/kg/day. In mice, renal cytomegaly was observed in both sexes following oral administration of 1000 mg/kg/day for 2 years.

Trichloroethylene liver effects have been reported in mice and rats with inhalational NOAELs of 200 ppm (1.1 mg/L) in rats and rabbits, and oral NOAELs of 375 and 500 mg/kg/day in mice and rats respectively.

Classification

Trichloroethylene does not meet the Approved Criteria for classification on the basis of severe effects after prolonged or repeated exposure.

According to the Approved Criteria a substance is classified as harmful where damage to health is likely to be caused by repeated or prolonged exposure by the following routes and dose ranges:

- oral, rat: ≤ 50 mg/kg/day
- inhalation, rat: ≤ 0.25 mg/L 6 h/day

The lowest NOAELs following exposure to trichloroethylene by the inhalation and oral routes are 100 ppm (0.55 mg/L) and 50 mg/kg/day respectively. These values are higher than the cut offs in the Approved Criteria for classification as harmful.

12.3.5 Reproductive effects

Reproductive effects of trichloroethylene have not been adequately investigated in humans. No developmental toxicity has been reported in humans.

Reproductive effects following oral administration have been well investigated in animals. Oral administration resulted in reduced sperm motility and slight reductions in neonatal bodyweight and survival in mice at doses at which general toxic effects were produced. In rats there was a reduction in the number of litters born and in the litter size. General toxic effects were also observed at these levels.

Several developmental studies have been conducted in animals. In inhalation studies on rats, mice and rabbits no clear evidence of developmental toxicity was reported at doses up to 1800 ppm. A series of oral studies from one laboratory suggest that trichloroethylene may induce developmental neurotoxicity following maternal exposure.

Classification

Trichloroethylene does not meet the Approved Criteria for teratogenicity nor the EC Criteria (European Commission Directive 93/21/EEC, 1993 27 April,) for effects on fertility or developmental toxicity as animal studies do not provide any evidence of fertility or developmental effects.

12.3.6 Genotoxicity

Trichloroethylene has been investigated for its mutagenic potential in a wide range of standard *in vitro* and *in vivo* assays. Many studies have been conducted using epoxide stabilised trichloroethylene, however these studies have not been considered in this hazard assessment, due to the known mutagenicity of epoxides.

Trichloroethylene in the vapour state tested positive in several bacterial assays using *Salmonella typhimurium* in the presence of metabolic activation. In several fungal studies, trichloroethylene tested positive to *Saccharomyces cerevisiae*, also in the presence of metabolic activation. Trichloroethylene also tested positive in a mouse lymphoma gene mutation assay and induction of unscheduled DNA synthesis (UDS) was reported in several studies. On this evidence, trichloroethylene can be regarded as weakly mutagenic *in vitro*.

In a host-mediated gene mutation assay in mice, trichloroethylene tested positive to *S. cerevisiae* in the kidneys and liver but not the lungs

In somatic cell studies *in vivo*, both positive and negative results were obtained in rat and mouse micronucleus tests, with some doubts about two of the studies with positive results. Negative results were obtained in rat and mouse studies for chromosomal aberrations, sister chromatid exchange and UDS, however, trichloroethylene induced DNA single strand breaks in the liver of rats and mice in one study, and in mouse liver and kidneys in a second study. A mouse spot test was equivocal, however, a preliminary test for mouse pink-eyed unstable mutation was clearly positive. In germ cell assays, dominant lethal tests were either negative or inconclusive.

Studies conducted in occupationally exposed groups have been considered to be inconclusive. These studies had limitations such as small group size and potential confounders not being considered. A study investigating somatic mutations in the von Hippel-Lindau (VHL) gene obtained from tumour tissue of patients with renal cell cancer reported that trichloroethylene specifically acts on the VHL gene which has been identified as a renal tumour suppressor gene. It is possible that renal cell cancers following trichloroethylene exposure develop with somatic mutation of the tumour suppressor gene being one of the events. The findings of this report are preliminary as all the VHL genes had not been confirmed by sequencing. Limitations of this study include exposure not being determined precisely for each individual, cases not selected from a well-defined study base and controls were not selected for the same base. Further work is underway in Europe to confirm the effects of trichloroethylene on the VHL gene.

Classification

Trichloroethylene meets the Approved Criteria for classification as a category 3 mutagen (R40M3) on the basis of

- positive results in a variety of tests in somatic cells *in vivo*, described above;

and, supported by:

- the study of mutations in VHL tumour suppressor gene;
- positive results from a number of *in vitro* mutagenicity assays; and,
- mutagenicity of known metabolites.

According to the Approved Criteria category 3 are those substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damage (Appendix 4).

12.3.7 Carcinogenicity

A number of epidemiological studies have investigated the carcinogenic potential of trichloroethylene. Most cohort studies, including those by Axelson et al (1994) and Spirtas et al (1991) which were large enough to detect an effect, individually did not show any association between cancer and occupational exposure to trichloroethylene. However, the cohort study by Anttila et al (1995) provided limited evidence of an association between exposure to trichloroethylene and cancer. Occupational exposures in the cohort studies of Axelson et al (1994) and Anttila et al (1995) were to low levels of trichloroethylene, approximately 20 to 30 ppm.

A high incidence of renal cancer in workers from a cardboard factory was reported by Henschler et al (1995) following exposure to high levels of trichloroethylene for long periods. This study appears to be a cluster investigation and has some weaknesses. The findings of this study are supported by a case control study by Vamvakas et al (cited in Deutsche Forchungsgemeinschaft, 1996) who have demonstrated an association between renal cell carcinomas and occupational exposure to trichloroethylene. The findings of these two studies are limited by weaknesses in the design of the studies, however they cannot be dismissed.

In animals trichloroethylene induces tumours at several sites and in different species. Tumours have been seen in mouse liver and lung and rat kidney and testis.

Studies have shown that mouse liver tumours are likely to be due to peroxisome proliferation induced by the metabolite trichloroacetic acid. Trichloroacetic acid does not induce peroxisome proliferation in human hepatocytes.

Mouse lung tumours are also thought to be related to the metabolism of trichloroethylene. Green et al (1997) have demonstrated that chloral hydrate levels were twenty times higher in mouse lung microsomal incubates than in rat lung microsomes and could not be detected in human lung incubates. Rat lung cytosol was found to be most active in metabolising chloral hydrate to trichloroethanol in this study, followed by mouse lung and then human lung. This study provides evidence that accumulation of chloral hydrate is unlikely to occur in human lung.

Testicular tumours were observed only in one strain of rats with a high incidence in the control group. These tumours are rare in men and are often associated with peroxisomal proliferators.

Renal cytotoxicity was observed in rodent studies with trichloroethylene at concentrations or doses that did not cause renal tumours. Renal tumours were observed in rats, only in the presence of cytotoxicity at very high concentrations of trichloroethylene. It has been proposed that a likely mechanism of renal tumours seen in rats exposed to trichloroethylene is repeated cytotoxicity and regeneration (United Kingdom, 1996).

The mechanism by which trichloroethylene causes rat kidney cytotoxicity is still unclear. It has been postulated that cytotoxicity could be due to formation of the metabolite dichlorovinyl cysteine (Henschler 1995). Dichlorovinyl cysteine has been identified in the urine of workers exposed to 50 ppm of trichloroethylene. Renal tumours have been reported in one study in workers exposed occupationally to high levels of trichloroethylene. However, other well conducted epidemiological studies failed to show an association between occupational exposure to trichloroethylene and renal cancer under the conditions of exposure in these studies.

A recent study has assessed quantitatively the metabolic pathway leading to the formation of dichlorovinyl cysteine in rats *in vivo* and in rats, mice and humans *in vitro (*Green et al, 1997a). The *in vitro* studies have shown that the rate of conjugation of trichloroethylene with glutathione is higher in the mouse (2.5 pmol/min/mg protein) than in the rat (1.6 pmol/min/mg protein) and is very low in human liver (0.02-0.37 pmol/min/mg protein). The β lyase activity in rat kidney was found to be ten-fold greater than in the mouse and the metabolic clearance through this pathway was found to be greater in rat kidney than in human kidney. *In vivo* studies have shown that the mouse is more sensitive to the nephrotoxic effects of DCVC than rats.

Green (1997) have postulated an alternative mechanism for the renal toxicity of trichloroethylene. Rats administered trichloroethylene, trichloroethanol and trichloroacetic acid excreted high levels of formic acid. This was also observed in mice exposed to trichloroethylene, though the amount of formic acid was lower than in rats. Formic acid excretion may be responsible for renal toxicity. Formic acid is not a metabolite of trichloroethylene and the source of formic acid needs to be studied further.

The mechanism of renal toxicity is being investigated further by several workers. Renal toxicity in rats is considered to be of concern to human health until the mechanism is elucidated.

Classification

Trichloroethylene meets the Approved Criteria for classification as a Carcinogen Category 2 (National Occupational Health and Safety Commission (NOHSC), 1994), that 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. Thus the available data provides suspicions of carcinogenic potential in humans (R45).

Review of carcinogenicity data by other countries/agencies

The carcinogen classification categories adopted by the various countries/agencies are similar. There are five major categories. Most countries/agencies have the first three categories listed below and several have all five categories. Although the classifications are similar, the reader is referred to the relevant country/agency classification system for further information on the criteria and basis for inclusion of a chemical into the various categories.

The five categories in the classification of carcinogens include:

- known human carcinogen;
- probable human carcinogen;
- possible human carcinogen;
- not a human carcinogen and
- insufficient information to classify.

The carcinogenicity of trichloroethylene has been reviewed recently by a number of countries and agencies principally with a view to classification. A brief description of the outcome of the reviews and the classification adopted by the countries/agencies is provided below.

IARC

IARC (International Agency for Research on Cancer) (IARC, 1995) considered three cohort studies to be relevant for the evaluation of trichloroethylene. Meta-analysis of the three studies (Spirtas et al., 1991; Axelson et al., 1994 and Anttila, 1995) by IARC indicated an excess relative risk for cancer of the liver and biliary tract (23 observed cases whereas 12.7 expected) and non-Hodgkin's lymphoma (27 observed and 18.9 expected). Results for liver cancer were given separately in the study by Anttila et al (1995) and for the maintenance workers in the study by Spirtas et al (1995). A total of 7 cases were observed whereas 4 were expected.

On the basis of these findings and the induction of tumours in animals at sites other than the liver, IARC concluded that trichloroethylene is probably carcinogenic to humans (Group 2A), that is limited evidence in humans and sufficient evidence in experimental animals.

Germany

The Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (1996) considered that the study by Henschler et al (1995) indicates an increased incidence of renal tumours in workers exposed to high concentrations of trichloroethylene. The Commission states that the findings of this study were confirmed by a recent case control study carried out by Vamvakas et al (cited in Deutsche Forschungsmeinschaft, 1996) suggesting an association between renal cell tumours and exposure to trichloroethylene. The tumours were histopathologically similar to those found in rats. In addition, the metabolic pathway postulated to be responsible for nephrocarcinogenicity has been found to be similar in rats and humans (Bernauer et al., 1996).

On the basis of these three findings ie increased incidence of renal cell tumours in exposed workers, nephrocarcinogenicity in rats and the molecular mechanism of renal toxicity, trichloroethylene is classified by the Commission in category IIIA1, ie compound capable of inducing malignant tumours as shown by experience with humans.

UK HSE

The HSE (United Kingdom, 1996) consider that the majority of epidemiological studies, including the studies by Axelson et al (1994) and Spirtas et al (1991) that

had substantial power to detect an effect, did not show any evidence of an association between trichloroethylene exposure and increased incidence of cancer. However, they noted that there is limited evidence of an increased risk of liver cancer in one cohort study (Anttila et al., 1995) and of renal cancer in another study (Henschler et al., 1995). These two studies indicate that trichloroethylene has some carcinogenic potential.

HSE have concluded that the liver tumours in mice are due to peroxisomal proliferation and are of no relevance to humans but that there is no evidence to indicate that the mechanism of induction of kidney tumours in rats and lung tumours in mice is not applicable to humans.

On the basis of the uncertainties of the epidemiological data and the tumours in animals, the HSE have proposed that trichloroethylene be classified as a category 3 carcinogen, ie a substance which causes concern for humans owing to possible carcinogenic effects, but in respect of which the available information is not adequate to make a satisfactory assessment.

Canada

The Canadian Priority Substances List Assessment (Government of Canada, 1993), conducted by Environment Canada and Health Canada, in accordance with the Canadian Environmental Protection Act (CEPA), states that an association between exposure to trichloroethylene and the development of any specific type of tumour has not been consistently observed in the epidemiological studies, including those by Spirtas et al (1991); Axelson et al (1984); Tola et al (1980) and Shindell and Ulrich (1980).

The Canadian report concluded that the increased incidence of hepatic tumours in mice appears to be induced by a mechanism not relevant to humans and that the relevance of renal tumours in male rats to humans is unclear. The most pertinent results in assessing the carcinogenicity of trichloroethylene are the pulmonary tumours in mice reported by Maltoni et al (1986, 1988) and Fukuda et al (1983) and the increases in testicular tumours in rats (Maltoni et al., 1986; Maltoni et al., 1988; US National Toxicology Program NTP, 1988). Trichloroethylene also appears to be weakly genotoxic in *in vitro* and *in vivo* assays.

The Canadian report categorised trichloroethylene in Group II, ie probably carcinogenic to humans.

ECETOC

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1994) state that five cohort epidemiological studies of populations occupationally exposed to trichloroethylene have shown no association between occurrence of cancer and exposure to trichloroethylene. The studies referred to are Spirtas et al (1991); Axelson et al (1994); Tola et al (1980) and Shindell and Ulrich (1980) and Wong and Morgan (1990).

ECETOC noted that animal studies have shown liver and lung tumours in mice and kidney tumours in rats. The mechanisms in these cases are linked to species specific metabolism of trichloroethylene or to biochemical responses which are specific to rodents. These tumours are therefore considered to be of no relevance to humans.

ECETOC concluded that trichloroethylene does not present a carcinogenic hazard to man.

ACGIH

ACGIH (1992) found no evidence in six epidemiological studies to suggest that an association between trichloroethylene exposure and increased cancer in humans. The six studies considered were Spirtas et al (1991); Axelson et al (1978); Tola et al (1980) and Shindell and Ulrich (1980) Paddle (1983) and Novotna et al (1979).

ACGIH concluded that the hepatocellular tumours in mice (National Cancer Institute (NCI), 1976) occur via a nongenetic mechanism following liver injury. No carcinogenic effects were seen in animals in other studies either orally (Maltoni & Maioli, 1977) or by dermal application (Van Duuren et al., 1979).

ACGIH categorised trichloroethylene in Group A5, ie not suspected as a human carcinogen.

13. Occupational Risk Characterisation

Occupational risk characterisation combines the results of the hazard and occupational exposure assessments to determine the potential risks of adverse health effects in workers exposed to trichloroethylene.

13.1 Methodology

The methodology used to characterise risk to human health from exposure to trichloroethylene in this report is the margin of exposure approach. This approach is commonly used in international assessments (OECD, 1993; UK Government, 1993, July; European Commission, 1994)

The following steps are used for risk characterisation of critical effects caused by repeated or prolonged exposure:

1. Identification of the critical health effect(s).
2. If appropriate and available, then identification of the most reliable NOAEL for the critical effect(s).
3. Estimation of the human dose (EHD)
4. Comparison of the NOAEL with the estimated human dose to give a margin of exposure, that is:

$$\text{margin of exposure} = \frac{\text{NOAEL}}{\text{estimated human dose (EHD)}}$$

5. Characterisation of risk by judging whether the margin of exposure indicates a concern.

Margin of exposure (MOE) is an indication of the magnitude by which the NOAEL exceeds estimated human exposure (EHD). Characterisation of risk requires consideration of a number of parameters such as the completeness and quality of the database (including exposure data), nature and severity of the effects, interspecies and intraspecies variability and characteristics of the human population exposed when judging whether the MOE indicates that exposure to the substance is of concern.

For acute effects, the risk characterisation process considers likely exposure patterns to assess whether single exposures are high enough to indicate a health concern.

13.2 Critical health effects

13.2.1 Acute effects

The main adverse effect observed following acute exposure to trichloroethylene is CNS depression. The NOAEL for CNS depression in humans is about 300 ppm for exposure of about 8 h. Exposure to high doses causes narcosis and recovery is generally complete. Symptoms of CNS depression such as lightheadedness, dizziness and lethargy have been reported in workers.

Trichloroethylene is considered to be a skin and eye irritant.

13.2.2 Effects due to repeated exposure

Severe renal tubular damage and tubular-glomerular damage have been observed in workers with long-term occupational exposure to trichloroethylene. However, the data is insufficient to identify a NOAEL as exposures were not known.

The toxic effects identified from repeated inhalational exposure to trichloroethylene in animal studies were liver, kidneys, CNS, lungs and hearing effects. The kidneys appear to be the most sensitive organs in animals hence the critical effect is kidney toxicity. In a 2-year inhalation study using rats, meganucleocytosis of the renal tubules was reported at 300 ppm (LOAEL) with no effects being seen at 100 ppm (NOAEL). Five rats in the highest exposure group (600 ppm) had renal tubular adenocarcinomas (Maltoni et al., 1986).

Long term carcinogenicity studies in animals by the inhalation and oral routes indicate that trichloroethylene is carcinogenic in rats and mice. The principal tumour sites are the liver and the lungs in mice and the kidneys in rats.

Renal adenocarcinomas have been reported in rats following gavage and inhalation exposure. Rat kidney tumours are thought to be due to persistent cytotoxicity and regeneration. Epidemiological studies, one cohort and one case control, have indicated an association between prolonged occupational exposure to high levels of trichloroethylene and kidney tumours.

The main route of exposure is inhalation, with dermal exposure occurring to a lesser extent. There is no dermal NOAEL available. The inhalation NOAEL chosen for risk characterisation is the NOAEL for kidney effects in rats of 100 ppm (546 mg/m^3). Assuming 100% absorption, an average rat weight of 215g and a respiratory rate of 0.16 m^3/day, this represents an absorbed dose of :

$$\frac{546\ mg/m^3 \times 0.16\ m^3/day \times 7h}{0.215 \times 24\ h} = 118.5\ mg/kg/day$$

13.3 Occupational health and safety risks of trichloroethylene

13.3.1 Risks from physicochemical hazards

Trichloroethylene is non-flammable and non-explosive under normal conditions of use. Its flammability limits in air are 8.0 to 10.5 and the chemical is flammable when exposed to a high energy source. At workplaces using old degreaser tanks with inadequate engineering controls, vapours may accumulate increasing the risk of flammability.

Trichloroethylene is relatively stable but at high temperatures may decompose to hydrochloric acid, phosgene and other compounds. Such conditions are seen in the vicinity of arc welding and degreasing operations.

In the presence of strong alkalis like sodium hydroxide, dichloroacetylene is formed which is explosive and flammable.

13.3.2 Margin of exposure

Margins of exposure (MOE) were calculated for the critical health effect, renal toxicity, for the various occupational scenarios.

$$\text{Margin of exposure} = \frac{118 \text{ mg/kg/day}}{\text{estimated human dose (EHD) in mg/kg/day}}$$

The EHD for each scenario is given in Appendix 1, with the summary in Chapter 8. The NOAEL for the critical effect, renal toxicity, is 118 mg/kg/day (100 ppm) based on a 2-year inhalation rat study. The estimated MOE for each scenario is given in Table 30.

Table 30 - Margins of Exposure (MOE)

Concentration of TCE	Combined Exposure mg/kg/day	Margin of Exposure (inhalational+dermal)
Formulation		
Product with 90% TCE, 4 hours/day		
10 ppm (54.6 mg/m^3)	0.26	456
30 ppm (163.8 mg/m^3)	0.76	156
50 ppm (273 mg/m^3)	1.26	94
Vapour Degreasing		
TCE, 8 h/day, 200 days/yr		
10 ppm (54.6 mg/m^3)	3.5	34
30 ppm (163.8 mg/m^3)	10.2	12
50 ppm (273 mg/m^3)	16.9	7

Cold Cleaning				
TCE, 8 h/day	**120 days/yr**		**200 days/yr**	
	Combined exposure	**MOE**	**Combined exposure**	**MOE**
0.4 ppm (2.18 mg/m^3) dip cleaning	0.68	174	1.13	105
3.8 ppm (20.75 mg/m^3 rag wiping	1.36	87	2.26	52
68.3 ppm (372.92 mg/m^3) rag wiping	14.26	8	23.77	5
0.9 ppm (4.91 mg/m^3) dip cleaning and rag wiping	0.78	152	1.29	91
7.5 ppm (40.95 mg/m^3) dip cleaning and rag wiping	2.10	56	3.5	34

Trichloroethylene products		
200 days/yr	**Combined exposure**	**MOE**
35% product spray painting		
0.7 ppm (3.82 mg/m^3)	0.3	395
4.8 ppm (26.21 mg/m^3)	1.71	69
20% product rag wiping		
3.8 ppm (20.75 mg/m^3)	1.31	90
4.1 ppm ((22.38 mg/m^3)	1.4	85
90% product brushing on		
2.5 ppm (13.65 mg/m^3)	1.01	117

13.3.3 Uncertainties in risk characterisation

In any risk assessment process, uncertainties arise due to assumptions made during the process because of inadequate information. Uncertainties inherent in the assessment of health risk of a chemical are listed in Table 31.

Table 31 – Uncertainties in risk characterisation

Area of uncertainty	Specific concern
Inadequate information	Lack of representative atmospheric exposure data
	Lack of dermal exposure data
Assumptions in assessment process	Assumption of a linear correlation between estimated human dose and variables such as atmospheric concentration and exposure time
	Assumptions in rate and extent of dermal absorption of vapours and liquid
	Use of standard constants for breathing rate, body weight and bioavailability
Experimental conditions	Selection of doses used in the critical study
	Variability in results between laboratories
	Amount and quality of the available toxicity data

These uncertainties need to be considered when discussing the implications of any margin of exposure, and in particular when deciding if an estimated exposure is of concern.

13.3.4 Uncertainties in risk characterisation of trichloroethylene

For the critical effect, renal toxicity, an inhalational NOAEL of 100 ppm was identified from the animal data with the LOAEL being 300 ppm. Renal adenocarcinomas were observed at 600 ppm. The actual NOAEL may be anywhere between 100 and 300 ppm.

Renal effects are thought to be related to the metabolism of trichloroethylene by the reductive pathway. In humans, as in rats, the mercapturates formed are only minor excretory products but are excreted slowly from the kidney. These metabolites have been identified in human urine even at low levels of exposure. The ratio of the two isomers N-acetyl-S-(dichlorovinyl) -L-cysteine excreted in urine is different in rats and humans. In humans the proportion of the two isomers are the same. However, in rats excretion of 2,2 isomer is 3 to 4 fold higher than the 1,2 isomer. Uncertainty exists as to whether small amounts of these metabolites are sufficient to cause renal toxicity or the metabolites need to exceed a certain threshold for appearance of renal toxicity.

The skin absorption rate used to estimate dermal exposure introduces an element of uncertainty in the assessment as no data on the skin permeability rate for trichloroethylene in humans was available in the open literature. The skin absorption rate used (0.32 mg/cm^2/h) was derived from experiments in hairless guinea pigs. The dermal absorption rate in mice was reported as 0.47 mg/cm^2/h in one study while the theoretical model of Fiserova-Bergerova predicts that for dermal absorption of trichloroethylene, the predicted flux is 0.27 mg/cm^2/h (Fiserova-Bergerova & Pierce, 1989). The skin absorption rate in guinea pigs was used to estimate dermal exposure as the rate in guinea pigs in general is closer to the rate in humans compared to mice.

These above uncertainties are likely to have a similar impact on MOE for all scenarios. Uncertainties such as lack of exposure data (inhalational and dermal) and extent and duration of skin absorption will have varying degrees of impact on the risk assessment. These will be discussed for each scenario.

13.3.5 Risk during formulation

Acute effects

No atmospheric monitoring data were available for formulation of products containing trichloroethylene. There is a range of processes, with some being open and others closed. Certain stages of the formulation process such as manual filling of the mixing vessels from drums or bulk storage sites and emptying of the tank into containers could result in high peak inhalation exposures and dermal contact.

In a well-controlled, enclosed process, acute exposures are likely to be low. There is a risk of irritant effects during formulation when mixing in open systems, during maintenance work or during clean-up of spills.

Adverse effects due to repeated exposure

No atmospheric monitoring data were available for formulation of products containing trichloroethylene. According to the data provided for assessment, formulation is a batch process occurring approximately 1 to 2 h a day for 1 to 60 days a year and this has been taken into account in the formulae used to estimate exposure. The MOE for inhalation exposure was estimated for 3 atmospheric concentrations, 10, 30 and 50 ppm and were found to be 474, 158 and 95 respectively. For combined exposure (inhalation and dermal) during formulation of a product containing 90% trichloroethylene the MOE for the 3 scenarios were 456, 156 and 94. In estimating dermal exposure, contact with liquid trichloroethylene was assumed to be incidental as skin contact is expected to be infrequent during formulation.

The MOE calculated indicate that the risk of kidney effects is considered to be minimal during formulation.

13.3.6 Risk during vapour degreasing

Acute effects

The atmospheric monitoring data available for assessment consisted of short- term measurements or instantaneous readings indicating peak concentrations of trichloroethylene, with all readings well below the NOAEL of 300 ppm for CNS effects. If it is assumed that the results are representative of vapour degreasing in Australia, then the risk of CNS effects is low. However a reading of 145 ppm was reported 15 cms above a degreaser, indicating that a worker involved in manually

lowering or lifting workloads from the degreaser could be exposed to high vapour concentrations with some risk of CNS effects.

As trichloroethylene vapour is irritant to the eyes, exposure to vapours during degreasing operations may lead to a risk of eye irritation. Trichloroethylene liquid is a skin and eye irritant, so any splashes or spills present a risk of irritation.

Adverse effects due to repeated exposure

The atmospheric monitoring data provided by end-users during assessment were inadequate as most of the data was limited and consisted of grab samples and not TWA measurements. However, there is sufficient UK monitoring data available for vapour degreasing. The mode of use of trichloroethylene in vapour degreasing in the U.K. is similar to that in Australia and the U.K. monitoring data was used to estimate worker exposure. Monitoring by HSE inspectors between 1984 and 1994 showed that of 25 personal samples (8 h TWAs), 96% were <30 ppm and all were less than 50 ppm (United Kingdom, 1996). Based on this data exposure was estimated for 3 scenarios, 10, 30 and 50 ppm. The combined MOE for both inhalation and dermal exposure for the three scenarios were 34, 12 and 7 respectively. The severity of the renal toxicity, with higher doses causing tumours in animals, suggests the need for a high margin of safety. The MOE at all the levels calculated for vapour degreasing are of concern.

Inhalational values may be overestimated to some extent as most workers are involved in other activities in addition to vapour degreasing. However in some workplaces workers are involved in only operating the degreasers. Poor work practices and working conditions such as poor ventilation or lack of proper protective equipment may lead to increased exposure. Some of the commonly reported examples of poor work practice in the literature included workers ignoring the recommended speed for lowering and raising workloads from the degreaser and not holding the workload in the freeboard zone for a sufficient time.

Exposure during vapour degreasing is mainly to vapours. Dermal absorption of trichloroethylene vapour is negligible resulting in minimal absorption through the skin. Dermal exposure to the liquid during vapour degreasing is considered to be incidental and may occur during activities such as filling degreaser with trichloroethylene or handling of the degreased parts containing trapped liquid chemical. More frequent dermal exposure will lower the MOE.

13.3.7 Risk during cold cleaning

Information obtained from industry indicates that 29% of the respondents use trichloroethylene in cold cleaning of metal parts. Common types of cleaning include immersion in tubs or tanks along with spraying or brushing of the metal parts. Manual wipe cleaning was another common method. Atmospheric monitoring has not been carried out at workplaces using trichloroethylene for cold cleaning.

Margins of exposure were estimated for exposure durations of 120 days/yr and 200 days/yr using the atmpspheric monitoring data obtained in the NICNAS cold cleaning project. Dermal exposure was assumed to occur for 5% of the shift. Estimated MOE for combined exposures (inhalation and dermal) for the various activities for 200 days/yr were 105 for dip cleaning, 91 - 34 for combined dip cleaning and rag wiping and 52 - 5 for rag wiping alone and for 120 days/year were 174 for dip cleaning, 152 - 56 for combined dip cleaning and rag wiping and 87 - 8 for rag wiping alone.

Other monitoring data available for assessment was available from Dow Chemical Company Product Stewardship Program, which focussed on the exposure profiles encountered during use of trichloroethylene in vapour degreasing and cold cleaning operations. For the average concentration obtained in this program (68.4 ppm), the estimated combined MOE (inhalational+dermal) was 4.4.

Some of the MOE calculated for rag wiping and dip cleaning combined with rag wiping (ie MOE < 50) indicate that there is a concern in these situations.

Dermal exposure may occur as cold cleaning involves immersion of metal parts in tubs or tanks accompanied by scrubbing or brushing of the immersed parts leading to agitation of trichloroethylene liquid with loss of vapour to the atmosphere and splashes and spills of the chemical. Dermal exposure may be higher where cold cleaning involves immersion of the hands into the tub or tank during scrubbing. High dermal and inhalation exposure is associated with manual wipe cleaning, where trichloroethylene is applied on a rag and used to clean surfaces. In many workplaces no engineering controls are in place during cold cleaning and, in one of the places interviewed, the gloves used during manual wipe did not offer any protection against trichloroethylene.

13.3.8 Risk during use of trichloroethylene products

Trichloroethylene is an ingredient in various products such as adhesives, electrical equipment cleaning solvents, metal degreasing solvents, waterproofing, paintstrippers, carpet shampoos and tyre repair products. Most of these products are for industrial use with some products identified for consumer use (tyre repair, paint stripper, aerosol waterproofing agent and component cleaner). Most of these products contain <60% trichloroethylene except for one tyre repair product and electrical equipment cleaning solvent. Very little information was provided on the use of trichloroethylene products. Due to the range of products and conditions and duration of use it is difficult to estimate exposure for all scenarios. The methods of use of these products are described in Chapter 8.

Acute adverse effects such as headache, dizziness and irritability have been reported by some workers using a degreasing product indicating exposure to high concentrations of trichloroethylene. The product was sprayed onto a cloth and used for wipe cleaning metal rods during the entire shift. Products used in spray form present a greater risk of exposure as the small aerosol particles are likely to be readily absorbed through the lungs and skin.

Some data was obtained on use of adhesives containing trichloroethylene. An atmospheric concentration of 1.15 ppm was detected in an adhesive spraying area with good natural ventilation. Concentrations of up to 21.4 ppm over a sampling time of 5-6 h were recorded in a US automotive factory using trichloroethylene containing adhesives.

As part of the project commissioned by NICNAS, WorkCover monitored atmospheric levels of trichloroethylene and urinary levels of trichloroacetic acid in workers using trichloroethylene products. Concentration of trichloroethylene in the products varied from spray painting (35% and 25%) to rag wiping for surface cleaning (20%) to brushing on the product (90%). Atmospheric levels monitored varied from 0.7 ppm to 4.8 ppm (spray painting); 3.8 ppm to 4.1 ppm (rag wiping); 2.5 ppm (brush application). Assuming incidental dermal exposure, the estimated margins of safety varied from 69 to 395 (spray painting) to 85 to 90 (rag wiping) to 117 (brush application). The MOE were estimated for an 8 h exposure and would be higher at places using the products for shorter periods.

13.3.9 Areas of concern

The risk assessment has indicated that there may be health concerns for workers exposed to trichloroethylene in some workplaces.

The limited short term exposure data available indicate that there may be a risk of acute CNS effects during certain stages of vapour degreasing when high exposure to trichloroethylene vapours may occur. Acute effects are also likely during use of trichloroethylene in cold cleaning for 8 h shifts in places with poor ventilation and during use of trichloroethylene products, especially in the form of aerosols. Although it is not possible to determine how representative monitoring data was in the NICNAS project for cold cleaning and trichloroethylene products, there is cause for concern as anecdotal evidence of dizziness, headache and irritability during these uses have been obtained during the assessment.

Estimates of MOE for repeated exposure indicated that there is little risk of adverse health effects during formulation, however there was concern for workers repeatedly exposed to trichloroethylene during vapour degreasing and cold cleaning, particularly from inhalation exposure. Dermal exposure was minor during vapour degreasing, however, as the risk of skin contact during cold cleaning is greater, the contribution by dermal exposure towards the risk of adverse health effects during cold cleaning may be significant.

In addition, while estimating human exposure in this assessment an average male weight of 70 kg was used. This may not be applicable to the majority of the population in sections of the metal industry and the textile and footwear industry which have a high proportion of female employees who are likely to be < 70 kg. The MOE would therefore be lower for these persons.

14. Risk Management

The key elements in the management of health and safety risks from exposure to hazardous substances include:

- control measures;
- hazard communication;
- atmospheric monitoring;
- regulatory controls; and
- emergency procedures.

An assessment of the measures currently employed and/or recommended to reduce occupational health risks associated with the use of trichloroethylene and trichloroethylene containing products is included in this chapter. MSDS and labels supplied by the importers and formulators are also assessed here.

14.1 Control measures

According to the *National Model Regulations for the Control of Workplace Hazardous Substances*, exposure to hazardous substances should be prevented, or where that is not practicable, controlled to minimise risks to health. A *National Code of Practice for the Control of Workplace Hazardous Substances*, lists the hierarchy of control measures, in priority order, that should be implemented to eliminate or minimise exposure to hazardous substances. These are:

- elimination;
- substitution;
- isolation;
- engineering controls;
- safe work practices; and
- personal protective equipment.

14.1.1 Elimination

Elimination means the elimination of chemicals from a process, such as using a physical process instead of a chemical process in cleaning.

A review of the manufacturing process by end-users may show that it is not necessary to use a chemical. For example, the requirements in a cleaning process may have changed due to improved materials or methods of production or a slight modification of the process may eliminate cleaning completely. Changing the work process can avoid components becoming soiled in the first place or reduce the level of soil, making cleaning easier.

Physical processes (Metal Finishing Association, 1996) that are effective for cleaning some types of soils from metals include:

- shot and vapour blasting;
- dry-ice blasting;
- steam cleaning; and

- ultraviolet or vacuum-thermal treatment

Hot aqueous cleaning for removing oils and grease is being used to clean metal parts at one workplace, instead of trichloroethylene.

14.1.2 Substitution

Substitution includes substituting a less hazardous substance, the same substance in a less hazardous form or the same substance in a less hazardous process.

A trichloroethylene substitute being used at one workplace for cleaning metal parts is sodium carbonate along with wetting agents applied at high temperature and pressure for removing heavy oils.

Alternatives to trichloroethylene in metal cleaning include aqueous and semi-aqueous systems and emulsion cleaning (Radian Corporation, 1990). Other aliphatic and aromatic organic solvents are also potential substitutes.

The aqueous systems involve parts being cleaned in a bath containing 5-10% surfactant or solvent, and being allowed to dry. The advantages of water-based processes are the absence of solvent emissions and generally lower material costs. Disadvantages are that the energy requirements may possibly be higher since the work may have to be dried after cleaning and rinse waters may need to be treated before discharge or reuse.

Semi-aqueous systems use solvents such as terpenes, dibasic esters and glycol ethers at 100% strength, or as a 50% emulsion followed by rinsing with water. These can be used to remove heavy oils and greases. The disadvantages are similar to those of aqueous cleaning such as the possible need for drying and appropriate effluent treatment.

A number of solvent blends are available for cold immersion and manual cleaning (United Nations Environment Programme Industry and Environment Programme Activity Centre (UNEPIE/PAC), 1992). These include mixtures of aliphatic and aromatic hydrocarbons (naphtha, toluene, xylene) and oxygenated solvents (ketones, esters and alcohols). Cold immersion in these blends removes heavy grease and other industrial contaminants. However, these alternatives are also likely to have adverse health effects.

Users need to evaluate the technical issues, cost, health and safety and environmental effects of each option when considering substitution of trichloroethylene. In particular, if replacement of trichloroethylene with another substance is considered, the human health and environmental effects and hazards of the substitute need to be considered to ensure that trichloroethylene is not being replaced by a more hazardous substance.

It should be noted that reverse substitution, that is, trichloroethylene replacing 1,1,1-trichloroethane, appears to be occurring with the phasing out of 1,1,1-trichloroethane under the Montreal Protocol. Current users of 1,1,1-trichloroethane should consider all available alternatives.

14.1.3 Isolation

Isolation involves separation of the process from people by distance or the use of barriers to prevent exposure.

During importation of trichloroethylene transfer of bulk trichloroethylene from ships to on-shore bulk tanks is largely isolated by means of dedicated pipe-lines. At two vapour degreasing sites, the vapour degreasing bath was isolated in a sealed, enclosed room.

14.1.4 Engineering controls

Engineering controls are plant or processes which minimise the generation and release of hazardous substances. They include enclosure or partial enclosure, local exhaust ventilation and automation of processes.

Bulk storage and transport

Engineering controls in use during bulk storage and transport include:

- automatic carbon adsorption vapour extraction system at a bulk storage site. This system draws air around hose connections at tanker and drum filling stations.
- mass flow meters for filling of tankers and drums to preset the volume and avoid overfilling.
- bunding of drum filling stations.

Formulation

The types of control measures used in formulation processes in Australia vary greatly, such as, the extent of enclosure of the process and type of ventilation.

Best practice to be followed during formulation is total enclosure of the process, including transfer of trichloroethylene to the mixing vessel through enclosed pipes. At the very least, the mixing vessel should be tightly closed during mixing and also when not in use and emptying of the mixing vessel into smaller containers should be through closed pipelines. Exhaust ventilation installed above the mixing tank ensures that the vapours are drawn away from the work area. Atmospheric monitoring at regular intervals ensures that the control measures are adequate to prevent exposure.

Vapour degreasing

The two main criteria of a well-controlled vapour degreasing operation are a good machine design and proper operating practices. A machine correctly sized for the work that is to be done minimises dissipation of trichloroethylene vapours into the working area and prevents release of large amounts of vapour to the workroom air.

Vapour degreasers vary in the degree of automation and closure of the plant. Some vapour degreasers are small to medium sized open-topped degreasers that are manually operated. Other degreasers vary from semi-automated plants with platform lifts that lower and lift work containers to large fully automated degreasers with conveyorised monorails that carry the work baskets through the tank.

The engineering controls that are currently in place at worksites and identified during this assessment include: fume extraction, rim ventilation, condensing coils, condenser water jacket, temperature control system, rolling or sliding tank cover, overhead crane/hoist, and adequate freeboard. Several workplaces stated that the degreaser tank was of “approved” design which was interpreted during assessment as conforming to the requirements of the Australian Standard AS 2661 (Standards Association of Australia, 1983).

The above standard, prepared by the Standards Association of Australia, includes safety requirements for design, construction, installation, and operation of a degreaser plant. The emission control measures indicated in AS 2661 include:

- adequately sized tank to prevent spillage or dissipation of solvent;
- suitably sized freeboard zone to prevent vapour turbulence, with a freeboard ratio of not less than 0.75;
- an exhaust if provided in open tanks to be incorporated along the top edge of the tank;
- a thermal cutout in the boiling sump liquors to protect against overheating of solvent;
- a thermal cutout in the freeboard zone above the condensing coils to protect against vapour emission from the tank;
- temperature indicator for sensing the temperature of the boiling sump;
- close fitting sliding or rolling covers below the rim ventilation slot. Hinged covers tend to draw the vapours out by a piston effect leading to solvent loss and exposure of the worker while flat covers slide horizontally off the machine and reduce the disturbance to the vapour layer;
- low temperature coolant such as water or refrigerant to be used to maintain vapour level in degreasing plant to a safe level;
- an overhead lifting device operating at a controlled rate not exceeding 3 m/min. Mechanical parts handling system reduce emissions by moving parts into and out of the machine at appropriate rates and eliminate the excess losses caused by manual operation. Another advantage of a mechanical transport system is that the operator works farther away from the degreasing tank. In manual operations, a person will be near the tank frequently and may have to bend over the top of the cleaner to lower or extract parts.

A carbon adsorption system is an additional control technique that can be used with a lip exhaust ventilation system. In this system the diffusing solvent vapours and the vapours evaporating from clean parts pass through the exhaust ducts to an activated carbon bed. The solvent molecules are adsorbed onto the activated carbon from the stream before discharging to the atmosphere. When the carbon becomes saturated with solvent the bed is desorbed to remove the solvent from the carbon. The solvent/stream mixture is then condensed and passed through a water separator, and the recovered solvent is returned to the tank.

Cold cleaning

Trichloroethylene is used for cold cleaning in a variety of ways in Australia (see Chapter 8). Based on the limited data obtained from the NICNAS survey, it would appear that there are few engineering controls in place during use of trichloroethylene in cold cleaning. Use of a fume cupboard or portable fan or local exhaust ventilation was stated by some workplaces. In one workplace where cold cleaning involved immersing parts in a tank containing trichloroethylene the tank was provided with a cover to minimise dissipation of the solvent into the atmosphere. Most places using the chemical in cold cleaning stated that it was done in an area with good natural ventilation.

The project commissioned by NICNAS indicated that no engineering controls are in place during use of trichloroethylene in cold cleaning.

Local exhaust ventilation is extremely important during cold cleaning as large amounts of trichloroethylene could be lost to the atmosphere during this process. Proper positioning of the local exhaust ventilation is important to prevent passage of solvent through the workers breathing zone.

Use of trichloroethylene products

A number of products containing trichloroethylene are in use in Australia, the most common being its use in adhesives. Although little information was available for the assessment of application of adhesives, it does indicate that ventilation provided is extremely variable. From the data available for assessment it appears that application of adhesives involving painting and spraying is generally carried out in spray booths. Control measures identified during use of other trichloroethylene products vary from extraction ventilation to fume cupboards to vented table.

14.1.5 Safe work practices

Safe work practices have an important role in reducing solvent emissions and therefore solvent consumption. Information obtained during the assessment indicates that the safe work practices followed at some of the work sites are:

- adherence to the manufacturer's instructions of starting up, operating and closing down of vapour degreasing tanks;
- holding workload in the degreasing zone for some time before drawing out to allow adequate draining/drying time;
- loading the parts to be degreased into the basket at an angle to facilitate draining of the solvent. Improper loading of parts can lead to trapping of solvent in the parts with evaporation into the atmosphere.
- regular checks of the sump temperature indicator to determine changing of solvent.

Other safe work practices that may be followed to reduce solvent loss are:

- avoid overloading of the tank. A general recommendation is that workloads not exceed more than 50% of the total interface area;
- baskets, racks or hangers used to hold the metal parts for degreasing should not be made of porous materials as they will absorb trichloroethylene and remove it from the degreaser;
- if sprays are used to assist in cleaning, spraying should be done below the vapour layer; spraying at a downward angle also helps to reduce emissions;
- slow speed for entry and exit of workloads. Increasing the speed of entry of workload displaces the solvent out of the tank while rapid extraction of parts leads to solvent vapour being pulled out of the tank;
- solvent soaked rags and swabs should be disposed of in closed metal bins;
- topping up of the tank with the solvent should not be done when the degreaser is hot. Trichloroethylene should be pumped in at a low level with the cooling water system and the rim ventilation operational. Adding solvent from the top while the plant is hot can lead to high worker exposure. Regular checks should be made of the solvent levels;
- placement of vapour degreaser tanks away from sources of direct draughts such as open windows or doorways or a fan as this is likely to lift vapour over the freeboard of the tank into the surrounding work areas;

- installation of the tank in a well ventilated area so that any vapour that may be dragged out with the work will be quickly removed;
- location of the tank away from naked flames and welding operations as trichloroethylene decomposes at high temperatures to phosgene, hydrochloric acid and chlorine.
- The Australian Standard AS 2865 (1995) "Safe working in a confined space" (Standards Australia, 1995) should be strictly adhered to for entry into and work in a confined space.
- Regular and frequent cleaning of degreasers avoids the baking of contamination on to internal walls. AS 2661 (Standards Association of Australia, 1983)includes the safe work practices to be adopted during maintenance and cleaning of a vapour degreasing plant.

14.1.6 Personal protective equipment

Personal protective equipment (PPE) is used to minimise exposure to or contact with chemicals. PPE should be used in conjunction with other engineering controls and not as a replacement. Where other control measures are not practicable or adequate to control exposure then PPE should be used. Exposure to trichloroethylene is mainly by inhalation and skin contact and the PPE selected should protect the worker against exposure by these routes.

Dermal exposure may be prevented by use of protective gloves. It is important to select gloves that are resistant to the chemical exposed. Information provided for assessment indicates that gloves are generally provided at most workplaces. However, most of the workplaces did not specify the type of gloves used. Types of gloves specified by some end users were nitrile, rubber and viton gloves.

Recommendations on types of glove to use with particular chemicals are provided by many glove manufacturers, and a number of books and databases. Recommendations are usually based on tests of degradation, that is, changes in physical properties of gloves following contact with the chemical such as swelling or hardening, and permeation, that is, the movement of the chemical through the material at a molecular level. Two common measures of permeation are breakthrough time and permeation rate. It should be noted that test results from gloves made of the same generic material can differ due to differences in manufacture, and so test data relating to specific glove brands may be preferable to test data relating only to material type.

Recommendations based on these types of tests should provide a starting point only for the selection of gloves, and in choosing gloves, regard should always be had for the particular work activities for which the glove is to be used. The glove with the highest breakthrough time and lowest permeation rate may not always be necessary. Factors that need to be considered in conjunction with test data include:

- duration, frequency and degree of chemical exposure;
- the degree of physical stresses that will be applied;
- the temperature of the chemical (heat may change the permeation rate of the chemical through the glove);
- in the case of formulations, the degree of protection that the glove provides for other ingredients, and possible synergistic effects;
- the likelihood of the glove coming into contact with water or other chemicals that may effect the glove's performance against the chemical for which it is recommended.

No work processes involving long periods of immersion of hands in trichloroethylene were identified, however some work processes presented the possibility of intermittent or occasional contact with liquid trichloroethylene (hot and/or cold) or trichloroethylene products. This information suggests that gloves with ratings that indicate protection against intermittent exposure, as opposed to total immersion, may be acceptable in most workplaces.

A comparison of the ratings provided by some primary sources for gloves made from various types of material as summarised in table 32 shows a general agreement on materials that are not recommended, or considered to provide poor protection against trichloroethylene. However, there is greater variability about the types of gloves which are recommended. Materials recommended by one or more sources include PE/EVAL, PE/EVAL/PE, Silvershield, chlorobutyl, chloroprene rubber, and teflon. The materials *not* recommended include butyl, chlorinated polyethylene (CPE), neoprene, polyethylene (PE), and nitrile/PVC. Materials over which there are different recommendations are: natural rubber, PVC and nitrile, which are recommended in the Australian Standard but not recommended by other sources; and PVA and viton, which are rated as poor by the ACGIH, but recommended by other sources. It can be seen that materials unanimously not recommended by sources included some materials that were recommended by some MSDS, i.e neoprene and polyethylene. PVC, nitrile and natural rubber were also recommended on some MSDS, although the majority of the sources recommended that they not be used.

A survey of six retail outlets for protective gloves in Sydney and Melbourne found that PVA gloves were the glove usually recommended for protection against trichloroethylene. Prices quoted for one brand varied from $37 to $44. Two outlets mentioned that PVA breaks down easily in the presence of water. Viton gloves were recommended by one outlet, with price quoted at $314 per pair. One outlet recommended PVC gloves for jobs involving low level of exposure, quoting a price of $2 a pair. This survey highlights the practical aspect of choosing gloves, and the role of manufacturers and suppliers in making available appropriate gloves and information.

For formulated products gloves should be selected on the basis of the component with the shortest breakthrough time.

Protective gloves are to be used when contact of skin with trichloroethylene is likely, such as during loading and unloading of work parts from the vapour degreaser, during cold cleaning, clean up of spills or during other work processes when splashes are likely.

Covering of arms and legs is useful during handling trichloroethylene and overalls or long sleeved shirts and trousers may be used.

Respiratory protection is not required in most situations. However a face mask with organic vapour cartridge should be worn when exposures are likely to be high, such as during clean up of large spills.

The NICNAS industry survey indicated that if entry into a degreasing tank was necessitated for cleaning, workers were provided with self-contained breathing apparatus.

14.2 Emergency procedures

Information on emergency procedures was not submitted for assessment.

Written procedures for workers for handling spills and other emergencies during formulation and use of trichloroethylene is good practice. Procedures to be followed during clean up of spills and first aid procedures should be recorded on the MSDS.

Trichloroethylene is listed in the Australian Code for the Transport and Handling of Dangerous Goods (ADG Code) which provides guidelines for handling emergencies during transport (Federal Office of Road Safety, 1998).

Table 32 -Ratings for glove materials for protection against trichloroethylene by various information sources

Type of material	Manufacturers' Guides				Literature		Database	Standards	
	Alsafe Safety Brochure[1]	Ansell[2], 1990	BEST[3], 1994	Siebe North[4], 1990	ACGIH Little, 1990[5]	Forsberg & Mandorf[6]	glovES+ Expert System[7]	AS2161[8]	AS2661[9]
Butyl			NR	POOR	POOR	NR			
Chlorinated Polyethylene (CPE)					POOR				
Viton	REC		EXC	GOOD	POOR	REC	REC		
Neoprene		NR	NR		POOR	NR			
Natural Rubber		NR	NR		POOR	NR		FAIR	
PVC		NR	NR		POOR	NR		FAIR	
Polyethylene (PE)					POOR	NR			
Polyethylene/ethylene vinyl alcohol (PE/EVAL)						REC			
PE/EVAL/PE							REC		
PVA	REC	EXC			POOR	REC			
Nitrile		NR	NR	POOR	POOR	NR		GOOD	REC
Teflon					GOOD	QUEST	REC		
Silvershield				EXC	GOOD		REC		
Chlorobutyl					GOOD				
Chloroprene rubber								FAIR	
Nitrile/PVC					POOR				

NR=Not recommended; EXC=Excellent; QUEST=May be unsuitable for use, except for situations where only short periods of use are needed and chemical has minimal dermal hazard. Breakthrough time between 1-4 hours, low permeation rate (<1 mg/m^2 min)

[1]Provides an overall rating for 'chemical resistance'.
[2] Ansell Edmont Industrial. *Ansell Edmont Chemical Resistance Guide* (5th Ed), 1990. Ratings are overall recommendations based on degradation and permeation data.
[3] Best. *Calender Guide to Chemical-Resistant Best Gloves* (2nd ed) 1994 'Not recommended' rating is used for gloves for which degradation resistance is poor. 'Excellent' rating is based on degradation and permeation data.
[4]'Excellent' = fluid has no effect and glove is good for total immersion. 'Good' = fluid has minor degradation effects and glove is good for accidental splash/intermittent exposure. 'Poor' = fluid has severe degradation effects and glove is not recommended.
[5] Little, A.D,. *Guidelines for the selection of chemical protective clothing, Vol I and II* (3rd ed), ACGIH, Cincinnati, Ohio.
[6] Forsberg, K and Mansdorf, S.Z, *Quick selection guide to chemical protective clothing* (2nd ed), Van Nostrand Reinhold, NY.
[7] *GlovES+ Expert System*, Keith L. Radian Corporation, Austin, TX, US. The results presented here are from a search conducted on the database by industry. The parameters input for this search included a) frequent exposure to trichloroethylene, that is, splash situations where glove is often but only partially exposed to trichloroethylene; b) task time of 240 minutes; c) moderate tactility. It should be noted that not all tasks involving trichloroethylene will conform to these parameters.
[8]Standards Association of Australia , *AS2161 - 1978: Industrial Safety Gloves and Mittens*, SAA, North Sydney, 1978
[9]Standards Association of Australia, *AS2661 - 1983: Vapour degreasing plant - design, installation and operation - safety requirements*, SAA, North Sydney, 1983.

14.3 Hazard communication

14.3.1 Assessment of Material Safety Data Sheets

Introduction

MSDS are the primary sources of information for the safe handling of chemical substances. Under the *National Model Regulations for the Control of Workplace Hazardous Substances* (the National Model Regs.) (National Occupational Health and Safety Commission (NOHSC), 1994) and corresponding State and Territory legislation, suppliers are required to provide MSDS to their customers for all hazardous substances. Employers must ensure that MSDS for any hazardous substance used in the workplace is readily accessible to employees with potential for exposure to the substance.

Trichloroethylene is currently on the *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994) as a hazardous substance in concentrations at or above 1%. During assessment of MSDS in this report comparisons are made with the current listing and classifications. Seven MSDS for trichloroethylene (>99%) and 46 MSDS for trichloroethylene-containing products were submitted and assessed for compliance with the *National Code of Practice for the Preparation of Material Safety Data Sheets* (the MSDS Code) (National Occupational Health and Safety Commission (NOHSC), 1994). The 46 products contain >1% trichloroethylene (range 10% - >90%) and are therefore considered hazardous substances. Most products contain high concentrations of trichloroethylene, with almost one half (20) containing >60% trichloroethylene (see table 3 in chapter 7 for more information on concentration of trichloroethylene in products). An MSDS for one other product, a paint stripper, was also submitted but not included in the assessment as it contained 0.05% trichloroethylene.

The MSDS were divided into two groups, ie MSDS for trichloroethylene (>99%) and products containing trichloroethylene, for assessment. The assessment focussed on the adequacy of the information provided in relation to the following core elements of an MSDS: product identification; health hazard information; precautions for use; safe handling information; and contact point. Information considered most important in each of these sections was identified and checked for inclusion. The presence of an emergency telephone number and a statement of hazardous nature as required under the MSDS Code were also checked. The statement of hazardous nature required to be on MSDS for all hazardous substances is: 'Hazardous according to criteria of Worksafe Australia'. The findings of the MSDS assessment are given in Table 33.

A sample MSDS for trichloroethylene, prepared in accordance with the MSDS Code, is provided in this report as Appendix 2. The sample MSDS, prepared from information obtained for the assessment of trichloroethylene is for guidance purposes only. Under the National Model Regulations, manufacturers and importers have the responsibility to compile their own MSDS and ensure that the information is up-to-date and accurate.

Table 33 - Findings of MSDS Assessment

	Trichloroethylene (>99%)		Trichloroethylene products	
Information	**Number MSDS**	**Comments**	**Number MSDS**	**Comments**
Total	**7**		**46**	
Statement of Hazardous Nature	3/7		9/46	
Emergency telephone no.	4/7		28/46	
Product Identification*				
Indicated major use(s)	6/7	(The same MSDS was missing all of these)	37/46	
UN Number, ADG Class, Hazchem Code	6/7		N/C	
Poison Schedule	6/7		27/46	
Ingredient concentrations				
Exact proportion or range	5/7		44/46	
Stabilisers present	5/7	3 did not disclose name of stabiliser	N/A	
Physical description/ properties	6/7		N/C	
Health Hazard Information				
Acute effects				
Irritant to upper respiratory tract	7/7		37/46	
Headache	4/7		42/46	
CNS depression symptoms such as dizziness, confusion, narcosis	6/7		40/46	
Unconsciousness/Death	7/7		33/46	
Cardiac effects	4/7		10/46	
Nausea/Vomiting	4/7		35/46	
Eye irritant/corneal damage	7/7	2 stated that corneal damage is unlikely	44/46	
Skin irritant	7/7		43/46	
Defatting of skin	7/7		39/46	
Absorption through skin	3/7	2 other MSDS stated that it was not readily absorbed through the skin	27/46	One other stated 'not absorbed rapidly'
Chronic effects				
CNS disturbance or symptoms of	6/7		21/46	
Hearing loss	2/7		0/46	
Liver damage	6/7		23/46	
Kidney damage	5/7		21/46	
Carcinogenicity	6/7	2 mentioned that it was listed by NOHSC as a Class 3 carcinogen; 3 mentioned IARC classification Group 3 (now outdated); one mentioned positive response in mice.	20/46	4 mentioned NOHSC Class 3 classification; 10 referred to the IARC classification Group 3 (now outdated); 6 others mentioned carcinogenicity in mice. 2 others (not included in these 20) stated there were no long-term data and 'probably not carcinogenic'
*First Aid Statements**				
If poisoning occurs, contact a doctor of Poisons Information Centre.	6/7		36/46	

Table 33 - Findings of MSDS Assessment (cont.)

	Trichloroethylene (>99%)		Trichloroethylene products	
If swallowed, do NOT induce vomiting. Give a glass of water.	4/7	2 others had contrary instructions to induce vomiting	30/46	8 had instruction to induce vomiting. 6 additional warned of dangers of aspiration and had instruction to leave decision to doctor.
Avoid giving milk or oils	2/7	2 others had contrary instructions to give milk	12/46	8 others said to give milk, 1 had conflicting instructions about giving of milk.
Avoid giving alcohol	2/7		21/46	
If skin contact occurs, remove contaminated clothing and wash skin thoroughly.	7/7		45/46	
Remove from contaminated area. Apply artificial respiration if not breathing	7/7		46/46	
If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.	7/7		46/46	
Advice to doctor				
Avoid sympathomimetic Amines	7/7		9/46	17 did not have an 'advice to doctor' section
Precautions for Use				
Correct value for TWA and STEL exposure standard	7/7	ACGIH was quoted as the source in 3 cases.	34/46 TWA 19/46 STEL	ACGIH and OSHA were quoted as the source on 12 MSDS. 5 gave TWA for mixture; 2 said no TLV established; 1 gave TWA of 100 ppm without saying for what chemical
Adequate ventilation	7/7		41/46	
Local exhaust ventilation	6/7		31/46	
Reference to AS 2661	0/7		N/A	
Gloves (non specific)	2/7		12/46	
- Nitrile or Fluorocarbon	1/7			
- PVC	2/7		4/46	
- PVC or Rubber	2/7			
- Neoprene or Viton			4/46	
- Neoprene, nitrile or rubber			6/46	
- Natural rubber			1/46	
- PVA			10/46	
- PVA, PE, or Viton			3/46	
- PVA, PVC or Viton			1/46	
- Viton			2/46	
Eye protection	6/7		41/46	
Respirator	6/7	(Specific types mentioned)	40/46	
Safe Handling Information	7/7		46/46	
Contact Point				
Title	3/7		22/46	
Telephone number	6/7		26/46	

N/C Information on UN Number, ADG Class, Hazchem Code, and the physical description/properties section for mixtures were not checked as the information would vary according to the ingredients.

N/A not applicable

* First Aid Statements as recommended by SUSDP for substances containing trichloroethylene.

Discussion of findings

Amongst both groups of MSDS, the Safe Handling Information section provided adequate information. Information considered important for this section was reference to appropriate conditions of storage, storage/transport incompatibilities, spills/disposal instructions, mention that fumes could evolve, and recommendations for fire fighters (see sample MSDS for details). However, deficiencies were noted in other sections, including:

- omission of a Statement of Hazardous Nature
- in the case of one MSDS for trichloroethylene, omission of several elements in the product identification section - major uses, UN Number, ADG Code, Hazchem Code and Poison Schedule.
- omission of information on use of products.
- in the acute health effects section, omission of information on skin absorption and cardiac effects; also nausea, headache, irritation to the upper respiratory tract, CNS symptoms, including unconsciousness, and skin defatting
- in the MSDS for products, omission of information on chronic health effects
- inappropriate first aid instruction to induce vomiting if ingested
- inappropriate first aid instruction to give milk if ingested
- omission of first aid instructions to avoid giving oils, milk or alcohol
- omission of Australian exposure standard for trichloroethylene or citing of the ACGIH or other overseas exposure standards instead of the Australian exposure standard.

Of the points listed above, the omission on one trichloroethylene MSDS of most product identification information is of concern. The UN Number, ADG class, Hazchem code and Poisons Schedule classifications contain information relating to hazard identification and emergency response and are important for safe handling.

In the health hazard section, inclusion of the fact that trichloroethylene is absorbed through the skin is especially important, as it highlights the need to avoid skin contact, such as through engineering controls, safe work practices or personal protective equipment. Cardiac effects was another significant health effect omitted on many of the MSDS, and is the reason that a statement on avoidance of sympathomimetic drugs is recommended for inclusion in the advice to doctor section. Many MSDS contained neither a reference to cardiac effects or a recommendation to avoid sympathomimetic drugs (17 did not have an 'advice to doctor' section at all).

With regard to first aid instructions, it was noted that instructions contrary to the recommended SUSDP instruction (c), that is, do NOT induce vomiting, were given on three MSDS for trichloroethylene and eight MSDS for mixtures. Vomiting creates a risk of aspiration of trichloroethylene into the lungs and while the presence of other poisons in mixtures may justify an instruction to induce vomiting, where the dangers of aspiration of trichloroethylene have been weighed against the dangers of ingestion of another poison, this was not the case in the cases examined in this survey.

Another significant omission in many MSDS was the Australian exposure standard for trichloroethylene, which should be listed in MSDS for mixtures as well as trichloroethylene. Listing of overseas exposure standards is allowed under the MSDS Code only where an Australian standard does not exist. A number of MSDS listed the ACGIH standard, which happens to be the same value as the Australian standard, or no standard at all.

Some information on carcinogenicity was provided in six of the seven MSDS for trichloroethylene and 20 of the MSDS for products. The variation in the information provided reflects the current uncertainty regarding its carcinogenic classification.

The need for adequate ventilation and local exhaust ventilation were mentioned in most MSDS, however none of the MSDS for trichloroethylene contained recommendations on engineering controls specific to the use of trichloroethylene in vapour degreasers, such as a reference to the Australian Standard 2661:*Vapour degreasing plant - design, installation and operation - safety requirements* (Standards Association of Australia, 1983). Under the MSDS Code, recommendations for engineering controls in the 'precautions for use' section should reflect the intended uses and common applications of the chemical. Vapour degreasing is a major use of trichloroethylene, reflected in the fact that four of the six MSDS for trichloroethylene specifically mention vapour degreasing in the 'use' subsection, while the two others that contained a 'use' subsection referred to metal degreasing.

The MSDS Code requires that if special requirements for gloves exist to prevent skin exposure, they should be clearly stated. For instance, 'protective gloves' may not be sufficient in some cases. The assessment of MSDS for trichloroethylene and trichloroethylene-containing products indicated wide variation in the type of glove recommended for use. Types recommended included: nitrile or fluorocarbon (1); PVC (5); PVC or rubber (2); neoprene or viton (4); neoprene, nitrile or rubber (6); natural rubber (1); PVA, PE, or viton (3); PVA, PVC or viton (1); viton (2); PVA (10). Some MSDS (14) recommended the use of gloves but did not specify a type of glove that should be used, while three MSDS did not mention the use of gloves at all.

14.3.2 Assessment of labels

Introduction

Labels for trichloroethylene and trichloroethylene-containing products were assessed for compliance with the requirements of the *National Code of Practice for the Labelling of Workplace Substances* (the Labelling Code) (National Occupational Health and Safety Commission (NOHSC), 1994) and the *Standard for the Uniform Scheduling of Drugs and Poisons* (the SUSDP) (Australian Health Ministers' Advisory Council, 1997).

Trichloroethylene is listed in schedule 6 of SUSDP, except when used therapeutically in which case it is listed in schedule 4. Labelling of domestic end-use products should comply with the SUSDP labelling requirements.

Substances which are covered by the SUSDP but which are packed and sold solely for industrial use should comply only with the Labelling Code. Products used industrially and domestically need to comply with both codes, ie the SUSDP along with additional labelling information in accordance with the Labelling Code.

A total of 44 labels were assessed, comprising of 8 for (>95%) trichloroethylene and 36 for trichloroethylene-containing products. Forty one labels, including the eight for trichloroethylene, were for industrial products. They were screened solely for compliance with the Labelling Code. One label was for a consumer product available to the general public and was screened only for compliance with the SUSDP. Two other products were available to the public but could be expected to be used in the workplace, so they were screened for compliance with both the SUSDP and the Labelling Code.

1) Industrial products - compliance with the Labelling Code

Hazardous substances used in the workplace should be labelled in accordance with the Labelling Code. According to the current *List of Designated Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994) industrial substances containing 1% of trichloroethylene are hazardous. Current risk and safety phrases are:

- R40 Possible risk of irreversible effects
- R36 Irritating to eyes
- R38 Irritating to skin

Current safety phrases are:

- S23 Do not breathe gas/fumes/vapour spray
- S36/37 Wear suitable protective clothing and gloves

Other requirements are: the presence of the signal word POISON; product name; details of the amount of trichloroethylene present (exact amounts or ranges); instructions on the control of leaks, spills or fires; the name and address in Australia of the supplier and a telephone number where advice can be obtained; a reference to the MSDS and first aid instructions. The ADG dangerous goods class label (6.1) and UN Number (1710) for trichloroethylene are also required under the Labelling Code. Until recently, trichloroethylene was classed as 6.1(b) and the class label was 'Harmful - Stow Away From Foods'. In December 1994, the UN Committee of Experts on Dangerous Goods decided to eliminate this class label and replace it with the skull and cross bones diamond, with the word 'Toxic'. The most recent edition of the ADG (Federal Office of Road Safety, 1998) has picked up these changes. Either were considered acceptable for the purposes of this assessment.

The products intended solely for industrial use all contained >1% trichloroethylene and the labels (33) were examined for compliance with the requirements listed above. The results are presented in table 34. Compliance with some other requirements of the Labelling Code, such as directions for use were not examined in this assessment.

Table 34 - Compliance with the Labelling Code

Requirement prior to this assessment	Trichloroethylene (8)	Products (33)
R40	2/8	13/33
R36	0/8	7/33
R38	0/8	7/33
S23*	8/8	28/33
S36/37	3/8	12/33
- S37 only	3/8	3/33
POISON	7/8	12/33
product name	8/8	33/33
disclosure of ingredient (trichloroethylene)	8/8	29/33
statement of strength (of trichloroethylene)	5/8	10/33
emergency instructions	2/8	7/33
supplier details	8/8	16/33
telephone number	5/8	14/33
reference to MSDS	2/8	9/33
ADG Code (6.1 or 6.1b)	5/8	n/a
UN Number (1710)	8/8	n/a
First aid statements (or equivalent phrases)		
a. If poisoning occurs, contact a doctor or Poisons Information Centre.	6/8	32/33
c. If swallowed, do NOT induce vomiting. Give a glass of water.	6/8	12/33
d. Avoid giving milk or oils.	5/8	9/33
e. Avoid giving alcohol.	5/8	9/33
f. If skin contact occurs, remove contaminated clothing and wash skin thoroughly.	6/8	18/33
g. Remove from contaminated area. Apply artificial respiration if not breathing.	6/8	17/33
s. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.	6/8	20/33

*equivalent phrases such as the SUSDP safety phrase 'Avoid breathing dust (or) vapour (or) spray mist' were considered adequate.

n/a=not applicable

Summary

Labels for trichloroethylene:

The majority of labels contained safety phrases S23 and S37, the signal word POISON, ingredient disclosure and statement of strength, UN Number, and ADG goods class label. One of the labels had the wrong ADG class label, 6.1(a), and two had no class label. No labels contained risk phrase R36 or R38, and most did not contain risk phrase R40, safety phrase S36, emergency procedures, or reference to the MSDS. Two labels did not have any first aid instructions.

Labels for products:

The majority of labels contained safety phrase S23 and disclosed the presence of trichloroethylene in the mixture, but did not disclose the proportion of trichloroethylene present. Few contained risk phrases R36, R38 or R40, safety

phrase S36/37, emergency procedure instructions, or reference to the MSDS. Less than half contained the signal word POISON. In addition, only 16 gave an Australian supplier's name. First aid instructions relating to ingestion (phrases 'c', 'd' and 'e') were present on less than half of the labels. Five labels, however, contained the SUSDP first aid statement 'b' "If swallowed and if more than 15 minutes from a hospital induce vomiting, preferably using Ipecac Syrup APF". This phrase is contrary to that recommended by the SUSDP for trichloroethylene, and an analysis of the other ingredients in these four mixtures against SUSDP requirements did not appear to justify the over-ruling of phrase 'a'.

2) Domestic products - compliance with SUSDP

Three of the labels provided were for products available to the public and should be labelled according to SUSDP requirements. The SUSDP requires that where the concentration of trichloroethylene in a product is 71.5 g/L or 71.5g/kg or more, the product should display the following safety directions and warning statement:

- SD1 Avoid contact with eyes
- SD4 Avoid contact with skin
- SD5 Wear protective gloves when mixing or using
- SD8 Avoid breathing dust (or) vapour (or) spray mist
- SD9 Use only in well ventilated area
- WS12 Vapour is harmful to health on prolonged exposure

Products containing less then 71.5 g/L or 71.5 g/kg need only contain statement 'a'.

Some other elements required to be present on labels for all products containing trichloroethylene (regardless of strength) are: the approved name 'trichloroethylene' and a statement of the quantity or strength; the signal words and phrases POISON; NOT TO BE TAKEN; KEEP OUT OF REACH OF CHILDREN; the name of the manufacture or distributor or the brand name or trade name used exclusively by the manufacturer or distributor. The three labels were checked for compliance with these requirements. Labels were also checked for the presence of first aid instructions recommended by the SUSDP for substances containing trichloroethylene. The results are presented in Table 35.

Table 35 -Results of assessment of three labels for compliance with the SUSDP.

Requirements prior to this assessment	Label 1	Label 2	Label 3
SD1	No	No	No
SD4	No	No	No
SD5	No	Equivalent	Equivalent
SD8	No	Equivalent	Equivalent
SD9	No	No	No
WS12	No	No	No
Approved name	No	Yes	Yes
Statement of strength	No	No	No
POISON	No	No	No
NOT TO BE TAKEN	No	No	No
KEEP OUT OF REACH OF CHILDREN	Yes	No	No
Name of manufacturer/distributor or brand/trade name	Yes	No	No
First Aid Instructions			
a. If poisoning occurs, contact a doctor or	Yes	Equivalent	Equivalent
Poisons Information Centre.	No	No	No
c. If swallowed, do NOT induce vomiting. Give a glass of water.	No	No	No
d. Avoid giving milk or oils.	No	No	No
e. Avoid giving alcohol.	No	No	No
f. If skin contact occurs, remove contaminated clothing and wash skin thoroughly.	No	No	No
g. Remove from contaminated area.	No	No	No
Apply artificial respiration if not breathing.	No	No	No
s. If in eyes, hold eyes open, flood with water for at least 15 minutes and see a doctor.			

Summary

All three labels demonstrated very poor compliance with the SUSDP. Label 1 is for a product used only for domestic purposes and contains over 60% trichloroethylene. Labels 2 and 3 were for products used both industrially and domestically and contained <60% and >90% trichloroethylene respectively. Labels 2 and 3 are required to comply with the Labelling Code as well as the SUSDP, and so they were checked for the additional elements required according to the Labelling Code. It was found that the labels contained risk phrase R40, but not risk phrases R36 or R38. They contained appropriate safety phrases (S23, 36/37), however they were lacking in emergency instructions, contact telephone number, and reference to the MSDS.

Discussion of findings

Deficiencies common to labels for pure trichloroethylene and mixtures used industrially were:

- omission of a risk phrase warning of irreversible effects (R40);

- omission of a risk phrase regarding irritation to eyes (R36);
- omission of a risk phrase regarding irritation to skin (R38);
- omission of a safety instruction regarding the wearing of protective clothing (S36); and
- omission of emergency procedures for clean-up of spills, leaks or fires.

In addition, labels for the mixtures had the following deficiencies:

- omission of safety instruction regarding the wearing of gloves (S37);
- omission of the signal word POISON; and
- omission of details of the amount of trichloroethylene in the mixture.

Compliance with the SUSDP in the case of three products used domestically was very poor, with most requirements not present.

14.3.3 Education and training

Guidelines for the induction and training of workers exposed to hazardous substances are provided in the National Commission's *National Model Regulations for the Control of Workplace Hazardous Substances,* (the Model Regulations) (National Occupational Health and Safety Commission (NOHSC), 1994). Under these regulations employers are obliged to provide training and education to workers handling hazardous substances.

The Model Regulations stipulate that training and induction should be appropriate for the workers concerned. It is important that each workplace implement a program that is suitably designed to accommodate the needs of different workers.

Training should be given to the workers at induction and repeated at regular intervals to reinforce the information. Training and education needs for workers should be reviewed on a regular basis.

For trichloroethylene, the training program should address:

- acute and potential chronic health effects of trichloroethylene;
- skin absorption potential and skin effects of trichloroethylene following prolonged exposure;
- explanation of MSDS and labelling of trichloroethylene and trichloroethylene products; and
- use and maintenance of personal protective equipment.

In addition, training for workers involved in vapour degreasing should include:

- basic plant operation, covering start up procedures, checking cut outs, cooling and solvent condition, loading, unloading and jigging work and delays in the freeboard zone;
- procedures to be followed during cleaning of degreasing tanks, particularly regarding procedures for working in confined spaces when entering the tank is required.

Information obtained for assessment indicates that very few places have written instructions or formal training for workers. Most of the worksites provide "on the job" training where the supervisor trains the new employee in the various activities involved. Only one of the six workplaces visited had a training manual and operating procedures and the training was repeated every 12 months.

Most importers of trichloroethylene provide technical bulletins which give information about the specifications of trichloroethylene, it's physical properties and uses. One importer provides a Product Stewardship Manual for chlorinated solvents to end users. The manual includes information on precautions for the safe handling, storage and use of chlorinated solvents including trichloroethylene. It also includes information on safe work practices to be followed while operating a degreaser and cleaning of a degreasing tank. These bulletins and manuals may be used as aids to draw up training programs that would be useful to workers.

14.4 Monitoring and regulatory controls

14.4.1 Atmospheric monitoring

Atmospheric monitoring is not conducted on a regular basis at workplaces in Australia using trichloroethylene. No monitoring data were available for worksites engaged in repacking or formulating. Some workplaces conduct air monitoring on an ad hoc basis during vapour degreasing. The reasons for conducting monitoring varied from a need to establish base-line monitoring results following modifications to the degreaser and complaints of solvent fumes following installation of a new plant to need to improve employee safety.

Under the National Commission's *National Model Regulations for the Control of Workplace Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994), employers need to carry out an assessment of the workplace for all hazardous substances, with methodology for the assessment provided in the *Guidance Note for the Assessment of Health Risks Arising from the Use of Hazardous Substances in the Workplace* (National Occupational Health and Safety Commission (NOHSC), 1994). When the assessment indicates that the risk of inhalation exposure is significant, atmospheric monitoring should be conducted to measure trichloroethylene concentrations in the workplace. Monitoring provides an indication of the effectiveness of the control measures in place and whether there is a need to improve measures to reduce worker exposure. Atmospheric monitoring should be repeated if any changes are made to the process or equipment.

Analytical methods for the measurement of trichloroethylene in air are detailed in Chapter 6.

14.4.2 Exposure standard

The current Australian occupational exposure standard for trichloroethylene, reviewed in 1990, is 50 ppm (8 h TWA) with a short term exposure limit (STEL) for 15 min. of 200 ppm. The National Occupational Health and Safety Commission's Exposure Standards Expert Working Group concluded in 1990 that studies of industrial situations reported subjective symptoms, such as mild

irritation, headache and dizziness at 50 ppm while controlled laboratory studies reported anaesthetic effects may begin to occur at about 100 ppm and would be mildly felt at 200 ppm. The STEL is recommended on the basis that it is low enough to protect against early anaesthetic effects. The documentation states that these levels should provide a safety margin for preventing other health effects such as liver toxicity.

Table 36 lists the exposure standards in various countries.

The hazard assessment indicates that:

- the critical effect is renal toxicity;
- the inhalation NOAEL for renal toxicity is 100 ppm and the LOAEL is 300 ppm (these values do not incorporate any safety factor);
- a classification of carcinogen Category 2 is appropriate;
- a classification of mutagen Category 3 is appropriate; and
- trichloroethylene is absorbed through the skin.

Table 36 - Occupational exposure limits

Country	TWA	STEL	Year adopted
Australia	50ppm	200 ppm for 15 min	1990
Canada			
Ontario	50 ppm	200 ppm	1995
British Colombia	50 ppm	150 ppm for 15 min	1991
France	75 ppm	200 ppm	
Germany	50 ppm C	250 ppm with a maximum duration of 30 min/shift occurring maximally twice per work shift.	
Netherlands	35 ppm	190 ppm	1992
New Zealand	50 ppm	200 ppm for 15 min	1994
Sweden	10 ppm	25 ppm for 15 min	1993
U.K.	100 ppm, skin notation	150 ppm for 10 min	1993
USA			
ACGIH	50 ppm	100 ppm	1992
NIOSH	25 ppm		
OSHA	50 ppm	200 ppm	1993

Note: C=pregnancy group C (no reason to fear risk of damage to the developing embryo when adhering to MAK or BAT values)

14.4.3 Biological exposure index

Biological monitoring is the assessment of exposure through measurement of the chemical or its metabolites in biological specimens. Estimations of trichloroacetic acid and trichloroethanol in urine and blood are recommended by ACGIH (ACGIH, 1992) and Germany (Deutsche Forschungsgemeinschaft, 1996) for biological monitoring of exposure to trichloroethylene. These are non-specific indicators of exposure to trichloroethylene as they can be metabolites of other chlorinated ethanes and ethylenes. Methods available for biological monitoring of trichloroethylene are detailed in Chapter 6 of the report.

The following biological exposure indices to determine exposure to trichloroethylene have been recommended by ACGIH and Germany.

Germany (1991):	Trichloroethanol in blood 5 mg/L at end of exposure or end of shift.
	Trichloroacetic acid in urine 100 mg/L at end of exposure or end of shift.
ACGIH: (1991-1992)	Trichloroacetic acid in urine 100 mg/g creatinine at the end of shift at the end of the workweek, as an indicator of integrated weekly exposure to trichloroethylene.
	Trichloroacetic acid and trichloroethanol in urine 300 mg/g creatinine with sampling time end of shift at end of workweek, as an indicator of integrated exposure to trichloroethylene.
	Free trichloroethanol in blood 4 mg/L at end of shift at end of workweek, as an indicator of recent exposure.

14.4.4 Health surveillance

Health surveillance is not routinely conducted for workers exposed to trichloroethylene.

Trichloroethylene was reviewed by the National Commission's Expert Working Group on Health Surveillance in 1993. It was decided not to include trichloroethylene in Schedule 3 (substances requiring health surveillance) of the *National Model Regulations for the Control of Hazardous Substances* (1994) as atmospheric monitoring was considered adequate to assess worker exposure and thus health surveillance was not warranted. There is therefore no formal requirement for health surveillance programs for workers.

Under the National Commission's *National Model Regulations for the Control of Hazardous Substances* (1994) health surveillance is required for employees where the workplace assessment has shown that there is a likelihood of an identifiable disease or health effect occurring under the particular conditions of work following exposure to a hazardous substance. The employer is responsible for providing health surveillance.

15. Public Health Assessment

15.1 Public exposure

The NICNAS industry survey revealed that half the users of trichloroethylene were engaged in metal forming/machining, while a further third of the users were powdercoating, automotive, aerospace or electrical industries. There is low potential for public exposure to trichloroethylene during industrial use.

When used in an industrial setting, most trichloroethylene which does not evaporate during use is recycled by distillation, although small amounts of trichloroethylene in tank washings may be discharged to sewerage as trade waste. No public exposure is anticipated from these activities. In domestic use, the principal fate of the solvent would be evaporation, although some trichloroethylene may be discharged to sewerage.

Several products containing trichloroethylene were identified as being available to the public. They comprise two tyre repair products (containing 60 and 90% trichloroethylene; total sales volume 5 tonnes/yr), a paint stripper (8% trichloroethylene, sales of 12 tonnes/yr), a component cleaner (100% trichloroethylene; sales of 1.2 tonnes/yr) and an aerosol waterproofing agent (containing 70% trichloroethylene, sales of 4 tonnes/yr).

Directions for use were provided for the waterproofing aerosol spray, which is applied to camping gear, outdoor clothing, ski wear, umbrellas and curtains at the rate of 400 mL/5m^2 fabric. Users of this product would be exposed to trichloroethylene by inhalation, especially when applying it indoors, with some potential for dermal exposure. Although no details were provided for the tyre repair products, component cleaner and paint remover, a similar pattern of exposure may also be inferred for these products.

15.2 Public health risk assessment

Notwithstanding the large annual import volume of trichloroethylene, the majority of the solvent is used in industrial processes which would result in negligible exposure of the public. Similarly, negligible public exposure is anticipated from activities involving the recycling of trichloroethylene, or disposal of wastes containing the solvent.

There is potential for exposure of persons using consumer products containing trichloroethylene, which comprise two tyre repair products, a paint stripper, a component cleaner and an aerosol waterproofing agent. Exposure would occur primarily by inhalation, with some dermal exposure possible. Given the nature of the products, significant airborne concentrations of trichloroethylene could be achieved if they were used in a poorly ventilated area. However, the pattern of public exposure would be discontinuous, even among persons who use multiple products containing trichloroethylene. Provided appropriate precautions are observed trichloroethylene is unlikely to cause health effects in humans similar to those observed in experimental animals or among persons having prolonged occupational exposure to trichloroethylene.

Significant short-term exposure of the public could occur after a transport accident, given the high vapour pressure of the chemical. In such circumstances, prompt isolation of the spill site could be required to minimise the risk to the public. However, accidental spills involving the public are expected to be extremely rare events.

15.3 Conclusions

Trichloroethylene is not expected to present a significant hazard to public health provided that consumer products containing trichloroethylene are labelled in accordance with the requirements of the Standard for the Uniform Scheduling of Drugs and Poisons (Australian Health Ministers' Advisory Council, 1997) and the instructions on the labels strictly adhered to. There are no objections to the continued use of trichloroethylene in the intended applications, subject to these provisions.

16. Environmental Assessment

16.1 Introduction

In discussions with the applicants, it was agreed that in view of the published reviews available on trichloroethylene, only new unpublished data needed to be provided on environmental fate and toxicity. In the event, no new data were provided, and this report relies heavily on two available assessment reports, one from Canada (Government of Canada, 1993), and one from the UK (United Kingdom, 1996).

At room temperature, trichloroethylene is a volatile, non-viscous liquid. It has a higher density and lower surface tension than water. In environmental terms, trichloroethylene is relatively soluble in water. With Log K_{OW} being greater that 2, there is a moderate potential for the chemical to bioaccumulate (Government of Canada, 1993). However, because of the high volatility of trichloroethylene, the majority of chemical released would be expected to partition to the atmosphere, with only negligible amounts partitioning to the water compartment, and very little (0.01%) to soil (see fugacity modelling section 16.2.3). The chemical is considered to be surface active (by EEC definition, a chemical has surface activity when the surface tension is less than 60 mN/m).

16.2 Environmental exposure

16.2.1 Releases

It has been estimated that western European emissions to air due to end-use (degreasing, adhesives etc.) of trichloroethylene is 60% of total consumption (ECSA, 1990). The fate of the remaining trichloroethylene is not clear from this document. It may be incinerated or released into other environmental media, and it is also possible that it may be recycled. Most uses of trichloroethylene are dispersive. For the purposes of this assessment, it will be assumed that the total annual releases to the Australian environment of trichloroethylene will be close to the net quantity of trichloroethylene consumed.

In Australia, emissions of trichloroethylene may arise during bulk handling, formulation of trichloroethylene products and from end use. Trichloroethylene imported in drums is generally transported direct to distributors or end-users, and except in the case of accidental spillage, no release is likely to occur.

Bulk handling

Imports of bulk trichloroethylene need to be pumped by shoreline from tanks on board ships to on-shore bulk tanks. It is then transferred into road tankers and drums, and transported to storage facilities. There is the potential for release during transfers of trichloroethylene from ship tanks to land tanks, road tankers and drums. Vapour emissions from openings on bulk storage tanks and from filling operations at tanker and drum filling stations are controlled by a continuously operating automatic carbon absorption vapour extraction system

that draws air from around hose connections through piping to a central carbon bed absorption unit.

No information was obtained from the NICNAS industry survey of release during handling of trichloroethylene. The Environmental assessment section on trichloroethylene in the UK SIAR (United Kingdom, 1996) has given worst case emission factors of 0.4% to air and <0.00025% to water from European sources. Assuming similar figures for Australian conditions, with 300 days per year when trichloroethylene is handled, on a continental scale around 0.025 kg per day will be released to water, and 40 kg per day to air.

Reformulation

Reformulation of trichloroethylene into trichloroethylene products is not extensive in Australia. Around 9 companies reformulate products, and consume a total of about 222 tonnes per year. Formulation generally involves manual addition of trichloroethylene through pouring or pumping to mixing vessels from drums, cold blending in mixing vessels and packing off from vessels to containers. Due to the relatively simple operations involved in formulation, release would be marginal and would be expected to be confined to vapour being released at hose connections or during pouring from drums.

End use

Vapour degreasing is the major use of trichloroethylene in Australia. Companies responding to the NICNAS survey indicated that the amount of trichloroethylene lost to the atmosphere ranges from <1% to 100%. For the environmental assessment section on trichloroethylene in the UK SIAR (United Kingdom, 1996), a figure of 70% release through degreasing operations was used, for which 90% was expected to go to air, and 10% to water. Adopting these figures, release of trichloroethylene during use as a metal degreaser could be as high as 1,680 tonnes per year. With 300 days handling per year, this equates to a continental release of 5,040 kg per day to air, and 560 kg per day to water.

Other uses, such as general solvent, hand application and boil dipping could have a release of up to 100% depending on individual systems. With around 600 tonnes per year going to other uses, all of which is potentially released to the environment, a further continental release of trichloroethylene of around 1800 kg per day to air, and 200 kg per day to water could occur.

These release levels are summarised in Table 37 below.

Table 37 - Estimates of daily release of trichloroethylene (TCE) Australia wide.

Situation	Daily quantity (kg/day)	Estimate of TCE release	Release to Air (kg/day)	Release to Water (kg/day)
Handling of imported TCE	10,000	0.4%	40	0.025
Vapour degreasing	8,000	70%	5,040	560
Other uses	2,000	100%	1,800	200
TOTAL			**6,880**	**760**

16.2.2 Levels in Australian media

Studies of groundwater contamination around the ICI Botany site at Botany Bay have registered up to 190 ppm trichloroethylene around the former trichloroethylene production plant, and up to 360 ppm in surficial sediments in the same area. Other readings taken from the site, but away from the old trichloroethylene plant area, show much lower readings. In 1982 the NSW State Pollution Control Commission (now EPA NSW) collected groundwater samples from four bores in the north end of the ICI Botany site. Two of these bores had trichloroethylene present at 5 ppm and 2 ppm, while it was below detection levels in the other two bores (Woodward-Clyde, 1995).

Investigations by individual states of Australia revealed limited data. The Australian Capital Territory monitors trichloroethylene in effluent both upstream and downstream of the Lower Molonglo Sewage Treatment Plant. To date, it has been measured in November 1995 and February 1996. On both occasions the concentration was below detection in all three samples (<80 µg/L in November, and <0.1 µg/L in February). In January 1996, Sydney Water compiled a risk assessment which included monitoring data for trichloroethylene (among other chemicals) in 10 coastal sewage treatment plants. In all plants, readings were below the detection limit of 10 µg/L.

16.2.3 Fate

As previously stated in the introduction, it was agreed with applicants that only recent unpublished data should be provided in view of the literature reviews available. No environmental fate data were provided and the following discussion on environmental fate of trichloroethylene is largely paraphrased from the Canadian Priority Substances List Assessment Report on Trichloroethylene (Government of Canada, 1993) with some interpretation for the local situation.

The fate of trichloroethylene released to the environment is influenced by transport processes, including volatilisation, diffusion and advection, and by transformation processes, including photo-oxidation and biodegradation.

The level 1 Fugacity Model (as modelled by ASTER, (U.S. Environmental Protection Agency (USEPA), 1996)) indicates that at equilibrium, 99.64% of trichloroethylene will partition to the atmosphere, 0.35% will partition to water with the remainder (0.01%) partitioning to soil.

Atmospheric fate

The majority of trichloroethylene is released to the atmosphere, where it may react with photochemically produced hydroxyl radicals to produce phosgene, dichloroacetyl chloride, formyl chloride and other degradation products. Trichloroethylene does not readily undergo chemical oxidation or hydrolysis in the atmosphere, and direct photolysis is a minor transformation process. The estimated half-life of trichloroethylene in the atmosphere varies with latitude, season and concentration of hydroxyl radicals. In Canada, the calculated half-lives range from 1 day in the south during summer months to several months in the far north during winter months. Due to the generally warmer conditions in Australia, half-lives of trichloroethylene in the atmosphere would be expected to be at the shorter end of the scale. The relatively short atmospheric half-life generally precludes long-range transport of trichloroethylene and transfer into the stratosphere. Under certain conditions (eg high winds, cloud cover), trichloroethylene will undergo short and medium range atmospheric transport.

Trichloroethylene is decomposed in the troposphere (lower atmosphere) and is not considered to be a significant contributor to either greenhouse warming or stratospheric ozone depletion (CEFIC, 1986).

Aquatic fate

Contamination of water arises from misuse, improper waste disposal, inadequate effluent water treatment or incidental spillage caused by improper handling and storage. The presence of chlorinated solvents in the hydrosphere has been widely reported, and it has been confirmed that the main contamination has come from improper waste disposal and spillage (ECSA, 1990). Since trichloroethylene is denser than water and moderately water-soluble, concentrated or continuous small discharges to surface and groundwater can lead to the formation of "puddles". These puddles can represent a chronic source of trichloroethylene contamination of surface and ground water.

Volatility

Trichloroethylene discharged to surface water can volatilise rapidly from the top layers, with rates varying according to temperature, water movement and depth, air movement and other factors. The estimated volatilisation half-lives in shallow ponds, lakes and running waters are less than 12 days. The measured volatilisation half-lives for trichloroethylene in experimental marine ecosystems range from 13 to 28 days.

Other tests have found much shorter half-lives. Geyer et al (1985), determined the half-life in an aqueous solution at 20°C to be 18 hours/m depth of solution, while Dilling (1975) found that the half-life for a stirred water body (initial trichloroethylene concentration of 1 mg/L) was between 19 and 24 minutes (United Kingdom, 1996).

Degradation

In an aerobic degradation study in seawater, 80% of trichloroethylene was degraded in 8 days. Photooxidation and hydrolysis are not significant degradation processes for trichloroethylene in surface waters.

Trichloroethylene does not partition to aquatic sediments to any appreciable degree, except in sediments with a high organic content. Trichloroethylene may biodegrade to carbon dioxide in sediment. In one study, methane-utilising bacteria isolated from sediment reduced the concentration of trichloroethylene from 630 µg/L to 200 µg/L in 4 days at 20°C.

Soil/groundwater

The majority of trichloroethylene released onto soil surfaces will volatilise to the atmosphere. Trichloroethylene present in subsurface soil may be transported by diffusion, advection or dispersion of the pure liquid, as a solute in water, or by gaseous diffusion throughout the spaces within porous soils. As a result, trichloroethylene can penetrate the soil and contaminate groundwater. Trichloroethylene partitions to soil particles of high organic content. Information on the importance of biodegradation in removing trichloroethylene from subsurface soil is limited. In one study, no degradation of trichloroethylene by anaerobic soil microorganisms was detected after 16 weeks; however, aerobic biodegradation has been demonstrated following artificial nutrient enrichment and induction. In some subsurface soils, sorption and desorption of trichloroethylene is slow. Thus, subsurface liquid trichloroethylene may continue to contaminate groundwater aquifers and soils long after sources have been eliminated.

In groundwater, biodegradation may be the most important transformation process for trichloroethylene, although it is usually slow, with half-lives ranging from months to years, depending on ambient conditions and enhanced remediation measures. The major products resulting from biodegradation of trichloroethylene in groundwater are dichloroethylene, chloroethane and vinyl chloride. High concentrations are frequently observed in contaminated groundwater where volatilisation and biodegradation are limited, where there are point sources or where releases are small but continuous over time. Relatively constant concentrations can therefore exist for decades.

This is demonstrated by the deep and shallow groundwater at the ICI Botany site in NSW containing trichloroethylene as a result of manufacturing operations on that site which ceased in 1976. The highest levels of trichloroethylene are found in sediments (up to 360 ppm) and shallow groundwater (up to 190 ppm) in the immediate vicinity of the old production plant. Much lower levels of trichloroethylene have been detected in groundwater (2-5 ppm) and soil (27 ppm), away from the old production plant (Woodward-Clyde, 1995).

Bioaccumulation

Based on its low *n*-octanol/water partition coefficient and the results of field studies, trichloroethylene is unlikely to bioaccumulate significantly in aquatic biota and piscivorous birds. Measured bioaccumulation factors ranged from <3 for muscle tissues of marine and freshwater birds to approximately 100 for fish livers.

16.2.4 Summary

Trichloroethylene will predominantly enter the environment as release to the atmosphere. The level 1 Fugacity Model indicates that, at equilibrium, 99.64% of trichloroethylene will partition to the atmosphere, 0.35% will partition to water, and 0.01% will partition to sediment. Due to the high water solubility, and relatively small partition co-efficient, trichloroethylene which doesn't partition to the atmosphere would be expected to be mobile, and largely remain in solution.

Degradation of trichloroethylene is expected to be in the order of days in the atmosphere and in the aquatic compartment. However, slow degradation of trichloroethylene in groundwater is likely. In the atmosphere, trichloroethylene reacts with photochemically produced hydroxyl radicals, and degradation is faster in warmer atmospheric conditions.

Bioaccumulation of trichloroethylene is unlikely to occur.

16.3 Environmental effects

As stated previously, it was agreed with applicants that only recent unpublished data should be provided in view of the literature reviews available. No new ecotoxicological data were provided, and the following discussion comes from a selection of available literature.

16.3.1 Aquatic organisms

The following ecotoxicological study results have been summarised from the UK SIAR (United Kingdom, 1996). The discussion in this section is also based on this reference, except where indicated.

Micro-organisms

Literature values for toxicity of trichloroethylene to microorganisms give a 24 h $E(I)C_{50}$ value range from 115 mg/L to 960 mg/L, although an IC_{50} of 13 mg/L has been measured for a methanogenic bacteria. Toxicity thresholds for microorganisms range from 65 to 1200 mg/L.

Algae and aquatic plants

Trichloroethylene has been shown to both inhibit and stimulate the growth of algae and aquatic plants, depending on species and trichloroethylene concentration. EC_{50} values for aquatic plants and algae range from 8 mg/L to 150 mg/L.

Aquatic invertebrates

Toxicity tests for trichloroethylene with aquatic invertebrates have been carried out, although many of the results are based on nominal concentrations. 48h $L(E)C_{50}$ values range from 2.2 mg/L to 132 mg/L. To overcome volatility, two static tests have been carried out on *Daphnia magna* and *Mysidopsis bahia* (mysid shrimp) using sealed containers. These gave a 48h EC_{50} of 7.8 mg/L and 96h EC_{50} of 14 mg/L.

A natural pond field experiment in 1981 (conducted in Germany) observed complete mortality of *Daphnia magna* in two test ponds within 3 days after exposure to an initial concentration of 110 mg/L, a concentration much higher than might be expected, except in a major accident situation. Approximately 70% mortality was observed after 3 days at an initial concentration of 25 mg/L (the half-life of trichloroethylene in these experiments was 2.7 days). At the end of the 43 day observation period, the daphnid population had recovered. However, species richness and abundance of phytoplankton remained severely depressed at the end of the observation period following exposure to 25 mg/L. The results of subsequent field studies in natural pond communities indicate that similar effects occur following continuous exposure to lower concentrations of trichloroethylene for longer periods of time. For example, exposure to 1.0 to 1.5 mg/L trichloroethylene for 11 weeks caused reductions of up to 70% in the population of *Daphnia pulex* (Government of Canada, 1993).

Fish

The toxicity of trichloroethylene to various fish species has been measured with LC_{50} values ranging from 16 mg/L to 213 mg/L. Several of the tests are flow-through tests and the lowest result from these tests is the 96 h LC_{50} for *Jordanella floridae* (American flagfish) of 28.3 mg/L. Chronic toxicity tests on this species have been carried out and the No Observed Effect Concentration (NOEC) was 5.76 mg/L.

Based on these results, trichloroethylene can be described as practically non-toxic to microorganisms; moderately to practically non-toxic to aquatic plants, algae and aquatic invertebrates; and slightly to practically non-toxic to fish.

Table 38 - Selected highest toxicity values of trichloroethylene to the aquatic compartment.

Species	Conditions	Result (ppm)
Microorganisms		
Activated Sludge	OECD Guideline 209, activated sludge respiration inhibition test (S)	EC_{50} 260
Pseudomonas putida	16 h, inhibition of cell multiplication (S; NC)	LOEC=65
Aquatic plants/algae		
Microcystis aeruginosa (Blue green algae)	8 d growth rate	LOEC=63
Phaeodactylum tricornutum (Marine diatom)	Photosynthesis	EC_{50}=8
Scenedesmus subspicatus	96 h, inhibition of cell multiplication	EC_{10} 46-61
Selenastrum capricornutum (Green algae)	96 h, growth rate	NOEC 175
Aquatic invertebrates		
Daphnia magna	48 h, EPA-660/3-75-009, age <24 h. (S; NC)	EC_{50}=18 NOEC=2.2
Daphnia magna	48 h, age 4-6 days. (S)	EC_{50} =7.8
Mysidopsis bahia (Mysid shrimp)	96 h, (S; MC)	EC_{50}=14
Fish		
Limanda limanda (Flatfish dab)	96 h (F; NC)	LC_{50}=16
Oncorhynchus mykiss (Rainbow trout)	48 h (S; NC)	LC_{50}=42
Pimephales promelas (Fathead minnow)	48 h (S; NC)	LC_{50}=32-56

S= Static test; F= Flow through test; NC= Nominal concentration; MC= Measured concentration.

16.4 Environmental hazards

Through the NICNAS industry survey it is apparent that, a large proportion of end users of trichloroethylene have their waste trichloroethylene disposed of via a solvent recycler. Precise figures are not available, however, and as a worst case scenario, it will be assumed that all trichloroethylene is lost to the environment, with 90% evaporation to the atmosphere, and 10% discharged to the sewer system.

Formulae from the EC Technical Guidance Document (European Commission,) have been used to predict an environmental concentration for trichloroethylene in Australian receiving waters.

The percentage of trichloroethylene in the STP being lost to the atmosphere is 91%, based on the SIMPLETREAT model, calculated by the UK in the SIAR (United Kingdom, 1996). Therefore, the value of P in the following equations is 0.91.

$$\mathbf{PEC_{local(water)} = C_{eff}/(1+K_{p(susp)} \cdot c_{susp}).D}$$

Where:

$PEC_{local(water)}$	=	predicted environmental concentration (g/L)
C_{eff}	=	concentration of the chemical in the sewage treatment plant (g/L)
$K_{p(susp)}$	=	Suspended matter-water adsorption coefficient (L/kg)
c_{susp}	=	Concentration of suspended matter in receiving waters (L/kg)
D	=	Dilution factor.

$$\mathbf{C_{eff} = W.(100-P)/100.Q}$$

Where:

W	=	emission rate (kg/day)
Q	=	volume of waste water.
P	=	percentage removal in the sewage treatment plant

$$\mathbf{K_{p(susp)} = a.Foc_{susp}.Kow}$$

Where:

Foc_{susp}	=	Fraction organic carbon in suspended matter.
Kow	=	Octanol-water partition coefficient

Assumptions:

1)	All trichloroethylene imported into Australia is released to the environment.
2)	90% is released to the atmosphere, with 10% to water. All release to water is via the sewage treatment plant.
3)	300 days per year of trichloroethylene handling, meaning a daily release of 10 tonnes.
4)	In the absence of data, 40% use of trichloroethylene will be assumed to occur in the Sydney metropolitan area, equating to a release of 4 tonnes per day. Of this, 400 kg will be sent to the sewer, which has a flow of 250 ml per day.

Values:

c_{susp}	=	15 mg/L (default value)
D	=	10
W	=	400 kg/day
Q	=	250 ML/day
P	=	91%

Foc_{susp}	=	0.1 (European Commission, 1994)
Kow	=	195
a	=	0.411 (European Commission, 1994)

Using the above formulae, data and assumptions, the predicted environmental concentration in receiving waters is **14.4 µg/L** (ppb).

These calculations represent a worst case scenario, and assume no degradation of trichloroethylene by microorganisms in the STP or in receiving waters. The estimates give a predicted environmental concentration two orders of magnitude below the lowest toxic level for aquatic organisms being a 48h EC_{50} = 7.8 ppm for *Daphnia magna*. Thus a low aquatic hazard may be concluded.

Because of the relatively short half-life in the atmosphere, trichloroethylene is thought to make only a minor contribution to global warming. It is unlikely to reach the stratosphere, and so is not likely to have an effect on stratospheric ozone. It will not make a significant contribution to photochemical ozone formation. However, the breakdown product, dichloracetyl chloride, may have an adverse effect on stratospheric ozone due to its long half-life (United Kingdom, 1996).

16.5 Conclusions

Based on available data for Australia, it can be predicted that trichloroethylene will not occur at concentrations potentially harmful to the aquatic environment or the atmosphere. If groundwater contamination occurs it would be of concern. There is no manufacture of trichloroethylene in Australia and measures for handling and storing bulk trichloroethylene are such that, except in the case of a major spill, future contamination of groundwater is unlikely.

17. Overall Conclusions and Recommendations

17.1 Hazard classification

The recommended classification is based on the following data:

Skin and eye irritant

Results of studies in human volunteers and reports of workers exposed to trichloroethylene have indicated that trichloroethylene caused burning sensation of the skin with redness and rashes and burning and irritation of the corneal epithelium. Studies in animals, not conducted according to accepted test guidelines, reported skin irritation and corneal abrasions. Based on human evidence and results of animal studies trichloroethylene meets the classification for skin and eye irritation.

Mutagenicity

Positive results in tests in somatic cells *in vivo* such as:

- single strand breaks in rat and mouse liver, kidney, lungs and stomach (Nelson & Bull 1988, Walles 1986);
- increased number of mutants in cultures from liver and kidneys but not from lungs in a host-mediated assay in mice (Bronzetti et al (1978);
- positive pink eyed unstable mutation test in mice (Schiestl et al, 1997)

Supported by:

- mutations in VHL tumour suppressor gene in renal cancer cases (Bruning et al, 1997);
- weak *in vitro* mutagen; and
- mutagenicity of known metabolites.

Some of the studies have limitations (Schiestl et al, 1997; Bruning et al, 1997) and these have been noted in the report. However, looking at the overall data, the results of these studies raise concern regarding possible mutagenic effects of trichloroethylene.

Carcinogenicity

Currently available data in animals and humans, as follows:

- Well conducted epidemiological studies (Axelson et al, 1994; Spirtas et al, 1991 updated by Blair et al, 1998) have shown no association between exposure to trichloroethylene and renal cancer under the conditions of these studies.
- However another well conducted study (Antilla et al, 1995) provided limited evidence of an association between cancer and trichloroethylene exposure.

- Studies by Henschler et al (1995) and Vamvakas et al (Deutsche Forschungsgemeinschaft, 1996) have indicated an association between renal cancer in workers exposed to trichloroethylene.
- Bruning et al (1997) in a preliminary study demonstrated that trichloroethylene caused somatic mutations of the VHL tumour supressor gene in renal cancer cases and concluded that a linkage existed between exposure to trichloroethylene and somatic mutation of the VHL gene.
- Bruning et al (1996b) also reported renal tubular damage in patients who had been diagnosed with renal cell carcinoma and had undergone nephrectomy.
- Kidney tumours observed in rats along with cytotoxicity.

Although it is noted that some of the the human studies provide limited data and have several methodological weaknesses, the findings in humans are supported by evidence in experimental animals, with tumours observed at the same site and the mechanism yet to be elucidated. Renal cytotoxicity has been observed in rats, however the mechanism is not clear.

Overall, for mutagenicity and carcinogenicity, the pattern of results observed is consistent with a chemical which is a weak mutagen and a weak carcinogen.

Overseas consideration and expected new data

The European Union (EU) is also considering the classification of trichloroethylene. The EU Specialised Experts Group considered the mutagenic and carcinogenic potential of trichloroethylene at their meeting in June 1997.

For mutagenicity the Group considered that:

- trichloroethylene was an *in vitro* mutagen;
- the results from the *in vivo* studies were however, less clear;
- based on the current data trichloroethylene could not be classified as a Category 3 mutagen.
- further data was required to clarify *in vivo* mutagenic potential. As trichloroethylene was under the Existing Substances Risk Assessment Regulations (ESR) where additional studies can be requested, the Specialised Experts recommended that the Kligerman micronucleus study be repeated with some modifications. This was subsequently agreed by the superior EU body as the basis on which the EU will determine whether to classify trichloroethylene as a category 3 mutagen (a positive result to result in classification). The EU also noted other data in generation.

For carcinogenicity, a majority of the Specialised Experts recommended that:

- trichloroethylene be classified as carcinogen category 2; R45 on the basis of clear data in one animal species (rat) with supportive evidence from epidemiology and genotoxicity studies;
- the mechanisms of action, particularly for the liver and kidney tumours, needed to be further elucidated to show that these tumours were not of relevance to humans.

The Specialised Experts recommended that as the genotoxicity of trichloroethylene was still in doubt it should be treated as a genotoxic carcinogen until proven otherwise and thresholds should not be anticipated to exist for cancer effects.

The above reflects the EU status as advised to NICNAS at the time of preparing this report. EU consideration of trichloroethylene has not been finalised.

During the final stages of preparation of this report, one applicant advised that additional laboratory work relevant to the question of mutagenicity and renal effects was expected to be completed by September 1998 (Dow Chemical, personal communication).

Recommendation on classification

Considering the available information and that further data are being generated, the following recommendations are made to the National Occupational Health and Safety Commission.

Recommendation 1:

The recommended classification for trichloroethylene based on the hazard assessment of currently available data and in accordance with the National Commission's *Approved Criteria for Classifying Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994) is:

> Skin and eye irritant (Risk phrase R36/38 Irritating to eyes and skin);
>
> Mutagen - category 3, ie substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satifactorily demonstrate heritable genetic damage (Risk phrase R40 (M3) May cause heritable genetic effect);
>
> Carcinogen - category 2, ie substances regarded as if they are carcinogenic to humans (Risk phrase R45 May cause cancer).

Products or mixtures containing 0.1% or more of trichloroethylene should also be classified as hazardous.

Recommendation 2:

The draft report was completed in May 1998 and included the following Recommendation:

On the basis that further data relevant to the classification is expected to be available prior to the end of 1998, it is recommended that the NOHSC Hazardous Substances Sub Committee consider the timing of their adoption of the revised classification into the *Designated List of Hazardous Substances* to allow this additional information to be considered. Any period allowed for consideration of further data should be limited. Such data would require secondary notification and assessment by NICNAS.

The hearing by the Administrative Appeals Tribunal was held in November 1999 and all the data available up to the hearing was considered by the AAT. The above recommendation should therefore be disregarded.

Risk Phrase R65 – Harmful: May cause lung damage if swallowed. The draft *Approved Criteria for Classifying Hazardous Substances* – Revised Edition (1998) includes a new risk phrase R65 – Harmful: May cause lung damage if swallowed. This risk phrase applies to aliphatic, alicyclic and aromatic hydrocarbons in total concentrations equal to or greater than 10% satisfying certain criteria. From the data currently available to NICNAS it is not possible to consider the applicability of this risk phrase for trichloroethylene.

Recommendation 3:

Any information relating to the criteria needs to be provided under the secondary notification provision of the *Industrial Chemical (Notification and Assessment) Act 1989* (section 18).

17.2 Control measures

Trichloroethylene is a hazardous substance with carcinogenic and irritancy potential. In accordance with the National Commission's *National Code of Practice for the Control of Workplace Hazardous Substances* (National Occupational Health and Safety Commission (NOHSC), 1994) exposure to hazardous substances should be prevented and where this is not practicable control measures should be implemented to minimise risks to health. Control measures should be implemented in accordance with the hierarchy of controls which is a list of control measures, in priority order, that can be used to eliminate or minimise exposure to hazardous substances. In some circumstances it may be appropriate to use two or more control measures to reduce exposure to as low a level as is practicable.

Trichloroethylene can be absorbed through the lungs and skin and control measures should minimise exposure through these routes.

17.2.1 Elimination

In the hierarchy of control measures elimination is the first option to be considered to minimise health risks. Elimination is the removal of all chemicals from the process. For example, elimination may occur through a modification of the manufacturing process of the metal parts removing the need for cleaning.

17.2.2 Substitution

Where elimination of chemicals from the process is not practicable, substitution with a less hazardous substance or method of application should be considered.

Recommendation 4:

It is recommended that greater research and development be directed to substitute processes and non-hazardous substances.

Other Uses

A number of alternative options are now available. Endusers should review their processes and the alternatives available before replacing trichloroethylene in the process.

Cold Cleaning

Most manufacturers do not support the use of trichloroethylene in cold cleaning. This assessment confirms this use is associated with a high and unacceptable risk.

Recommendation 5

It is therefore recommended that trichloroethylene not be used in cold cleaning, with this use phased out over a period of two years.

Information on solvent substitution is available on the Internet, for example, the Solvent Alternatives Guide (SAGE) and the Hazardous Substances Solvent Substitution Data System (HSSDS).

Products in aerosol form

Recommendation 6:

It is recommended that trichloroethylene not be used in industrial aerosol product form, due to the high and unacceptable risk identified in this assessment.

17.2.3 Engineering controls

Formulation

Recommendation 7:

It is recommended that all stages of the formulation process, transfer, mixing and packaging, be enclosed. Transfer of trichloroethylene to the mixing tank and emptying of the tank into containers through closed pipelines will minimise emission of vapours. It is recommended that local extraction ventilation be installed above the mixing tank to remove any fugitive emissions. The area around the mixing tank should be bunded to contain any large spills.

Vapour degreasing

Recommendation 8:

To control worker exposure during vapour degreasing it is recommended that the vapour degreasing tank must conform to the requirements of the Australian Standard AS 2661 - 1983 (Standards Association of Australia, 1983).

Based on past experiences, the following engineering controls have been identified as important.

ENGINEERING CONTROLS

- Local exhaust ventilation. The exhaust ventilation should be installed to prevent any agitation of the solvent surface or vapours which will result in vapour being drawn out of the tank;
- Modification of old degreaser tanks (including rim ventilation) to include the controls recommended in AS 2661 - 1983 as they limit emission into the environment and therefore worker exposure. This would also reduce solvent requirement because of reduced loss resulting in economic benefit
- fitting of roller or sliding doors below the rim ventilation to prevent escape of vapours into the atmosphere. Covers should be used when the tank is in use and when idling; and
- use of an overhead lifting device to immerse and remove parts at a controlled rate. This eliminates excess loss and also keeps the operator away from the degreaser

Cold cleaning

Use of trichloroethylene in cold cleaning is not supported by this assessment. Appropriate engineering controls such as local exhaust ventilation must be used to minimise exposure, while use is phased out.

Trichloroethylene products

Use of industrial trichloroethylene products in aerosol form is not supported by this assessment. Local exhaust ventilation will help to minimise exposure of workers to other trichloroethylene products.

17.2.4 Safe work practices

Recommendation 9:

Safe work practices are critical in keeping solvent emissions to a minimum. Safe practices that help to minimise emissions are detailed below and must be followed.

SAFE WORK PRACTICES

- location of the degreaser tank (it should be located away from draughts such as open windows or doors) (Standards Association of Australia, 1983);
- keeping tanks closed when in use and idling (Standards Association of Australia, 1983);
- minimising turbulence during lowering of the workload into the tank by reducing the rate of introduction (Standards Association of Australia, 1983);
- proper placement of the parts to be degreased in the basket thus avoiding solvent collecting in the parts;
- sufficient time in the freeboard zone to allow adequate draining/drying time (Standards Association of Australia, 1983);
- routine equipment inspections to locate leaks or any other problems (Standards Association of Australia, 1983);
- avoiding splashes or spills during solvent filling, draining or transfer operations;
- prompt clean up of spills;
- All ignition sources should be eliminated in areas where high concentrations of vapour may accumulate;
- frequent cleaning of the tank to prevent buildup of caked material at the bottom (Standards Association of Australia, 1983). Regular maintenance will reduce the need for entry into the tank during cleaning;
- the requirements of AS 2865-1995 "Safe Working in a Confined Space" (Standards Australia, 1995) should be conformed to if entry into a tank is necessitated for cleaning purposes. A number of fatalities have been reported when people have entered tanks to clean them.

17.2.5 Personal protective equipment

Personal protective equipment (PPE) is used to minimise exposure or contact to chemicals. PPE should be used in conjunction with other engineering controls and not as a replacement.

Protective gloves help to prevent dermal exposure to trichloroethylene. It is important to select gloves that are resistant to the chemical exposed and are appropriate for the duration of exposure. If swelling of the gloves occurs they should be discarded.

Recommendation 10 :

It is recommended that when selecting gloves the manufacturers and suppliers information be used as gloves made of the same generic material can differ due to

differences in manufacture. For formulated products, gloves should be selected on the basis of the component with the shortest breakthrough time. Protective gloves should be used when skin contact with trichloroethylene is likely, such as during loading and unloading of work parts from the vapour degreaser, during cold cleaning, clean up of spills or during other work processes where splashes are likely.

Protective clothing which includes protection of the arms, legs and feet should be worn where exposure of trichloroethylene may occur. Eye protection is recommended when vapours may be generated or when splashing may occur. Personal protective equipment should be in accordance with the relevant Australian standards.

If cleaning of degreaser tanks involves entry into the tank respiratory protection is required. A suitable supplied-air respiratory protective device complying with AS/NZS1716 (Standards Australia & Standards New Zealand, 1994) should be worn.

17.3 Hazard communication

Trichloroethylene is a hazardous chemical and employers are obliged to provide employees with MSDS, training on the proper use of trichloroethylene and information on the health hazards of the chemical and ensure that all containers used at work are adequately labelled.

17.3.1 MSDS

Recommendation 11:

It is recommended that suppliers significantly improve and amend their MSDS where necessary in order to rectify deficiencies identified in the assessment.

17.3.2 Labels

A large number of deficiencies were identified in the labels provided for assessment.

Consumer Products

The labels on products available for domestic use did not comply with the requirements of the SUSDP, (Australian Health Ministers' Advisory Council, 1997) which is a legal requirement under State and Territory legislation.

Recommendation 12:

It is recommended that suppliers review their labels as a matter of urgency and comply with the requirements of SUSDP:

Safety directions

- SD1 Avoid contact with eyes
- SD4 Avoid contact with skin
- SD5 Wear protective gloves when mixing or using

- SD8 Avoid breathing dust (or) vapour (or) spray mist
- SD9 Use only in well ventilated area
- WS12 Vapour is harmful to health on prolonged exposure

First aid instructions

- If poisoning occurs contact a doctor or Poisons Information Centre.
- If swallowed do not induce vomiting. Give a glass of water.
- Avoid giving milk or oils.
- Avoid giving alcohol.
- If skin contact occurs, remove contaminated clothing and wash skin thoroughly.
- Remove from contaminated area. Apply artificial respiration if not breathing.
- If in eyes, hold eyes open, flood with water for at least 15 mins and see a doctor.

In addition other elements that are required to be on the label are:

- the signal word POISON;
- phrases KEEP OUT OF REACH OF CHILDREN; NOT TO BE TAKEN; and
- percentage of trichloroethylene in the product.

Industrial Products

Substances used industrially need to comply with the requirements of the NOHSC *National Code of Practice for the Labelling of Workplace Substances* (National Occupational Health and Safety Commission (NOHSC), 1994).

Recommendation13:

It is therefore recommended that, where necessary, labels of industrial products be amended to include:

- risk phrases
- safety phrases
- emergency procedures;
- details of the amount of trichloroethylene present (exact amount or ranges); and
- reference to MSDS.

Products or mixtures containing 0.1% or more of trichloroethylene should be classified as hazardous and labelled in accordance with the Labelling Code.

17.3.3 Training and education

Recommendation 14:

Workers potentially exposed to trichloroethylene should be provided with training in the safe handling of the chemical. Workers should be aware of the health hazards of the chemical.

For trichloroethylene, the training program should address those aspects detailed below.

CONTENT OF TRAINING PROGRAMS

- acute health effects of trichloroethylene;
- chronic health effects of trichloroethylene;
- skin absorption potential and skin effects of trichloroethylene following prolonged exposure;
- explanation of MSDS and labelling of trichloroethylene and trichloroethylene products; and
- use and maintenance of personal protective equipment.

In addition, training for workers involved in vapour degreasing should include

- basic plant operation, covering start up procedures, checking cut outs, cooling and solvent condition, loading, unloading and jigging work and delays in the freeboard zone;
- procedures to be followed during cleaning of degreasing tanks; and
- procedures to be followed during clean up of spills.

Training should be given to the workers at induction and repeated at regular intervals to reinforce the information. Training and education needs for workers should be reviewed on a regular basis. Guidelines for the induction and training of workers are provided in the NOHSC *National Model Regulations and Code of Practice for the Control of Hazardous Substances* (NOHSC, 1994)

17.4 Exposure standard

Recommendation 15:

It is recommended to NOHSC that the present occupational exposure standard for trichloroethylene of 50 ppm TWA be reviewed noting:

- the critical effect is renal toxicity;
- the inhalation NOAEL for renal toxicity is 100 ppm, the LOAEL is 300 ppm. These values do not include a margin of exposure (uncertainty factor);
- a classification of carcinogen Category 2 has been recommended;
- a classification of mutagen Category 3 has been recommended; and
- trichloroethylene is readily absorbed through the skin.

- recent monitoring data indicate that exposures around the current occupational exposure standard (TWA) or even higher are occurring at workplaces; and
- the monitoring data included and other relevant information included in this assessment report.

17.5 Public health protection

Trichloroethylene is not expected to present a significant hazard to public health provided that consumer products containing trichloroethylene are labelled in accordance with the requirements of the Standard for the Uniform Scheduling of Drugs and Poisons (Australian Health Ministers' Advisory Council, 1997) and the instructions on the labels strictly adhered to (See Section 17.3.2).

During preparation of this report, it was noted that the lowest oral LD_{50} value for trichloroethylene in rats is 4900 mg/kg bw (IPCS (International Programme on Chemical Safety), 1985).

Recommendation 16:

It is therefore recommended that the T-value for trichloroethylene in Appendix E Part 2 of the SUSDP, be revised from 715 to 490.

There are no objections to the continued use of trichloroethylene in the indicated applications, subject to the above provisions.

If the conditions of use are varied, greater exposure of the public to the product may occur. In such circumstances, further information may be required to assess the hazards to public health.

17.6 Environmental protection

Recommendation 17:

Solvents such as trichloroethylene should not be allowed to contaminate either surface water or ground water. The residue obtained following distillation of the used solvent, in the form of a highly concentrated final waste, should be disposed of by a licensed contractor.

17.7 Further studies

There is a large body of literature on trichloroethylene, however, some gaps identified in the database for trichloroethylene are:

- the mechanism of action of carcinogenicity in kidneys (to elucidate the relevance of these tumours to humans);
- methodical studies with ‘pure’ trichloroethylene in systems that detect a point mutation end point;
- information to estimate the skin absorption rate of trichloroethylene in humans (to provide a better estimate of skin absorption);
- information relating metabolism of trichloroethylene in humans to that in rats and mice (to determine the most appropriate model for humans. Differences

in metabolism across species may account for the different outcomes in cancer studies in rats and mice. Additionally saturation of metabolism at high doses is postulated to occur in humans but sufficient data is lacking); and

- studies on the developmental neurotoxicity of trichloroethylene in animals (as a series of oral studies from a laboratory have indicated that trichloroethylene may produce developmental neurotoxicity);
- data on the fate and persistence of trichloroethylene released into Australian groundwater, sediments and subsurface soils, including any sites contaminated with this substance, other than Orica Botany, would enable a more complete evaluation of the potential environmental hazard of trichloroethylene in Australia.

18. Secondary Notification

Under section 65 of the Act, the secondary notification of a chemical may be required if there has been a change in circumstances which warrants a reassessment of any of the hazards of the chemical.

In the case of trichloroethylene, a secondary notification may be required if significant new information about its health and/or environmental effects becomes available, for example new data on the mutagenic or reproductive effects of trichloroethylene.

Notification will also be required if trichloroethylene is used in wool scouring or any other new use resulting in a significant increase in the quantities imported into Australia.

APPENDIX 1
OCCUPATIONAL EXPOSURE CALCULATIONS

1. Formulae for exposure calculations

A total internal dose, (D) that is an estimated human dose, is the sum of the doses resulting from absorption of vapours (D_v) and dermal absorption of liquid (D_{dl}).

$$D = D_v + D_{dl}$$

Vapour absorption (D_v) comprises of inhalation absorption across the lungs (D_{iv}) plus dermal absorption of vapours (D_{dv}).

$$D_v = D_{iv} + D_{dv}$$

However, as dermal absorption of trichloroethylene vapour is negligible, only inhalation absorption is considered in this assessment. Therefore, for trichloroethylene $D = D_{iv} + D_{dl}$

Exposure to vapours

The dose arising from the inhalation of vapours (D_{iv}) is as follows:

$$D_{iv}\ \text{in} = \frac{C \times R \times E \times B}{BW}\ \text{mg/kg/day}$$

Where C=concentration of substance in air (mg/m^3)
R=inhalation rate (m^3/h)
E=exposure duration = $\frac{\text{h/day days/yr}}{365\ \text{days/yr}}$
B=bioavailability of vapours across the lungs (1=100%)
BW=average body weight of worker (kg)

Bioavailability (B) is the proportion of inhaled substance absorbed through the lungs. After inhalation of trichloroethylene, 40 to 70% of the administered dose is metabolised with the rest being exhaled (IARC, 1995). The default value used often in international assessments is 0.75 (75%) and as the values for trichlorethylene are similar, a value of 0.75 was used for this assessment.

For consistency with international assessments, a value of 1.3 m^3/h was used for the inhalation rate (R) for occupational exposure during light work activities (OECD, 1993; European Commission, 1994) and a value of 70 kg was used for body weight (BW).

The exposure duration (E), that workers may be potentially exposed to trichloroethylene, during the various activities were obtained from responses to questionnaires.

Exposure to liquid

The daily total dose from liquid exposure (D_{dl}) is calculated as follows:

$$D_{dl} = \frac{W \times S \times A \times E \times F}{BW} \text{ mg/kg/day}$$

W = weight fraction of substance in product, eg., 0.1 for a 10% solution
S = skin absorption rate (mg/cm^2/h)
A = skin surface area exposed (cm^2)
E = exposure duration = $\frac{\text{h/day x days/yr}}{\text{365 days/yr}}$
F = skin contact time (as fraction of exposure duration, e.g. 0.2 for 20% of time).
BW = average body weight of worker (kg)

For skin absorption rate, no human data either *in vivo* or *in vitro* using human tissue were available. The skin absorption rate (0.32 mg/cm^2/h) used in the calculations was derived from an experiment in hairless guinea pigs (Bogen et al, 1992)(see Section 9).

For skin surface area (A) standard area estimates for the adult male include the following standard US EPA values (in cm^2):

arms	2280
upper arms	1430
forearms	1140
hands	840
head	1180

For calculation purposes, dermal exposure was considered to reasonably consist of no more than exposure to both hands (840 cm^2) or a hand and a forearm (990 cm^2). For consistency, a value of 1000 cm^2 was considered appropriate for dermal exposure estimates.

Liquid trichloroethylene can be in contact with the skin for various fractions (F) of the exposure duration (E) so skin contact can be extensive, intermittent or incidental. Extensive dermal exposure is taken as continuous contact (F=1) with the skin. Taking into account assumptions made in the UK EASE* (Estimation and Assessment of Substance Exposure) model for dermal exposure, intermittent exposure is taken as being skin contact for 20% of the time (F=2), and incidental exposure as skin contact for 1% of the time (F=0.01).

* The EASE model is the second version of the knowledge based electronic system in development by the UK Health and Safety Executive (HSE), and was formerly called EES (Exposure Expert System).

2. Calculations for various scenarios

2.1 Formulation

Exposure to vapours

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times 0.75 \times (E\ h/day \times days/yr)}{70\ kg \times 365}$$

Exposure time (E) during the formulation process was assumed to be 4 h/day, 30 days/yr from the information provided in the NICNAS survey.

Dermal exposure to liquid

Skin contact is assumed to be incidental (F=0.01)

Area of skin exposed assumed to be a hand and forearm (1000cm^2)

$$D_{dl} = \frac{W \times 0.32\ mg/cm^2/h \times 1000\ cm^2}{70} \times \frac{4\ h \times 30\ days \times 0.01}{365\ days}$$

Concentration ranges for formulated products were <10%, 10-80%, 10->60% and 60-90%. Dermal exposure estimates were based on formulation of products containing 90% trichloroethylene (W = 0.9)

Combined inhalational and dermal exposure

The combined inhalational and dermal exposure estimates for formulation for the various scenarios are tabled below.

Table 1 - Combined inhalational and dermal exposure during formulation of product containing 90% trichloroethylene

C		Daily dose (mg/kg/day)		
ppm	mg/m^3	D_v	D_{dl}	D_v+D_{dl}
10	54.6	0.25	0.013	0.26
30	163.8	0.75	0.013	0.76
50	273	1.25	0.013	1.26

C = concentration of trichloroethylene in air (mg/m^3)
D_v = dose resulting from absorption of vapours
D_{dl} = dose resulting from dermal absorption of liquid

2.2 Vapour degreasing

The combined inhalational and dermal uptakes for exposures during vapour degreasing were calculated as for formulation except that exposure time (E) was assumed to be 8 h/day for 200 days/yr. The equations used for inhalation and dermal exposure were:

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times 0.75 \times (8\ h/day \times 200\ days/yr)}{70\ kg \times 365}$$

$$D_{dl} = \frac{W \times 0.32\ mg/cm^2/h \times 1000\ cm^2}{70} \times \frac{8\ h/day \times 200\ days \times 0.01}{365\ days}$$

W = 1 as 100% trichloroethylene is used.

Table 2 - Combined inhalational and dermal exposure during vapour degreasing

C		Daily dose (mg/kg/day)		
ppm	mg/m³	D_v	D_{dl}	D_v+D_{dl}
10	54.6	3.3	0.2	3.5
30	163.8	10.0	0.2	10.2
50	273	16.7	0.2	16.9

C = Concentration of trichloroethylene in air (mg/m³)
E = duration of exposure (h/day)
D_v = Dose resulting from inhalation absorption of vapours
D_{dl} = Dose resulting from dermal absorption of liquid

2.3 Cold cleaning

The combined inhalational and dermal uptakes for exposures during cold cleaning were calculated as for vapour degreasing with exposure time (E) being 8 h/day for 200 days/yr as these were the scenarios encountered in the project commissioned by NICNAS. Dermal exposure was assumed for 5% of the total time. The equations used for inhalation and dermal exposure were:

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times 0.75 \times (8\ h/day \times 200\ days/yr)}{70\ kg \times 365}$$

$$D_{dl} = \frac{W \times 0.32\ mg/cm^2/h \times 1000\ cm^2}{70} \times \frac{8\ h/day \times 200\ days \times 0.01}{365\ days}$$

W = 1 as 100% trichloroethylene is used.

Table 3 - Combined inhalational and dermal exposure during cold cleaning for 8 h/day, 200 days/yr

C			Daily dose (mg/kg/day)		
ppm	mg/m³		D_v	D_{dl}	D_v+D_{dl}
0.4	2.18	dip cleaning	0.13	1.0	1.13
3.8	20.75	rag wiping	1.27	1.0	2.47
68.3	372.92	rag wiping	22.77	1.0	23.97
0.9	4.91	dip cleaning and rag wiping	0.29	1.0	1.29
7.5	40.95	dip cleaning and rag wiping	2.5	1.0	3.5

C = Concentration of trichloroethylene in air (mg/m³)
E = duration of exposure (h/day)
D_v = Dose resulting from inhalation absorption of vapours
D_{dl} = Dose resulting from dermal absorption of liquid

Exposure during cold cleaning was also estimated for a scenario of 120 days/yr as the industry survey indicated that at some worksites trichloroethylene is used 2-3 days/week.

Table 4 -Combined inhalational and dermal exposure during cold cleaning for 8 h/day, 120 days/yr

C			Daily dose (mg/kg/day)		
ppm	mg/m³		D_v	D_{dl}	D_v+D_{dl}
0.4	2.18	dip cleaning	0.079	0.60	0.68
3.8	20.75	rag wiping	0.76	0. 60	1.36
68.3	372.92	rag wiping	13.66	0. 60	14.26
0.9	4.91	dip cleaning and rag wiping	0.179	0. 60	0.78
7.5	40.95	dip cleaning and rag wiping	1.5	0. 60	2.1

2.4 Trichloroethylene products

The combined inhalational and dermal uptakes for exposures during use of trichloroethylene products were calculated as for vapour degreasing with exposure time (E) being 8 h/day for 200 days/yr as these were the scenarios encountered in the project commissioned by NICNAS. The equations used for inhalation and dermal exposure were:

$$D_v = \frac{C\ mg/m^3 \times 1.3\ m^3/h \times 0.75 \times (8\ h/day \times 200\ days/yr)}{70\ kg \times 365}$$

$$D_{dl} = \frac{W \times 0.32\ mg/cm^2/h \times 1000\ cm^2}{70} \times \frac{8\ h/day \times 200\ days \times 0.01}{365\ days}$$

W varied depending on the concentration of trichloroethylene in the products used at the various sites.

Table 5 - Combined inhalational and dermal exposure during use of trichloroethylene products

C		Daily dose (mg/kg/day)		
ppm	mg/m^3	D_v	D_{dl}	D_v+D_{dl}
35% product spray painting				
0.7	3.82	0.23	0.07	0.3
4.8	26.21	1.6	0.07	1.67
20% product rag wiping				
3.8	20.75	1.27	0.04	1.31
4.1	22.38	1.6	0.04	1.64
90% product brushing on				
2.5	13.65	0.83	0.18	1.01

C = Concentration of trichloroethylene in air (mg/m^3)
E = duration of exposure (h/day)
D_v = Dose resulting from inhalation absorption of vapours
D_{dl} = Dose resulting from dermal absorption of liquid

APPENDIX 2

SAMPLE MATERIAL SAFETY DATA SHEET

Page x of Total y
Date of Issue

Trichloroethylene is considered hazardous according to the criteria of Worksafe Australia

COMPANY DETAILS

Company Name:

Address:

Telephone Number:

Emergency Telephone Number:

Telex and Fax Numbers:

IDENTIFICATION

Chemical Name: Trichloroethylene

Other Names: 1,1,2-Trichloroethylene
1,1-Dichloro-2-chloroethylene
Ethylene trichloride
Acetylene trichloride
Ethinyl trichloride

Manufacturer's Product Code:

UN Number: 1710

Dangerous Goods Class: 6.1 Toxic

Subsidiary Risk: None

Hazchem Code: 2Z

Poisons Schedule Number: 6

Packaging Group: III

Use: As a solvent mainly in degreasing operations.

PHYSICAL DESCRIPTION/PROPERTIES

Appearance: clear colourless liquid

Odour: chloroform like odour

Boiling Point: 86.7°C

Vapour Pressure: 77 hPa

Density: 1.465 g/mL

Flashpoint: Not relevant

Flammability Limits: 8.0-10.5% at 25°C

Solubility in Water: 1.07 g/L at 20°C

OTHER PROPERTIES

Reactivity: in contact with hot metals, such as magnesium and aluminium at very high temperatures (300-600°C) it decomposes readily to form phosgene and hydrogen chloride. Such conditions are seen in areas where are welding occurs next to degreasing operations. Aluminium is more reactive than magnesium.

in the presence of strong alkalis such as sodium hydroxide, dichloroacetylene is formed which is explosive and flammable.

Autoignition Temperature: 410°C

Decomposition Temperature: >125°C

INGREDIENTS

Chemical Entity	CAS Number	Proportion
Trichloroethylene	79-01-6	

HEALTH HAZARD INFORMATION

HEALTH EFFECTS

Acute

Inhalation: Vapour is irritant to the upper respiratory tract. Inhalation of vapour can result in headache, dizziness and confusion with high doses causing narcosis. Exposure to high doses may cause irregular heart beats.

Swallowed: Swallowing may cause nausea, vomiting, headache and confusion. Ingestion of larger volumes (>50 ml) can cause central nervous system depression and effects on the heart. The main cardiac effects are increase in heart rate and irregular heartbeats.

Eye: Irritant to the eyes. Liquid and vapour can produce corneal damage.

Skin: Severe skin irritant. Repeated skin exposure can cause defatting of the skin and reddening. Liquid can be absorbed through the skin.

Chronic

Repeated exposure can cause central nervous system disturbances such as vertigo, dizziness, headaches, memory loss and impaired ability to concentrate.

Hearing loss, liver and kidney damage have been reported in rats.

Repeated or prolonged exposure in animals caused liver and lung tumours in mice and kidney tumours in rats.

FIRST AID

Inhaled: Remove person from exposure - avoid becoming a casualty. Remove contaminated clothing and loosen remaining clothing. Allow patient to assume most comfortable position and keep warm. If breathing stops artificial respiration to be given by trained personnel. Keep at rest until fully recovered. Seek medical advice.

Eye: Immediately irrigate with copious quantities of water for at least 15 minutes. Eyelids to be held open. Seek immediate medical assistance.

Skin: Wash contaminated skin with plenty of water. Remove contaminated clothing and wash before re-use. Seek medical assistance if irritation persists.

Swallowed: Rinse mouth with water. Give water to drink, avoid giving milk, oils or alcohol. Do not induce vomiting. If person is losing consciousness do not give anything by mouth. Seek immediate medical assistance.

ADVICE TO DOCTOR

Treat symptomatically. Avoid sympathomimetic amines as they may cause cardiac arrhythmias.

PRECAUTIONS FOR USE

Exposure Standards: Trichloroethylene 50 ppm TWA
200 ppm STEL (Short Term Exposure Limit)

Engineering Controls

Adequate ventilation should be provided to maintain air concentrations below exposure standard.

When opening/decanting/transferring trichloroethylene local exhaust ventilation should be used.

When used as a vapour degreaser the degreasing bath should comply with the requirements of Australian Standard AS 2661 (Standards Association of Australia, 1983).

Personal Protection

Avoid eye and skin contact and inhalation of vapours.

Protective overalls conforming to Australian Standard AS 3765.1 (Standards Australia & Standards New Zealand, 1990) should be worn.

If splashes are likely to occur during use safety goggles conforming to Australian Standard AS/NZS 1337 - 1992 (Standards Australia & Standards New Zealand, 1992) should be worn.

Appropriate gloves should be worn if contact with liquid trichloroethylene is likely.

If inhalation exposure is likely, e.g. during cleanup of spills, a respirator fitted with a gas filter such as type A (organic vapour) should be worn during use of trichloroethylene.
If working in a confined space or in poorly ventilated areas an air-line respirator should be worn. Respiratory protective equipment should be in accordance with AS/NZS 1715 (Standards Australia & Standards New Zealand, 1994) and AS/NZS 1716 (Standards Australia & Standards New Zealand, 1994).

Flammability

Trichloroethylene is not flammable under normal conditions of use. Vapour concentrations between 12.5% -90% v/v between 30-82°C may ignite in contact with high temperature heat sources. The vapour may ignite above 25°C if mixed with pure oxygen.

SAFE HANDLING INFORMATION

Storage and Transport

Store in a cool, dry, well ventilated area away from direct sunlight or ignition sources. Containers should be kept closed at all times. Store away from alkalis.

Correct Shipping Name: Trichloroethylene
UN No: 1710 Packaging Group III
ADG Code: Classified as a dangerous good for the purpose of transport, Class 6.1 (toxic).

Should not be transported or stored with explosives, nitromethane, fire risk substances of Class 5, cyanides and acids or foodstuffs and foodstuff empties.

Spills And Disposal

Contain spills using an absorbent (soil, sand or other inert material). Collect and seal in labelled containers for disposal. Wear appropriate personal protective equipment to prevent skin and eye contamination and to prevent inhalation. Prevent contamination of drains and waterways. Local environment protection authority or emergency services should be advised if contamination of sewers or waterways occurs.

Fire/Explosion Hazard

Not combustible. Evolves highly toxic fumes such as hydrogen chloride and phosgene at high temperatures. Fire fighters should wear full protective equipment including self-contained breathing apparatus. Evacuation of people from the neighbourhood should be considered if necessary. For fires, water fog or fine water spray may be appropriate.

OTHER INFORMATION

Toxicological Information

4-h LC_{50} in rats is 12000 ppm and 8450 ppm in mice.
Oral LD_{50} varies from 5400 to 7200 mg/kg in rats.
Oral LD_{50} in mice is 2900 mg/kg.

Ecological Information

96 h LC_{50} (Flatfish dab): 16 ppm
48 h LC_{50} (Rainbow trout) 42 ppm
48 h LC_{50} (Fathead minnow) 32-56 ppm

CONTACT POINT

Title
Telephone Number

APPENDIX 3

TRICHLOROETHYLENE (TCE) QUESTIONNAIRE

Company Information

Company name:
Company address:
Contact name:
Position:
Telephone: **Fax:**

Date:

Part A: Use Information

Please tick applicable boxes

		TCE	Quantity L/ month	TCE products	Quantity L/mth
A1.	Do you				
	import	☐	_____	☐	_____
	buy from Australian source	☐	_____	☐	_____
A2.	Do you:				
	on sell	☐	_____	☐	_____
	formulate			☐	_____
	use	☐	_____	☐	_____

Part B: Questions for resellers of TCE or products containing TCE.

If you on sell (distribute) TCE or products containing TCE please provide the following details. Otherwise go to Part C of the questionnaire.

B1. Please give details.

Product Name	% TCE	Typical end use	Avail to public? Yes/No	Annual sales volume

Please supply copies of MSDS for these products where available

B2. If you repackage TCE or TCE products before sale briefly describe the process.

_____

_____

_____

B3. What industry sectors do you sell to?

- ☐ Automotive
- ☐ Aerospace
- ☐ Electrical
- ☐ Telecommunications
- ☐ Metal forming/Machining
- ☐ Chemical processing
- ☐ Printing
- ☐ Paint
- ☐ Other (please specify) _____

If you repackage TCE or TCE products please go to Part E of the questionnaire.

Part C: Questions for Formulators

If you formulate products containing TCE, please answer the following questions. Otherwise go to Part D of the questionnaire.

C1. Do you purchase products in : ☐ Bulk
☐ Drums

C2. Please provide the following details for products you formulate:

Product Name	Typical end uses	% TCE	Product resold Yes/No	Avail. to public? Yes/No	Annual sales volume.

Please supply copies of the MSDS and labels.

C3. Briefly describe your formulating process.

_____

_____

_____

_____

If you do not use TCE products, please go to Part E of the questionnaire

Part D: Questions for end users

D1 Please indicate the type of industry in which you operate:

- ☐ Automotive
- ☐ Aerospace
- ☐ Electrical
- ☐ Telecommunications
- ☐ Metal forming/Machining
- ☐ Chemical processing
- ☐ Printing
- ☐ Other (please specify) _____

D2. Do you purchase products in :

- ☐ Bulk
- ☐ Drums

D3. Do you use TCE in any of these processes:

- ☐ Vapour degreasing
- ☐ Boil dip
- ☐ Aerosol manufacture
- ☐ Hand application eg surface cleaning
- ☐ Cold ultrasonic cleaning
- ☐ General solvent e.g. cleaning of small parts
- ☐ Other (specify) _____

D4. Please specify the temperature of your process if above the ambient temperature: _____°C.

D5. Briefly describe how you use TCE/TCE products

_____

_____

_____

_____

_____

Part E: Workplace Exposure

Questions for formulators, end users and on sellers (distributors) involved in repackaging TCE before sale.

E1. Are the processes you employ:

- ☐ Open
- ☐ Partially closed (eg covered tanks, trichloroethylene added by workers manually to tanks)
- ☐ Closed (fully sealed process including automated addition of trichloroethylene to tanks)
- ☐ Other (please specify) _____

_____

E2. Please describe the skill level, number and activities of workers using TCE or TCE products.

Classification/ skill level	Num-ber	Description of Work	H/day	Days/yr

E3. Please describe the engineering controls that are in place to reduce exposure of workers to TCE.

Process/Activity	Engineering Controls	Year installed

E4. Please list the personal protective equipment used by workers.

Process/Activity	Personal Protective Equipment

E5. Has atmospheric monitoring been conducted to determine levels of TCE in the workplace? _____

E6. Are you aware of any adverse health effects experienced by workers after exposure to trichloroethylene? If so please describe.

_____

_____

Part F: Environmental Effects

Questions for all respondents

F1. Please estimate the percentage of trichloroethylene lost to the atmosphere from your process or during use.

Process or end use	% lost to atmosphere

F2. Are you aware of any discharges of TCE to land or water? If so, please give details. _____

_____

_____

_____

F3. Do you actively recycle or otherwise recover TCE for re-use? If so, how much and please describe process. _____

_____

_____

_____

F4. What forms of trichloroethylene waste do you generate?

- ☐ None
- ☐ Soiled rags
- ☐ Sludge
- ☐ Contaminated solvent
- ☐ Other (please describe) _____

_____

F5. What methods do you use to dispose trichloroethylene waste?

- ☐ Blending with other products and re-use
- ☐ Evaporation to atmosphere
- ☐ Licensed discharges
- ☐ Incineration eg boiler fuel
- ☐ Send to solvent recycler
- ☐ Waste collection
- ☐ Other (please specify) _____

F6. How much trichloroethylene waste is disposed of monthly (total of all above methods)? _____ litres/month.

F7. Please indicate how you handle empty containers.

- ☐ Rinse and/or re-use
- ☐ Return to supplier
- ☐ Sell to drum recycler
- ☐ Send to landfill
- ☐ Other (please specify) _____

Thank you for responding to the questionnaire

APPENDIX 4

APPROVED CRITERIA FOR CLASSIFYING HAZARDOUS SUBSTANCES

CARCINOGENIC SUBSTANCES

4.76 Substances are determined to be hazardous due to carcinogenic effects if they fall into one of the following categories:

Category 1 Substances known to be carcinogenic to humans.

Category 2 Substances which should be regarded as if they are carcinogenic to humans.

Category 3 Substances which cause concern for humans owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF CARCINOGENIC SUBSTANCES

4.77 The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

CATEGORY 1

4.78 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.

R45 MAY CAUSE CANCER

R49 MAY CAUSE CANCER BY INHALATION[2]

4.79 A substance is included in Category 1 if there is sufficient evidence to establish a causal association between human exposure and the

[2] For substances which present a carcinogenic risk only when inhaled, for example, dust, vapour or fumes (and where other routes of exposure, for example, by swallowing or in contact with the skin do not present any carcinogenic risk) the specific risk phrase R49 should be used.

development of cancer on the basis of epidemiological data. The existence of a causal relationship would be any of the following:

- an increased incidence of one or more cancer types in an exposed population in comparison with a non-exposed population,
- evidence of dose-time-response relationships, that is, an increased cancer incidence associated with higher exposure levels or with increasing exposure duration,
- an association between exposure and increased risk observed in more than one study,
- demonstration of a decline in risk after reduction of exposure, and
- specificity of any association, defined as an increased occurrence of cancer at one target organ or of one morphological type.

CATEGORY 2

4.80 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.

R45 MAY CAUSE CANCER

R49 MAY CAUSE CANCER BY INHALATION[2]

4.81 A substance is included in Category 2 if there is sufficient evidence, on the basis of appropriate long term animal studies or other relevant information, to provide a strong presumption that human exposure to that substance may result in the development of cancer.

4.82 For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity dam, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

[2] For substances which present a carcinogenic risk only when inhaled, for example, dust, vapour or fumes (and where other routes of exposure, for example, by swallowing or in contact with the skin do not present any carcinogenic risk) the specific risk phrase R49 should be used.

4.83 Human data providing suspicions of carcinogenic potential may warrant a Category 2 classification irrespective of the nature of

any animal data. Increased confidence in the credibility of a causal relationship would be provided by evidence of carcinogenicity in animals and/or of genotoxic potential in short term screening tests.

CATEGORY 3

4.84 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.85 A substance is included in Category 3 if there is some evidence from appropriate animal studies that human exposure can result in the development of cancer, but this evidence is insufficient to place the substance in Category 2.

Category 3 actually comprises 2 sub-categories

(a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

(b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for humans. This classification is provisional; further experiments are necessary before a final decision can be made.

4.86 For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high dose levels exceeding the 'maximal tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain,

- appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,

- appearance of tumours, only at the site of application, in very sensitive test systems (eg intraperitoneal, or subcutaneous application of certain locally active compounds), if the particular target is not relevant to humans,

- lack of genotoxicity in short-term tests *in vivo and in vitro,*

- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (eg hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation),

- existence of a species-specific mechanism of tumour formation (eg by specific metabolic pathways) irrelevant for humans.

NO CARCINOGEN CLASSIFICATION

4.87 For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for humans:

- a substance should not be classified in any of the categories if the mechanism(s) of experimental tumour formation is/are clearly identified, with good evidence that such mechanism(s) cannot be extrapolated to humans for each tumour,

- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories,

- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.

MUTAGENIC SUBSTANCES

4.88 Substances are determined to be hazardous due to mutagenic effects if they fall into one of the following categories:

Category 1 Substances known to be mutagenic to humans.

Category 2 Substances which should be regarded as if they are mutagenic to humans.

Category 3 Substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damage.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF MUTAGENIC SUBSTANCES

4.89 A mutation is a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations, may involve a single gene, a block of DNA, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

4.90 It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in Category 3: 'induction of genetically relevant events in somatic cells', is generally also regarded as an alert for possible carcinogenic activity.

4.91 Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered.

CATEGORY 1

4.92 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R46 in accordance with the criteria given below.

R46 MAY CAUSE HERITABLE GENETIC DAMAGE

4.93 A substance is included in Category I if there is sufficient evidence to establish a causal relationship between human exposure to a substance and heritable genetic damage.

4.94 To place a substance in Category 1, positive evidence from human mutation epidemiology studies will be needed. Examples of such substances are not known to date. It is recognised that it is extremely difficult to obtain reliable information from studies on the incidence of mutations in human populations, or on possible increases in their frequencies.

CATEGORY 2

4.95 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R46 in accordance with the criteria given below.

R46 MAY CAUSE HERITABLE GENETIC DAMAGE

4.96 A substance is included in Category 2 if there is sufficient evidence to provide a strong presumption that human exposure to the substance may result in the development of heritable genetic damage, generally on the basis of appropriate animal studies and other relevant information.

4.97 To place a substance in Category 2, positive results are needed from assays showing

(a) mutagenic effects, or

(b) other cellular interactions relevant to mutagenicity, in germ cells of mammals *in vivo*, or

(c) mutagenic effects in somatic cells of mammals *in vivo* in combination with clear evidence that the substance or a relevant metabolite reaches the germ cells.

4.98 With respect to placement in Category 2, at present the following methods are appropriate:

(a) *in vivo* germ cell mutagenicity assays:

- specific locus mutation test,
- heritable translocation test,
- dominant lethal mutation test.

These assays actually demonstrate the appearance of affected progeny or a defect in the developing embryo.

(b) *in vivo* assays showing relevant interaction with germ cells (usually DNA):

- assays for chromosomal abnormalities, as detected by cytogenetic analysis, including aneuploidy caused by malsegregation of chromosomes,
- test for sister chromatid exchanges (SCEs),
- test for unscheduled DNA synthesis (UDS),
- assay of (covalent) binding of mutagen to germ cell
- DNA,
- assaying other kinds of DNA damage.

These assays provide evidence of a more or less indirect nature. Positive results in these assays would normally be supported by positive results from *in vivo* somatic cell mutagenicity assays, in mammals or in humans (see under Category 3).

(c) *in vivo* assays showing mutagenic effects in somatic cells of mammals (see sub section 4.98(a)), in combination with toxicokinetic methods, or other methodologies capable of demonstrating that the compound or a relevant metabolite reaches the germ cells.

For paragraphs 4.98(b) and 4.98 (c), positive results from host- mediated assays or the demonstration of unequivocal effects in *in vitro* assays can be considered as supporting evidence.

CATEGORY 3

4.99 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.100 A substance is included in Category 3 if there is evidence from appropriate mutagenicity studies, of concern that human exposure can result in the development of heritable genetic damage, but that this evidence is insufficient to place the substance in Category 2.

4.101 To place a substance in Category 3, positive results are needed in assays showing

(a) mutagenic effects, or
(b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*.

The latter especially would normally be supported by positive results from *in vitro* mutagenicity assays.

4.102 For effects in somatic cells *in vivo* at present the following methods are appropriate:

(a) *in vivo* somatic cell mutagenicity assays:

- bone marrow micronucleus test or metaphase analysis,
- metaphase analysis of peripheral lymphocytes,
- mouse coat colour spot test.

(b) *in vivo* somatic cell DNA interaction assays:

- test for SCEs in somatic cells,
- test for UDS in somatic cells,
- assay for the (covalent) binding of mutagen to somatic cell DNA,
- assay for DNA damage, for example, by alkaline elution, in somatic cells.

4.103 Substances showing positive results only in one or more *in vitro* mutagenicity assays should normally not be classified. Their further investigation using *in vivo* assays, however, is strongly indicated. In exceptional cases, for example, for a substance showing pronounced responses in several *in vitro* assays, for which no relevant *in vivo* data are available, and which shows resemblance to known mutagens/carcinogens, classification in Category 3 could be considered.

APPENDIX 5

Additional material considered by the Administrative Appeals Tribunal: Unpublished studies and published articles available after preparation of the draft report.

Blair A, Hartge P, Stewart PA, et al (1998) Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up. Occup Environ Medicine, **55**: 161-171

Boice JD, Marano DE et al. (1999) Mortality among aircraft manufacturing workers. Occup Environ Med, 56: 581-597.

Brauch H, Weirich G et al. (1999) Trichloroethylene exposure and specific somatic mutations inpatients with renal cell carcinoma. Journal of the National Cancer Institute, **9**(10): 954-961.

Bruning T, Sundberg, AGM et al (1999) Glutathione transferase alpha as a marker for tubular damage after trichloroethylene exposure. Arch Toxicol, **73**:246-254.

Clay P (1999) Trichloroethylene and S-(1,2-dichlorovinylcysteine): *in vivo* COMET and UDS assays in the rat kidney. Zeneca Central Toxicology Laboratory Report No. CTL/R/2976. First supplement to CTL/T/2976.

Clay P (1998) Trichloroethylene and S-(1,2-dichlorovinylcysteine): *in vivo* COMET and UDS assays in the rat kidney. Zeneca Central Toxicology Laboratory Report No. CTL/R/2976.

Dekant W and Henschler D (1999) Organ-specific carcinogenicity of haloalkenes mediated by glutathione conjugation. J Cancer Res Clin Oncol, **125**: 174-181.

Green T, Dow J, Ellis M.K. et al (1997) The role of glutathione conjugation in the development of kidney tumours in rats exposed to trichloroethylene. Chemico-Biolgical Interactions **105**: 99-117

Green T. (1997) Formic acid excretion in rats and mice exposed to trichloroethylene. Report No: CTL/R/1312, Central Toxicology Laboratory, Cheshire UK.

Green and Dow (1999) Trichloroethylene induced vitamin B12 and folate deficiency leads to increased formic acid excretion in the rat. Report No: CTL/R/1431, Central Toxicology Laboratory, Cheshire, UK.

Green T, Dow J, Foster JR et al (1999) Trichloroethanol: Long-term drinking water study in the Fischer rat. Interim report at one year. Report No: CTL/R/1312, Central Toxicology Laboratory, Cheshire UK.

Green LC and Lash TL (1999) Re: "Renal cell cancer correlated with occupational exposure to trichloroethylene". J Cancer Res Clin Oncol, **125**: 430-432.

Green T (1998) Analysis of urine samples from humans occupationally exposed to trichloroethylene. Zeneca Central Toxicology Laboratory Report No. CTL/R/1364.

Griffin JM, Lipscomb JC et al. (1998) Covalent binding of trichloroethylene to proteins in human and rat hepatocytes. Toxicology Letters, **95**: 173-181.

Halmes NC, Samokyszyn VM et al. (1997) Covalent binding and inhibition of cytochrome P4502E1 by trichloroethylene. Xenobiotica **27**(1): 101-110.

Hayashi M, Ueda T et al. (1998) Development of genotoxicity assay system that use aquatic organisms. Mutagen Research, **399**: 125-133.

Kautianen A, Vogel JS et al. (1997) Dose-dependent binding of trichloroethylene to hepatic DNA and protein at low doses in mice. Chemico-Biological Interactions, **106**: 109-121.

Lash LH, Lipscomb JC (1999) Glutathione conjugation of trichloroethylene in human liver and kidney: kinetics and individual variation. Drug Metabolism and Disposition, **27**(3): 351-359.

Lash LH, Putt DA et al. (1999) Identification of *S*-(1,2-dichlorovinyl) glutathione in the blood of human volunteers exposed to trichloroethylene. Journal of Toxicology and Environmental Health, Part A, **56**: 1-21.

McLaughlin JK & Blot WJ (1997) A critical review of epidemiology studies of trichloroethylene and perchloroethylene and risk of renal-cell cancer. Int. Arch. Occup. Environ. Health, **70**: 222-231.

Morgan RW, Kelsh MA et al. (1998) Mortality of aerospace workers exposed to trichloroethylene. Epidemiology, **9**(4): 424-431.

Ritz B (1999) Cancer mortality among workers exposed to chemicals during uranium processing. J Occup. Med., 41;14:556-566.

Robbiano L, Mereto E et al. (1998) Increased frequency of micronucleated kidney cells in rats exposed to halogenated anaesthetics. Mutation Research, **413**: 1-6.

Sujatha TV and Hegde MJ (1998) C-mitotic effects of trichloroethylene (TCE) on bone marrow cells of mice. Mutation Research, **413**: 151-158.

Terracini B and Parker VH (1965) A pathological study on the toxicity of *S*-dichlorovinyl-L-cystine. Food Cosmet Toxicol **3**: 67-74.

Vamvakas S, Bruning, T et al. (1998) Renal cell cancer correlated with occupational exposure to trichloroethylene. J Cancer Res Clin Oncol, **124**: 374-382.

APPENDIX 6

DECISION AND REASONS FOR DECISION [1999] AATA 1023

ADMINISTRATIVE APPEALS TRIBUNAL)
) No V1998/955
General ADMINISTRATIVE DIVISION))

Re Dow Chemical (Australia) Limited
Applicant

And Director, Chemicals Notification and Assessment
Respondent

DECISION

Tribunal Deputy President A M Blow OAM, QC.,
Professor G A R Johnston AM, FRACI, FTSE
Miss E A Shanahan

Date 31 December 1999
Place Melbourne
Decision The decisions under review are affirmed.

[Sgd A M Blow]
Deputy President

CATCHWORDS
Health Law – industrial chemicals – classification of a "priority existing chemical" – trichloroethylene –carcinogenicity and mutagenicity.
Industrial Chemicals (Notofication and Assessment) Act 1989 – ss.60E(5), 102(1)(b)
Melbourne Pathology Pty Limited v Minister for Human Services and Health (1996) 40 ALD 565
Friends of Hinchinbrook Society Inc v Minister for Environment (1997) 69FCR 28.

REASONS FOR DECISION

31 December 1999 Deputy President A M Blow OAM, QC.,
Professsor G A R Johnston AM, FRACI, FTSE
Miss E A Shanahan

1. This is an application pursuant to s.102(1)(b) of the **Industrial Chemicals (Notification and Assessment) Act 1989** ("the Act"). The applicant is seeking the review of a series of

decisions made by the respondent on 14 July 1998 under s.60E(5) of the Act whereby she refused to vary a draft report in a number of respects. The draft report relates to a chemical called trichloroethylene. The decisions under review relate to passages in the draft report concerning the carcinogenicity and mutagenicity of trichloroethylene.

2. The objects of the Act are set out in s.3 thereof, which reads as follows:-

> *"(3) The object of this Act is to provide for a national system of notification and assessment of industrial chemicals for the purposes of:*
> *(a) aiding in the protection of the Australian people and the environment by finding out the risks to occupational health and safety, to public health and to the environment that could be associated with the importation, manufacture or use of the chemicals; and*
> *(b) providing information, and making recommendations, about the chemicals to Commonwealth, State and Territory bodies with responsibilities for the regulation of industrial chemicals; and*
> *(c) giving effect to Australia's obligations under international agreements relating to the regulation of chemicals; and*
> *(d) collecting statistics in relation to the chemicals;*
> *being a system under which information about the properties and effects of the chemicals is obtained from importers and manufacturers of the chemicals."*

3. On 4 April 1995 the Minister for Industrial Relations published a notice in the Chemical Gazette under s.51 of the Act declaring trichloroethylene a priority existing chemical. On 16 June 1995 ICI Australia Operations Pty Limited applied under s.55(2) of the Act for the assessment of trichloroethylene. On 19 June 1995 the applicant made a similar application. When such an application is made, s.57(1) of the Act obliges the respondent to cause the relevant chemical to be assessed, and to cause a report to be prepared. That sub-section reads as follows:-

> *"Where the Director receives an application or applications for the assessment of a priority existing chemical, he or she must cause the chemical to be assessed in accordance with section 60A and a report of the assessment to be prepared."*

4. The Act makes provision for the assessment process and the preparation of a draft assessment report in ss.60A, 60B and 60C, which read as follows:-

> *"**60A Nature of assessment***
> *(1) The officer preparing the report of the preliminary assessment of a priority existing chemical must determine the significance, for the making of a determination described in subsection (2) in relation to that chemical, of each of the matters required to be taken into account by the notice declaring the chemical as a priority existing chemical.*

(2) The officer preparing the report of the full assessment of a priority existing chemical must determine the risk (if any) of adverse health effects, safety effects or adverse environmental effects that could be caused by:

(a) importation of the chemical (if it is proposed to import the chemical); or

(b) manufacture of the chemical (if it is proposed to manufacture the chemical in Australia); or

(c) the use, storage, handling or disposal of the chemical.

(3) In making a determination under subsection (1) or (2), the officer must take into account the matters required to be taken into account by the notice declaring the chemical as a priority existing chemical.

60B Contents of assessment reports

(1) An assessment report (whether it is a draft assessment report made under section 60C or a final assessment report made under section 60F) must include a summary of health, safety and environmental matters considered in the assessment and such recommendations as may reasonably be made in relation to each of the following matters:

(a) the content of a Material Safety Data Sheet in respect of the chemical;

(b) the precautions and restrictions to be observed during the importation, manufacture, handling, storage, use of disposal of the chemical to protect persons exposed to the chemical;

(c) controls to limit emissions of the chemical into the environment, including permissible concentrations in emissions of the chemical into the air or water from a manufacturing plant or other facility;

(d) the packaging, labelling, handling or storage of the chemical;

(e) the measures to be employed in emergencies involving the chemical to minimise hazard to persons and damage to the environment;

(f) the uses of the chemical;

(g) the means of disposal of the chemical;

(h) the circumstances (if any) in which secondary notification of the chemical is required;

(i) any prescribed matter.

(2) The assessment report (whether draft or final) must not contain exempt information.

60C Draft assessment report

On completing an assessment of a priority existing chemical, the Director must cause a draft report of the assessment to be prepared."

5. The draft report was completed by 13 March 1998. On that day a copy of the draft report was sent to the applicant with a notice under s.60D(1)(b) of the Act asking the applicant to notify the respondent of any errors in it. Some non-controversial corrections were made as a result. Once that stage is reached, s.60E of the Act provides for interested parties

to request the respondent to make variations to the draft report. The relevant provisions in that section read as follows:-

> *"**60E Variation of draft assessment report***
> *(1) Within 56 days of giving the draft assessment report to each applicant, the Director must:*
> *(a) give a copy of the draft report with any corrections to each applicant and to any person who has provided information for the assessment in response to a notice under section 58; and*
> *(b) publish a notice in the Chemical Gazette:*
> *(i) describing the matters contained in the draft report; and*
> *(ii) stating that the draft report has been given to each applicant and person who provided information under section 58; and*
> *(iii) describing how a person may obtain a copy of the draft report; and*
> *(iv) describing how a person may ask the Director to vary the draft report.*
> *(2) Within 28 days of the publication of the notice under subsection (1), a person may request the Director, in the approved form, to vary the draft report.*
> *(3) The Director must make a decision about the variation within 56 days after the publication of the notice under subsection (1).*
> *(4) The Director must decide to vary the draft report as requested if he or she is satisfied that the report, varied as requested, would be correct.*
> *(5) The Director must decide to refuse to vary the draft report as requested if he or she is not satisfied that the report, varied as requested, would be correct."*

6. A notice was published in the Chemical Gazette on 5 May 1998 pursuant to s.60E(1)(b). The applicant faxed to the respondent a request dated 1 June 1998 seeking a number of variations to the draft report. Three other requests under s.60E were also sent to the respondent. On 24 July 1998 the respondent made a series of decisions in relation to each of the four requests she had received. She made a separate decision in relation to each variation that had been requested to the draft report – either a decision under s.60E(4) making a requested variation, or a decision under s.60E(5) refusing to make a requested variation. Some of the variations requested by the other parties were made under s.60E(4). The applicant has applied to this Tribunal in respect of the requests made by it all of which were refused by respondent under s.60E(5).

7. In March 1994 the National Occupational Health and Safety Commission published a booklet entitled "Approved Criteria for Classifying Hazardous Substances [NOHSC:1008 (1994)]". Although she was under no legal obligation to do so, the respondent in her draft report assessed trichloroethylene by reference to the Approved Criteria as published in March 1994. A fresh edition of the Approved Criteria has been published in 1999. That document constitutes a standard declared by the

Commission under s.38(1) of the **National Occupational Health and Safety Commission Act 1985**. It is common ground that, in reviewing the respondent's decisions as to the draft report, we should apply the 1999 edition of the Approved Criteria. The relevant passages in the 1999 edition do not vary significantly from those in the March 1994 edition.

8. Generally speaking the Approved Criteria are intended to be the same in substance as the criteria used by the European Communities in their legislation for classifying dangerous substances. Appendix 3 to the Approved Criteria lists a series of "risk phrases" relevant to different types of health effects. These have been taken from an EEC Council Directive. The following risk phrases are relevant in this case:

"**R40** Possible risk of irreversible effects."
"**R45** May cause cancer."`
"**R46** May cause heritable genetic damage"
"**R49** May cause cancer by inhalation."

9. Chapter 3 of the Approved Criteria sets out how those criteria are to be applied. It contains the following paragraphs that are relevant to this case:

> *"3.4 Classifying the substance will involve finding and putting together all the available information on the substance and assessing this information against the criteria. This process will identify the health hazards of the substances and appropriate risk phrases to be used.*
>
> *…*
>
> *3.10 If evidence is available to show that in practice the toxic effect of a substance on humans is, or is likely to be, different from that suggested by the results of animal testing, then the substance should be classified according to its toxicity in humans.*
>
> *3.11 If only some information is available for the substance, then the health effects criteria and other suitable information should be applied as far as possible to classify the substance. …*
>
> *3.12 The classification for a substance may need to be revised periodically as new information about that substance becomes available."*

10. Chapter 4 of the Approved Criteria, entitled "Health Effects Criteria", contains the following provisions relevant to this case:

> *"4.1 The criteria in this chapter are those used by the European Communities in EC Council Directive 67/548/EC[3] for classifying dangerous substances based on their hazards to health. These criteria take into account both short and long term health effects, and are applicable to both pure substances and mixtures.*
>
> *…*
>
> *4.4 For the purposes of classification, health effects are subdivided into:*
>
> *…*
>
> - *carcinogenic effects (R40, R45, R49);*
> - *mutagenic effects (R40, R46);*
>
> *…*

A substance may have more than one health effect.

Criteria for classification and choice of risk phrases for ingredients and mixtures.

…

4.9 For specific effects on health (carcinogenicity, mutagenicity and reproductive toxicity) the criteria in paragraphs 4.76 to 4.133 are to be used.

…

CARCINOGENIC SUBSTANCES

4.76 Substances are determined to be hazardous due to carcinogenic effects if they fall into one of the following categories:

Category 1	*Substances known to be carcinogenic to humans.*
Category 2	*Substances which should be regarded as if they are carcinogenic to humans.*
Category 3	*Substances which cause concern for humans owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.*

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF CARCINOGENIC SUBSTANCES

4.77 The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

…

CATEGORY 2

4.80 Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.

R45 MAY CAUSE CANCER

R49 MAY CAUSE CANCER BY INHALATION[2]

[2]For substances which present a carcinogenic risk only when inhaled, for example, dust, vapour or fumes (and where other routes of exposure, for example, by swallowing or in contact with the skin do not present any carcinogenic risk) the specific risk phrase R49 should be used.

4.81 A substance is included in Category 2 if there is sufficient evidence, on the basis of appropriate long term animal studies or other relevant information, to provide a strong presumption that human exposure to that substance may result in the development of cancer.

4.82 For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an

association.

4.83 Human data providing suspicions of carcinogenic potential may warrant a Category 2 classification irrespective of the nature of any animal data. Increased confidence in the credibility of a causal relationship would be provided by evidence of carcinogenicity in animals and/or of genotoxic potential in short term screening tests.

CATEGORY 3

4.84 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.85 A substance is included in Category 3 if there is some evidence from appropriate animal studies that human exposure can result in the development of cancer, but this evidence is insufficient to place the substance in Category 2.

Category 3 actually comprises 2 sub-categories

(a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

(b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for humans. This classification is provisional; further experiments are necessary before a final decision can be made.

4.86 For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- *carcinogenic effect only at very high dose levels exceeding the `maximal tolerated dose'. The maximal tolerated does is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain,*
- *appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation,*
- *appearance of tumours, only at the site of application, in very sensitive test systems (eg intraperitoneal, or subcutaneous application of certain locally active compounds), if the particular target is not relevant to humans,*
- *lack of genotoxicity in short-term tests in vivo and in vitro,*
- *existence of a secondary mechanism of action with the*

implication of a practical threshold above a certain dose level (eg hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation),

- *existence of a species-specific mechanism of tumour formation (eg by specific metabolic pathways) irrelevant for humans.*

…

MUTAGENIC SUBSTANCES

4.88 Substances are determined to be hazardous due to mutagenic effects if they fall into one of the following categories:

Category 1 Substances known to be mutagenic to humans.

Category 2 Substances which should be regarded as if they are mutagenic to humans.

Category 3 Substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damage.

EXPLANATORY NOTES REGARDING THE CATEGORISATION OF MUTAGENIC SUBSTANCES

4.89 A mutation is a permanent change in the amount or structure of the genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations, may involve a single gene, a block of DNA, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes, including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

4.90 It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in Category 3: 'induction of genetically relevant events in somatic cells', is generally also regarded as an alert for possible carcinogenic activity.

4.91 Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered.

…

CATEGORY 3

4.99 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.100 A substance is included in Category 3 if there is evidence from appropriate mutagenicity studies, of concern that human exposure can result in the development of heritable genetic damage, but that this evidence is insufficient to place the substance in Category 2.

4.101 To place a substance in Category 3, positive results are needed in assays showing

(a) mutagenic effects, or

(b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals in vivo.

The latter especially would normally be supported by positive results from in vitro mutagenicity assays.

4.102 For effects in somatic cells in vivo at present the following methods are appropriate:

(a) in vivo somatic cell mutagenicity assays:

- *bone marrow micronucleus test or metaphase analysis,*
- *metaphase analysis of peripheral lymphocytes,*
- *mouse coat colour spot test.*

(b) in vivo somatic cell DNA interaction assays:

- *test for SCEs in somatic cells,*
- *test for UDS in somatic cells,*
- *assay for the (covalent) binding of mutagen to somatic cell DNA,*
- *assay for DNA damage, for example, by alkaline elution, in somatic cells.*

4.103 Substances showing positive results only in one or more in vitro mutagenicity assays should normally not be classified. Their further investigation using in vivo assays, however, is strongly indicated. In exceptional cases, for example, for a substance showing pronounced responses in several in vitro assays, for which no relevant in vivo data are available, and which shows resemblance to known mutagens/carcinogens, classification in Category 3 could be considered.

11. In the draft report, the respondent concluded that trichloroethylene should be classified as a "mutagen category 3 (R40(M3) Possible risk of irreversible effects, mutagen category 3) and carcinogen category 2 (R45-May cause cancer)". The applicant contends that trichloroethylene should have been categorised as a category 3 carcinogen (not category 2), and

that it should not have been classified as a mutagen at all.

12. In reviewing the respondent's decisions in relation to the draft report by reference to the Approved Criteria, we are bearing in mind that, whilst those criteria do not have the force of law for our purposes, they are intended to be adopted by State and Territory occupational health and safety legislation, and thus have been drafted with the intention that for certain purposes they should have the force of law. However the criteria are addressed to practical people skilled in their particular trades and industries, and should be construed in the light of practical considerations, rather than being treated like an Act of Parliament: **Melbourne Pathology Pty Limited v Minister for Human Services and Health** (1996) 40 ALD 565 at 580-581.

13. Counsel for the respondent submitted that we should take into account the "precautionary principle" that was discussed by Sackville J in **Friends of Hinchinbrook Society Inc v Minister for Environment** (1997) 69 FCR 28 at 78-80. In simplistic terms, that principle requires that a cautious approach be taken when there is a threat of harm and scientific uncertainty. That is a principle of common sense, rather than a rule of law. It is a very relevant principle in this case. But it would be a mistake if, out of an abundance of caution, we were to give trichloroethylene a carcinogenicity classification or a mutangenicity classification otherwise than in accordance with the Approved Criteria.

CARCINOGENESIS

14. The Applicant accepts that trichloroethylene is a category 3 carcinogenic substance, i.e. that it is a substance which causes concern for humans owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

15. The Applicant rejects the Respondent's proposal to classify trichloroethylene as a category 2 carcinogenic substance, i.e. that it is a substance which should be regarded as if it is carcinogenic to humans.

16. The Approved Criteria (para 4.77) states that the placing of a substance into Categories 2 and 3 is based primarily on animal experiments.

Rat kidney tumours: animal studies

17. Counsel for the Applicant maintains that 'the only relevant animal studies are the rat kidney tumour studies (Transcript 391/30).

18. Counsel for the Respondent maintains that there is 'clear positive evidence that TCI produces renal tubular cell tumours in rats' (Transcript 387/14) and that the mice lung and liver cancers can be discounted but not ignored (Respondent's Submissions in Reply, para 14).

19. The full list of animal studies considered by the Director of NICNAS is given in Table 26 of Exhibit A8, the marked up draft report on trichloroethylene at pages 89-92.

20. The key studies of rat kidney tumours are: the US National Toxicology Program studies NTP 1988 (Exhibit A1 Vol 2.2 Tab 24) and NTP 1990 (Exhibit A1 Vol 2.2 Tab 20), and Maltoni et al. 1988 (T6 Vol 4 Tab 36; this is the full study of Maltoni et al., 1986 listed in Exhibit A8, Table 26).

21. As pointed out by Counsel for the Respondent (Transcript 387/16) the best evidence that trichloroethylene produces kidney tumours in rats comes from the Applicant's expert witness, Dr Green.

22. Dr Green in exhibit A12 stated 'in some of the lifetime studies a low incidence of kidney cancer has been observed in male rats. The instances in the national toxicology program studies and Maltoni, these tumours have rarely achieved statistical significance but have nevertheless been considered treatment related because of the rarity of renal cancer in rats.'

23. Further, in his oral evidence Dr Green stated 'In all of these studies you see kidney damage, then you see a very low incidence of kidney cancer. If you look at the individual bioassays, and whether they are statistically significant, whether they are adequate, inadequate or not, many of those bioassays will fail, but at the end of the day there is a clear correlation between kidney damage and a low incidence of cancer.' He answered 'That's correct, yes' to the question 'And the clear correlation that you have referred to was supported by the existence of cases of kidney cancer in multiple strains and in studies which administer TCI by both the oral route and the inhalation route. Is that correct?' (Transcript 91/15)

24. Counsel for the Applicant maintained that there is 'some weak evidence on the rat kidney tumours, because the rat kidney tumours were only observed at toxic doses or doses above the maximum tolerated dose'. (Transcript 392/13)

25. The maximum tolerated dose was not exceeded in the Maltoni et al., 1988 study (T6 Vol 4 Tab 36) as indicated by Counsel for the Respondent (Respondent's Submissions in Reply, para 15).

26. The maximum tolerated dose may have been exceeded in the two NTP studies at 500 and 1000 mg/kg/day given that the final mean body weight of the trichloroethylene treated animals was approximately 10% less than that of the control animals. Dr McConnell pointed out that this difference was due to the trichlorethylene treated animals failing to keep up with the control animals in gaining body weight after some 15 weeks. (Transcript 142/20).

27. The lack of weight gain in the animals treated with trichloroethylene is consistent with kidney damage. Nonetheless, as stated above kidney tumours are rare in rats and thus highly likely to be treatment related as acknowledged by the Applicant's witness, Dr Green, as noted above.

28. In exhibit R9 (Report of Carcinogens Sub-committee 1997), trichloroethylene is listed as 'reasonably anticipated to be a human carcinogen'. Dr McConnell explained that what the US NTP did with this report on carcinogens 'is to look at the totality of the data, much like you're doing here, and they would take the same studies that they previously, the National Toxicology Program has said are inadequate, but then they would look at the totality of all these studies together with the totality of other information, exactly as you're doing, and to form this opinion that whether this material has potential or can be reasonably anticipated to be a human carcinogen.' (Transcript 144/3)

29. Dr McConnell explained further that the US only have 2 categories of carcinogen. He stated 'In a sense, they put our categories 2 and 3 into reasonably anticipated to be a human carcinogen '. (Transcript 144/19)

Rat kidney tumours: precursor lesions

30. Dr McConnell (former Chair, Science Advisory Panel of the US Environmental Protection Agency), showed the Tribunal colour slides of tissue sections (Exhibit R13) from the US National Toxicology Program (NTP) studies into kidney damage in rats exposed to trichlorethylene. Dr McConnell interpreted these slides as clearly showing precursor lesions. He stated 'If I had not seen the precursor lesions in those rat studies, I would have not - because the incidence was so low, I would have thought that this could have been a spurious observation, the kidney tumours, but with the presence of the precursor lesion this strengthened my view that these kidney tumours were, indeed, related to exposure to TCI.' (Transcript 103/13)

31. Dr McConnell provided a plausible explanation for the mode of kidney tumour production by trichloroethylene: 'a progression from toxicity to hyperplasia to neoplasia and benign-neoplasia and finally malignant neoplasia'. (Transcript 103/5). The precursor lesions that he described in the slides from the NTP study were a marker of this progression - 'We think that if you see precursor lesions in the same organ that you have the carcinogenic response, then that carcinogenic response has more significance'. (Transcript 103/6) Dr Green also gave 'considerable weight' to the finding of precursor lesions. (Transcript 91/2)

32. The Tribunal was satisfied that Dr McConnell's progression mechanism from precursor lesions to malignant neoplasia was a reasonable explanation of the mode of action of trichloroethylene producing the observed rat kidney tumours.

Rat kidney tumours: mechanism(s) of production

33. The Tribunal then went on to consider the detailed mechanism(s) whereby trichloroethylene produced kidney tumours in rats.

34. Evidence was presented to the Tribunal on how trichloroethylene produced kidney tumours in rats. Did the kidney tumours result from cytotoxicity and subsequent regeneration, or from genotoxicity?

35. The Applicant's position was that 'so far as carcinogenicity is concerned is that it is accepted by all the experts that the cause of the rat kidney tumours is cytotoxicity and regeneration, It was accepted by both Dr Green and Dr McConnell that there was no genotoxic effect which produced the tumours observed.' (Transcript 392/5)

36. The Respondent's Submission in Reply (para 19) maintained "There is no inconsistency between cytotoxicity and regeneration on the one hand and mutation of the VHL (tumour suppressor) gene on the other. Indeed, mutation of the VHL gene may be an explanation for the appearance of neoplasia in the regeneration. '

37. At issue is the mechanism(s) by which trichloroethylene may have produced kidney tumours. In exhibit R11 (The 1995 ASCEPT Toxicology Workshop on 'Health-Based Risk Assessment of Contaminated Land: Focus on Carcinogens'), Dr Iain Purchase (Zeneca UK) points out that 'many chemicals found to produce cancer in animals do not interact directly with DNA but have an indirect, non-genotoxic mechanism of action' (Page 7), while Dr Jim Fitzgerald (South Australian Health Commission) states 'in reality it is difficult to prove that a carcinogen is really non-genotoxic, and here mechanistic understanding is very important' (Page 13).

38. Three possible mechanisms for the production of kidney tumours were put before the Tribunal: (1) the DCVC pathway, referring to the trichloroethylene metabolite S-(dichlorovinyl)-cysteine; (2) the formic acid pathway, referring to the increased production of formic acid as a result ingestion of trichloroethylene; and (3) the mutation of the tumour suppressor gene, VHL, a mechanism arising from molecular biological studies on humans exposed to trichloroethylene in the workplace.

39. These three mechanisms (and other possible mechanisms) are not mutually exclusive and each could contribute to the production of kidney tumours.

The DCVC pathway

40. Dr Green provided evidence (A9) on the metabolism of trichlorethylene. Most (80-90%) of ingested trichloroethylene is exhaled, the remainder being metabolised and excreted in the urine (Transcript 95/25). The major metabolic pathway involves metabolism by cytochrome

P-450 to trichloroacetic acid. A minor pathway involving glutathione S-transferase leads to the production of DCVC. The DCVC pathway was estimated to represent less than 0.005% of the injected dose of trichloroethylene.

41. Dr McConnell, when asked had he come across any other chemical that produces similar precursor lesions to trichloroethylene, stated 'the chemical that comes to mind is this DCVC'. (Transcript 106/26). However, Dr McConnell agreed that he knew 'of no evidence from your appraisal of any of the literature which demonstrates that dichlorovinylcysteine has an effect on or produces rat kidney tumours'. (Transcript 112/26)

42. From this and other evidence present, the Tribunal considered that the DCVC pathway was unlikely to be of major significance in the production of rat kidney tumours by trichloroethylene, although it cannot be completely excluded.

The formic acid pathway

43. Dr Green and his colleagues (Exhibit A13 - Green, Dow, Foster and Hext, Formic acid excretion in rats exposed to trichloroethylene: a possible explanation for renal toxicity in long-term studies, Toxicology, 1998, 127, 39-47) discovered that rats exposed to trichloroethylene excrete large amounts of formic acid, a chemical associated with kidney damage in a number of species.

44. Formic acid is not a metabolite of trichloroethylene. It is a chemical normally present in mammals who use it to make amino acids and components of DNA. It is not normally excreted in the urine in any significant amount. Dr Green and his colleagues found that the trichlorethylene metabolites, trichloroethanol and trichloroacetic acid inhibit the enzyme methionine synthetase, which is involved in the methionine salvage pathway. This results in a reduction in the production of tetrahydrofolate by some 50%, which in turn leads to the reduced utilisation of formic acid normally used to make N-formyl tetrahydrofolate. The net result is greatly increased excretion of formic acid in the urine. Dr Green described this for the Tribunal using exhibit A9(3).

45. Increased levels of formic acid in the urine are a possible explanation for the kidney damage in rats following long-term administration of trichloroethylene. Dr Green considered that this mechanism could explain the tubular hyperplasia seen in the kidneys of rats dosed for 12 months with trichloroethanol in their drinking water (Exhibit A9(8)).

46. Dr McConnell, however, found that there was no evidence that formic acid duplicated the histopathology of the kidney tumours produced by trichloroethylene, stating 'I think the formic acid hypothesis becomes suspect with regard to its causation of the tumours in the rats'. (Transcript 107/30).

47. Dr Green and his colleagues (Exhibit A13) acknowledge that 'Renal toxicity is not normally reported following exposure to chemicals such as methanol and formaldehyde which are metabolised to formic acid. ..... However, the clearance of formic acid produced metabolically from these chemicals is rapid and markedly different from the high and sustained formic acid exposure which is seen in trichloroethylene treated rats.'

48. The Tribunal considered that the formic acid pathway provided a mechanistic hypothesis regarding the causation of kidney tumours in rats by trichloroethylene that merited further investigation.

Folates, methylation and the methionine salvage pathway

49. Other possible mechanisms arise out of the finding by Green and his colleagues that metabolites of trichloroethylene inhibit the methionine salvage pathway.

50. Dr Green was asked about metabolic changes resulting from inhibition of methionine synthetase in addition to the increased excretion of formic acid. (Transcript 96/10). He noted that there was a build up of methyl-tetrahydrofolate in plasma and considered that there may be a reduction in methionine levels although they had not measured this. He had previously drawn attention to a 50% reduction in the levels of tetrahydrofolate. (Exhibit A9(3))

51. Dr Green was asked about any association between folates and cancer. He noted that there are chemotherapeutic drugs that act on folate metabolism but that these acted higher up the metabolic pathway between folate and dihydrofolate, or between dihydrofolate and tetrahydrofolate. (Transcript 97/3)

52. Subsequent to the hearing, the Tribunal was able to find an extensive literature on folate and methionine deficiencies and cancer, including lack of DNA methylation. For example, Kim et al. (Kim, Pogribny, Basnakian, Miller, Selhub, James and Mason, Folate deficiency in rats induces DNA strand breaks and hypomethylation within the p53 tumour suppressor gene, American Journal of Clinical Nutrition, 1996, 65, 46-52) found that folate deficiency induced DNA strand breaks both at the genomic level and within specific sequences of the p53 tumour suppressor gene. Diets deficient in methyl donors such as folate and methionine are known to lead to carcinogenesis (Henning and Swendseid, The role of folate, choline, and methionine in carcinogenesis induced by methyl-deficient diets, Advances in Experimental Medicine and Biology, 1996, 399, 143-155). Such dietary deficiencies are known to increase spontaneous and chemically induced carcinogenesis (Rogers, Methyl donors in the diet and responses to chemical carcinogens. American Journal of Clinical Nutrition, 1995, 61(3 Suppl), 659S-665S).

53. The substantially increased excretion of formic acid (a one-carbon acid) demonstrated by Green et al in rats receiving trichloroethylene is

considered highly likely to result in a significant metabolic deficit of one-carbon fragments for methylation. This could lead to reduced methylation of DNA and RNA, hyperplasia, increased peroxidative damage and altered carcinogen or promoter metabolism (as discussed in Rogers, 1995).

54. Clearly the consequences of disruption of the methionine salvage pathway by metabolites of trichloroethylene are not limited to the increased urinary secretion of formic acid. A number of possible mechanisms exist that could result in the kidney tumours produced by trichloroethylene, other than by formic acid. These mechanisms can be tested experimentally.

55. These other possible mechanisms leading to kidney tumours are at least as plausible as the formic acid pathway but no evidence regarding them was presented to the Tribunal.

Rat kidney tumours: cytotoxicity and regeneration and/or genotoxicity?

56. Genotoxicity is a key factor in the classification of chemicals as carcinogens and is a critical issue in the classification of trichloroethylene.

57. Dr Green (Exhibit A2) in his expert witness statement stated 'Although there is evidence in some tests of weak genotoxicity, particularly chromosomal effects, the mechanistic studies described above suggest that the tumours seen in rats and mice develop without genotoxicity'.

58. On the balance of evidence, the Tribunal was not convinced that any of the studies ruled out genotoxic components in the progression from precursor lesions to the production of the rat kidney tumours.

59. Indeed, given the definitive evidence from the human studies of effects on tumour suppressor genes, together with the rat metabolic evidence of disruption of the methionine salvage pathway and changes to levels of methionine and folate derivatives, the Tribunal was aware of highly plausible molecular mechanisms for trichloroethylene induced tumours involving genotoxicity.

Carcinogenesis supporting evidence

60. As listed in the Outline of Respondent's Submissions at 3.2.2., supporting evidence for carcinogenesis resulting from trichloroethylene exposure comes from the findings of identical precursor lesions in the mouse and rat kidney, and the findings of short-term repeat dose studies in rats and mice showing kidney as the target organ of toxicity.

61. Kidney damage was the major consequence of a suicide attempt by a 17-year-old male who attempted suicide by drinking approximately 70 ml of trichloroethylene (Brüning et al., 1998; exhibit A10).

62. Substantially more cases of tubular damage were found in kidney cell carcinoma patients who had been exposed to high levels of trichloroethylene over many years than among kidney cell carcinoma patients who had not been exposed to trichloroethylene (Brüning et al., 1996; T6 Vol 3 Tab 10). This supports the hypothesis that chronic tubular damage may be regarded as a necessary precondition for trichlorethylene to produce kidney carcinomas.

63. Elevated incidence ratios for kidney cancer in workers exposed to trichloroethylene in three of seven retrospective cohort studies as tabulated by Counsel for the Respondent in Exhibit R10. This is consistent with the possibility of a causal connection between trichloroethylene exposure and the incidence of kidney carcinomas.

64. The study reporting an increased incidence of kidney tumours in a cohort of cardboard workers in Germany exposed to trichloroethylene by Henschler, Vamvakas, Lammert, Dekant, Kraus, Thomas and Ulm (Archives of Toxicology, 1995, 69, 291-299; T6, Vol 3, Tab 30) was the subject of much discussion at the hearing.

65. It was clear that the study by Henschler et al. (1995) was not a retrospective cohort study as claimed but a cluster study and that it should carry lesser weight than if it had been a retrospective cohort study.

66. The study of Henschler et al. (1995) was the subject of two letters to the editor of Archives of Toxicology, and a reply from Henschler et al., published together in the same issue of Archives of Toxicology: Swaen (Archives of Toxicology,. 1995, 70, 127-128; T6, Vol 4, Tab 51), Bloeman and Tomenson (Archives of Toxicology, 1995, 70, 129-130; T6, Vol 3, Tab 7) and Henschler et al. (Archives of Toxicology, 1995, 70, 131-133; T6, Vol 3, Tab 29).

67. In their reply statement Henschler et al. (Archives of Toxicology, 1995, 70, 131-133; T6, Vol 3, Tab 29) make the following statement about the letters of Swaen, and Bloeman and Tomenson: 'The letters are the final manifestation of vigorous efforts of a group of scientists employed in or engaged by industrial companies to prevent our study from being published and acknowledged, put forward on any accessible level, even at times violating the integrity which normally governs relations among scientists'.

68. Henschler et al. have not withdrawn their results or retracted the conclusions that they drew from their results, other than conceding that theirs was a cluster study.

69. Counsel for the Applicant questioned the value of Henschler's conclusions as Henschler, on his own admission was not an epidemiologist. It was noted, however, that three of the seven authors on the Henschler et al., 1995 paper and reply gave their addresses as the Institute for Medical Statistics and Epidemiology at the Munich Technical

University.

70. Henschler and his colleagues followed up their cohort-study with a hospital based case control study claimed to demonstrate an association of kidney cancer with long-term exposure to trichloroethylene (Vamvakas, Brüning, Thomasson, Lammert, Baumüller, Bolt, Dekant, Birner, Henschler and Ulm, Renal cell cancer correlated with occupational exposure to trichloroethene, Journal of Cancer Research and Clinical Oncology, 1998, 124, 374-382; Exhibit A1, Vol 3, Tab 6).

71. The studies of Henschler et al. (1995) and Vamvakas et al. (1998) were the subject of criticism at the hearing by witnesses Dr Swaen and Professor Sim.

72. Counsel for the Respondent stated in the Respondent's Submissions in Reply (para 21) that the Director's case does not rest upon the studies by Henschler et al. (1995) and Vamvakas et al. (1998) and that it was common ground that the studies should be given little weight.

The tumour suppressor gene mechanism

73. Clear-cell renal carcinoma is one of the few human tumours known to evolve from mutations of a specific gene, the von Hippel-Lindau (VHL) tumour suppressor gene. Specific somatic mutations in this gene have been described in humans exposed to trichloroethylene in the workplace (Exhibit A1 Vol 4.1 Tab 1); Brauch, Weirich, Hornauer, Störkel, Wöhl and Brüning, Trichloroethylene exposure and specific somatic mutations in patients with renal cell carcinoma, Journal of the National Cancer Institute, 1999, 91, 854-861).

74. This study is the full publication following up from the short communication by Brüning, Weirich, Hornauer, Höler and Brauch, Renal cell carcinomas in trichloroethylene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppression gene, Archives of Toxicology, 1997, 71, 332-335 (T6 Vol 3 Tab 9). The Brüning et al. (1997) study concluded 'In addition to the available epidemiological studies the results are now further proof for human renal carcinogenicity induced by high occupational exposure to TRI'.

75. Brauch et al. (1999) found somatic mutations in the VHL gene in 75% of trichloroethylene-exposed patients. The mutations were frequently multiple and there was an association between the number of mutations and the severity of the trichloroethylene exposure.

76. Further, they observed a 'specific mutational hot spot at VHL nucleotide 454' in the renal cell carcinomas of 39% of the patients exposed to trichloroethylene. This mutation was neither detected in any of the renal cell carcinomas (RCCs) from patients without trichlorethylene exposure nor in any of the healthy subjects.

77. Brauch et al. (1999) concluded 'Our findings of unique and frequent VHL: mutations in RCCs of TRI-exposed patients present, to our knowledge, the first molecular evidence between exposure to a defined carcinogen, gene damage, and kidney cancer'.

78. The Tribunal heard evidence regarding the detailed methodology of the Brauch et al. (1999) study, none of which detracted from the overall conclusions of the authors. Indeed the evidence was that this study had been very well carried out.

79. The Tribunal regarded the Brauch et al. (1999) findings as definitive evidence providing a molecular basis, i.e. mutation of the VHL tumour suppressor gene, for the kidney tumours produced in humans exposed to trichloroethylene.

Category 3 carcinogenic substances

80. The Applicant accepts that trichloroethylene is a Category 3 carcinogen but disputes that there is sufficient evidence to place it in Category 2.

81. Paragraph 4.85 of the Approved Criteria states that Category 3 actually comprises 2 sub-categories: *(a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification; (b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for humans. This classification is provisional; further experiments are necessary before a final decision can be made.*

82. Weighing the evidence before it, the Tribunal considers there is more than sufficient evidence to place trichloroethylene in Category 2.

83. Paragraph 4.86 of the Approved Criteria states: *For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. The arguments especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals.* Each of the dot points that follow this statement will be discussed in turn.

84. *'carcinogenic effect only at very high dose levels exceeding the 'maximum tolerated dose'. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain.*,' The evidence is that kidney tumours and precursor lesions have been reported in rats at doses of trichloroethylene below the maximum tolerated doses.

85. *'appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation.,'* Rat kidney tumours of the type produced by trichloroethylene are relatively rare.

86. *'appearance of tumours, only at the site of application, in very sensitive test systems (eg intraperitoneal, or subcutaneous application of certain locally active compounds), if the particular target is not relevant to humans,'* The tumours induced by trichloroethylene in rat kidney are remote from the site of application and they are regarded as being relevant to humans given the epidemiological evidence of an association between trichloroethylene exposure and kidney tumours in humans.

87. *'lack of genotoxicity in short-term tests in vivo and in vitro,'* The genotoxicity of trichloroethylene is still under investigation but highly plausible mechanisms for genotoxicity exist, i.e. mutations in tumour suppressor genes in humans exposed to trichloroethylene.

88. *'existence of a secondary mechanism of action with the implication of a practical threshold above certain dose level (eg hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation.'* Trichloroethylene is known to disrupt metabolism resulting in the increased excretion of formic acid (a secondary mechanism yet to be linked to tumour production) and disruption of methionine and folate biochemistry (possible genotoxic mechanisms yet to be thoroughly investigated).

89. *'existence of a species-specific mechanism of tumour formation (eg by specific metabolic pathways irrelevant to humans.'* There is no evidence that trichloroethylene produces rat kidney tumours by mechanism(s) irrelevant to humans.

Category 2 carcinogenic substances

90. In order to be categorised as a Category 2 carcinogenic substance, the evidence regarding trichloroethylene must satisfy paragraph 4.80 in the Approved Criteria, i.e. *Substances are determined to be hazardous and classified as Toxic (T) and assigned risk phrase R45 or R49 in accordance with the criteria given below.*

91. The criteria referred to in paragraph 4.80 are specified in paragraphs 4.81, 4.82 and 4.83. The evidence pertaining to each of these paragraphs will be discussed in turn.

92. Paragraph 4.81 states: *A substance is included in category 2 if there is sufficient evidence on the basis of appropriate long term animal studies or other relevant information, to provide a strong presumption that human exposure to that substance may result in the development of cancer.*

93. Taking into account the submissions before it on the interpretation of

the key phases 'sufficient evidence', 'strong presumption' and 'may result', the Tribunal finds that there is more than sufficient evidence on the basis of the long term studies in rats to provide a strong presumption that human exposure to trichloroethylene may result in the development of kidney cancer.

94. Paragraph 4.82 states: *For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting as association.*

95. Taking a weight of evidence approach on all of the evidence before it, the Tribunal concludes that there is clear positive evidence that trichloroethylene produces kidney tumours in rats by two different routes of long term exposure (oral and inhalation) in different strains of rats and in different test laboratories.

96. Taking a weight of evidence approach on all of the evidence before it, the Tribunal concludes that there is, at the very least, supporting evidence that trichloroethylene produces anatomical, metabolic and biochemical changes in rats consistent with the production of kidney tumours.

97. Taking a weight of evidence approach on all of the evidence before it, the Tribunal concludes that there is, at the very least, supporting evidence from epidemiological studies that there is an association between exposure to trichloroethylene and kidney tumours in humans.

98. Paragraph 4.83 states: *Human data providing suspicions of carcinogenic potential may warrant a Category 2 classification irrespective of the nature of any animal data. Increased confidence in the credibility of a causal relationship by evidence of carcinogenicity in animals and/or of genotoxic potential in short term screening tests.*

99. The Tribunal concludes that the finding of specific mutations in a tumour suppressor gene in kidney carcinoma cells from humans exposed to trichloroethylene but not in kidney carcinoma cells from humans not exposed to trichloroethylene is most certainly 'human data providing suspicions of carcinogenic potential' and provides a plausible causal genotoxic mechanism for such trichloroethylene associated cancers.

Category 1 carcinogenic substances

100. Paragraph 4.77 of the Approved Criteria states: *The placing of a substance into category 1 is done on the basis of epidemiological data;*

101. Paragraph 4.79 states: *A substance is included in Category 1 if there is sufficient evidence to establish a causal relationship between human exposure and the development of cancer on the basis of epidemiological*

data.

102. The Tribunal considers that there is not yet sufficient evidence from epidemiological studies that to establish a causal relationship, as distinct from an association, between exposure to trichloroethylene and kidney tumours in humans.

103. Further, the Tribunal considers that, based on current findings on tumour suppressor genes, a molecular biological approach to the epidemiological studies based on analysing disorders in specific genes could provide data sufficient to warrant a Category 1 carcinogen status in the future for trichloroethylene.

Trichloroethylene as a Category 2 carcinogenic substance

104. On the above basis the Tribunal finds that trichloroethylene should be categorised as a Category 2 carcinogenic substance.

MUTAGENICITY & TRICHLOROETHYLENE (TCE)

105. The Director, in her draft report, notified in the Chemical Gazette on 5 May 1998, recommended that TCE be categorised as a category 3 R40 mutagen. In response to an application for variation in the draft decision requested by Dow Chemicals, among others, the Director notified her decision on the variations in the Chemical Gazette on 4 August 1998, having advised the applicants of her decision by mail on 24 July 1998. The categorisation of TCE remained that of category 3.

106. In reaching both decisions the Director considered the criteria entitled "Approved criteria for classifying hazardous substances" made pursuant to the *Industrial Chemical (Notification and Assessment) Act* 1989. In addition, she reviewed all relevant scientific data published to the date of her decision and the European Union Specialised Expert Group's considerations regarding the mutagenic and carcinogenic potential of TCE discussed at their meeting in June 1997.

107. The approved criteria in regard to mutagenic substances state:

> *"**MUTAGENIC SUBSTANCES***
> *4.88 Substances are determined to be hazardous due to mutagenic effects if they fall into one of the following categories:*
> *Category 1 Substances known to be mutagenic to humans.*
> *Category 2 Substances which should be regarded as if they are mutagenic to humans.*
> *Category 3 Substances which cause concern for humans owing to possible mutagenic effects, but in respect of which available information does not satisfactorily demonstrate heritable genetic damages.*
> ***EXPLANATORY NOTES REGARDING THE CATEGORISATION OF MUTAGENIC SUBSTANCES***
> *4.89 A mutation is a permanent change in the amount or structure of the*

genetic material in an organism, resulting in a change of the phenotypic characteristics of the organism. The alterations may involve a single gene, a block of DNA, or a whole chromosome. Effects involving single genes may be a consequence of effects on single DNA bases (point mutations) or of large changes including deletions, within the gene. Effects on whole chromosomes may involve structural or numerical changes. A mutation in the germ cells in sexually reproducing organisms may be transmitted to the offspring. A mutagen is an agent that gives rise to an enhanced occurrence of mutations.

4.90 It should be noted that substances are classified as mutagens with specific reference to inherited genetic damage. However, the type of results leading to classification of chemicals in Category 3: 'induction of genetically relevant events in somatic cells', is generally also regarded as an alert for possible carcinogenic activity.

4.91 Method development for mutagenicity testing is an ongoing process. For many new tests no standardised protocols and evaluation criteria are presently available. For the evaluation of mutagenicity data the quality of the test performance and the degree of validation of the test method have to be considered."

108. The applicant, Dow Chemical, argues that TCE should not be categorised as a mutagen and that the Director's finding that it is a Category 3 R40 mutagen is incorrect.

*"**CATEGORY 3***

4.99 Substances are determined to be hazardous and classified as Harmful (Xn) and assigned risk phrase R40 in accordance with the criteria given below.

R40 POSSIBLE RISK OF IRREVERSIBLE EFFECTS

4.100 A substance is included in Category 3 if there is evidence from appropriate mutagenicity studies, of concern that human exposure can result in the development of heritable genetic damage, but that this evidence is insufficient to place the substance in Category 2.

4.101 To place a substance in Category 3, positive results are needed in assays showing

mutagenic effects, or

other cellular interaction relevant to mutagenicity, in somatic cells in mammals in vivo.

The latter especially would normally be supported by positive results from in vitro mutagenicity assays.

4.102 For effects in somatic cells in vivo at present the following methods are appropriate

(a) in vivo somatic cell mutagenicity assays:

- *bone marrow micronucleus test or metaphase analysis,*
- *metaphase analysis of peripheral lymphocytes,*
- *mouse coat colour spot test.*

(b) in vivo somatic cell DNA interaction assays:

- *test for Sister Chromatid Exchanges (SCEs) in somatic cells,*
- *test for Unscheduled DNA Synthesis (UDS) in somatic cells,*

- *assay for the (covalent) binding of mutagen to somatic cell DNA,*
- *assay for DNA damage, for example, by alkaline elution, in somatic cells.*

4.103 Substances showing positive results only n one or more in vitro mutagenicity assays should normally not be classified. Their further investigation using in vivo assays, however, is strongly indicated. In exceptional cases, for example, for a substance showing pronounced responses in several in vitro assays, for which no relevant in vivo data are available, and which shows resemblance to known mutagens/carcinogens, classification in Category 3 could be considered."

109. In addition to the T documents containing the Director's Draft Report, and including her reply to the requests for variation, and all the scientific reports upon which the Director based her recommendations, the Tribunal received into evidence the witness statements of Dr B.M. Elliott (Ex. A6) and Dr Elliott's witness statement in reply (Ex. A7), and the witness statement of Professor Donald MacPhee (Ex. R5); Professor MacPhee's review of the Director's report (Ex.R5B), Professor MacPhee's witness statement in reply (R6), and several scientific papers addressing the subject of mutagenicity of TCE published since the Director's report was released. Dr Elliott gave expert witness evidence to the Tribunal on behalf of the applicant and Professor MacPhee on behalf of the respondent.

110. The applicant's argument is based primarily on the failure of the Director to critically survey the existing scientific data as of 5 May 1998 and the weight given to the negative and positive study results in reaching her decision. The applicant contends that had these matters been addressed correctly and the criteria interpreted more rigidly, TCI would not be categorised as a mutagen. (Applicant's request at p130 of report and 17.1 at p183.)

111. The term genotoxicity appears to be a generic term embracing cytotoxic cellular damage, changes leading to carcinogenesis be they based on cytotoxicity or mutagenesis, and mutagenicity.

***IN VITRO* STUDIES**

112. In her report, the Director dealt with the *in vitro* studies assessing the presence or absence of mutations in TCE-exposed bacteria, fungi, mouse lymphoma cells and the evidence for DNA damage as shown by chromosomal aberration, SCE's and UDS's in rat hepatocytes. A summary of these results is provided in Table 24 of her report (at p6), which shows 13 positive results and 11 negative results. The Director concluded that TCE was a weak *in vitro* mutagen. Both Dr Elliott for the applicant and Professor MacPhee for the respondent agreed with the Director's conclusion and that such positive results could only be supportive evidence (4.101 of the criteria).

IN VIVO STUDIES

113. Item 4.101 of the approved criteria states that to place a substance as a category 3, positive results are needed in assays showing (a) mutagenic effects or, (b) other cellular interaction relevant to mutagenicity, in somatic cells in mammals *in vivo*. Item 4.102 of the criteria delineates a somatic cell interaction/DNA damage methods considered appropriate.

114. The studies considered by the Director and whether or not they were positive or negative are summarised in Table 25 of the Director's report (at p83). Whilst noting the limitations of some of the studies and, in particular, Schiestl et al (1977) and Bruning et al (1997), the Director concluded that the overall data raised concern about possible mutagenic effects of TCE.

115. The majority of tests in common usage measure DNA damage as an end point. The Tribunal notes that DNA damage does not equate with mutagenic effects, but are a pointer to potential mutagenicity (MacPhee, R5, p7). The Director considered in some detail the report of the micronucleus tests performed by Kligerman et al in rats and mice exposed to inhalation of various doses of TCE. This study reported a dose related increase in micronuclei in rat bone marrow polychromatic erythrocytes. At doses of 5000 ppm the increase was four-fold and was reproducible. There was associated evidence of cytotoxicity in the erythrocytes in bone marrow. No significant changes were seen in mice similarly exposed. Rats exposed for six hours per day for four days did not exhibit an increase in micronuclei although, as the Director pointed out, the concurrent control group had an unusually high number of micronuclei (Kligerman et al (1994) Inhalation studies of the genotixicity of trichloroethylene to rodents. Mutat Res, 322: 87-96). Whilst the Director viewed this study as a positive result, she expressed reservations regarding the four day inhalation group. A dose related increase in micronucleated polychromatic erythrocytes in mice was reported by Duprat & Gradiski (Duprat P & Gradiski D (1980) Cytogenetic effect of trichloroethylene in the mouse as evaluated by the micronucleus test. ITRCS Med Sci, 8:182). She expressed doubts as to the significance of the study resulting from uncertainties of the scoring method used and the unusually high frequency of micronucleated PCEs in the control group.

116. The Director also considered the results of TCE intra-peritoneal administration to pink-eyed unstable mutation mice (C57BL-6JPUN/PUN) as reported by Robert H. Schiestl et al in 1997 (Carcinogens induce reversion of the mouse pink-eyed unstable mutation. Proc Natl Acad Sci, 94:4576-4581). In this study a positive response was noted with a spotting frequency of 32% in the offspring of mice subjected to intra-peritoneal trichloroethylene whereas the corn oil alone control group had a spotting frequency of 3.9%. The Director noted that this was a preliminary study, but raised concern regarding mutagenic effects of TCE.

117. In the section of her report entitled *Human Health Effects* (p99) the

Director dealt with a short communication by Bruning et al with the Editor of the journal *Archives Toxicology 1997* (Thomas Bruning et al *Arch Toxicol 1997* 71:332-335). This report dealt with observed increased incidence of renal cell carcinoma in persons with prolonged high exposure to TCE. It compared this test group with an unexposed control group and measured somatic mutations of the von Hippel Lindau (VHL) tumour suppressor gene. Mutations in the VHL suppressor gene are known to be a feature of renal cell carcinoma. Bruning had previously reported TCE associated tubular damage preceding and perhaps enhancing the nephrocarcinogenic effect. This nephrocarcinogenic effect had been attributed to the TRE metabolyte dichlorovinylcysteine (DCVC). Somatic VHL mutations had been known to be a common molecular event in renal cell carcinoma from 1994. Bruning reported aberrations of the VHL gene in all 23 renal cell carcinoma patients who had had lengthy and high exposure to TCE. The control group of non-TCE exposed patients with renal cell carcinoma showed 33% to 55% incidence of VHL mutations in various studies. The Director regarded the Bruning report as being supportive evidence raising concern regarding possible mutagenic effects of TCE.

118. The Director did not have available to her more recent studies placed in evidence before this Tribunal, and addressed in their witness statements and oral evidence by Dr Elliott and Professor MacPhee. These reports were six in number and are entitled as follows:

- T.V. Sujatha, M.J. Hegde - *C-Mytotic Effects of Trichloroethylene (TCE) on Bone Marrow Cells of Mice.* Mutation Research 413 (1998) 151-158. In this study the authors concluded that preliminary results indicated that TCE is capable of inducing C-mytotic effects in mice bone marrow cells which is suggestive of its aneuploidy induction potential.
- Luigi Robbiano et al. *Increased frequency of micronucleated kidney cells in rats exposed to halogenated anaesthetics.* Mutation Research 413 (1998) 1-6. This study reported a potential genotoxic activity of halogenated anaesthetics (including trichloroethylene) for the rat kidney.
- Clay (Study Director) Report No. CTL/T/2976. *Trichloroethylene and S-1,2-Dichlorovinylcysteine: In vivo comet and UDS assays in the rat kidney* dated 29 September 1998; and First Supplement to CTL-T-2976 *Trichloroethylene and S-1,2-Dichlorovinylcysteine: in vivo comet and UDS assays in the rat kidney* dated 4 February 1999. Both of these studies from The Central Toxicology Laboratory at Alderley Park, Macclesfield, Cheshire, United Kingdom, were interpreted as showing no evidence of DNA damage in rats exposed to DCVC or TCE.
- George R. Douglas et al. *Evidence for the lack of base change and small deletion mutation induction by trichloroethylene in lacZ transgenic mice.* Environmental and Molecular Mutagenesis 34:190-194 (1999). This study was report as showing that TCE did not induce base change or small deletion mutations in transgenic mice.
- Brauch, H. et al. *Trichloroethylene exposure and specific somatic*

mutations in patients with renal cell carcinoma. Journal of the National Cancer Institute. Vol. 91, No. 10, May 19, 1999. This report from the Bruning group was a more detailed study of their preliminary report of 1997. They reported an incidence of VHL mutations of 75% in TRE exposed patients with renal cell carcinoma. Mutations were frequently multiple and an association was observed between the number of mutations and the severity of TRE exposure. They identified specific mutational hotspot at VHL nucleotide 454 in 39% of the exposed renal cell carcinoma group. A nucleotide of 454 mutation was not detected in any of the renal cell carcinoma patients without TRE exposure, nor in any healthy subjects.

119. Dr Barry Elliott, a scientist within the AstraZeneca Central Toxicology Laboratory in Macclesfield gave expert evidence on behalf of the applicant. He addressed the overlap between cytotoxicity and mutagenicity in many of the assays considered by the Director in her report. He addressed the problem of the assays which rely on DNA damage such as single strand break assays and micronucleus assays. Comet assays fall into the same group. He expressed concern for the results in those studies wherein TCE was delivered by the intraperitoneal route and in a corn oil carrier. He was of the opinion that the use of the intraperitoneal route could result in local deposition of TCE in close proximity to major organs, such as the liver and the uterus. This was particularly relevant to the Schiestl study. Dr Elliott felt that the intraperitoneal route injection of TCE in corn oil may be deposited near the uterus and preferentially absorbed through the uterine wall. This may result in local cytotoxicity and may contribute to the results of less than expected number of live offspring. He also questioned the adequacy of the control group in the Schiestl study and the frequency of spontaneous mutations in this group. He did not believe the observed threefold increase in frequency of spotting was necessarily a positive result, and also questioned the dose range used in the experiment. Dr Elliott pointed out that the European Committee on Mutagenicity of Chemicals and Food Consumer Products and the Environment had recommended that no weight should be attached to the Schiestl investigation in view of the limited study design, given negative findings reported in a mouse spot test by a separate research group. Dr Elliott's major criticisms of Schiestl's work are related to the design of the experiment, the dose level selection, the causes of death *in utero* of the foetuses and was of the opinion that trichloroethylene had not been identified in this study as the relevant agent resulting in increased frequency of spotting.

120. Dr Elliott did not address the findings of Kligerman in either his witness statement or examination-in-chief. In cross-examination Mr Gageler questioned Dr Elliott as to why he thought the Kligerman study had not been repeated in relation to TCE, as recommended by the European Commission's group of specialised experts in the field of mutagenicity, in 1997. Dr Elliott indicated that the cost of a bone marrow micronucleus assay would be of the order of £UK10,000 to repeat the experiment of Kligerman which was positive for TCE association with DNA

damage as measured by bone marrow micronucleus assay.

121. Dr Elliott addressed the results of the Bruning paper of 1997, both in his witness statement and in oral evidence before the Tribunal. He was of the opinion that the Bruning study was well conducted, but that they had simply shown that the DNA from the VHL suppressor gene from these patients ran atypically on a gel. Questioned as to the appropriateness of the control population and the general lack of knowledge of the control population, he stated there was no evidence that TCE was causally associated with VHL suppressor gene mutations (Transcript, p271). In cross-examination by Mr Gageler, Dr Elliott agreed that whatever the form of mutation it can only occur if the target cell remains alive (Transcript p280). Dr Elliott agreed that the results in the Schiestl study were statistically significant and that there had not been any published criticism of this particular paper. He reiterated that his basic criticisms of the study related to the dose level and the route of administration, and also the conclusion reached that the statically significant increase in frequency spotting was due to TCE having induced mutations in the offspring.

122. In relation to the Bruning and Brauch studies, Dr Elliott did not question the methodology used in these studies but questioned the interpretation of the results of the studies. He noted the high spontaneous mutation rate in the control renal cell carcinoma patient group (60%). He also expressed concern as to detailing of the control group based on age, sex, smoking history and other parameters. The paper states that these factors were taken into consideration, but does not in fact state the incidence of such parameters as smoking nor the method of selection of the control group other than that they all had renal cell carcinomas. Dr Elliott agreed that the 454 mutation incidents showed a clear dose response according to the severity of exposure. There is also a clear dose response in terms of the number of mutations. He agreed that these were statistically significant.

123. In reply to a question posed by the Tribunal, Dr Elliott stated that he had no experimental evidence of local absorption of chemicals such as TCE into the uterus. Dr Elliott agreed that TCE was rapidly absorbed from all tissues and distributed to other organs by circulation. Also in response to questioning by the Tribunal Dr Elliott agreed that the Brauch paper revealed that in 52% of mutations in the VHL suppressor gene, the mutation was located in exon one, 20% in exon two and 28% in exon three. Dr Elliott agreed that the nucleotide 454 mutations located in exon one were of significance in the TCE exposed renal cell carcinoma patient group. He retained concern regarding the selection and analysis of the control population, but agreed that the control population showed a zero incidence of nucleotides 454 mutation and a zero incidence of multiple mutations. Dr Elliott concluded that his interpretation was such that the association of the mutations in the VHL gene to any particular causative agent was, at the present time, unknown (transcript 299). Dr Elliott agreed that the results of the Brauch studies would generate further research and follow up experimentation in numerous laboratories.

124. Professor MacPhee in his witness statement and in oral evidence provided a useful (for the Tribunal's understanding) dissertation upon the differences between genotoxicity and mutagenity. He emphasised that mutagenicity is a property of a physical agent which changed the DNA in living organisms in live cells and live tissues and in live animals. This change is heritable. (Transcript p304). As a corollary to this statement, cytotoxicity and cell death cannot result in mutagenic changes. He also pointed out that while there are thousands of chemical mutants the mechanism of mutagenesis is limited to a change in four bases in the DNA molecule and two deletions in the DNA molecule.

125. In his statement "A report on the mutagenicity evaluation of the trichloroethylene (TCE)", Professor MacPhee addressed the results of Schiestl (1997) and concluded that TCE is capable of generating mutations in the somatic cells of mice and that the bulk of the mutations produced are extended deletions. In oral evidence he confirmed that the Schiestl study was a test for mutagenicity. He found this study of particular interest in that the pink eyed unstable mutation in the mouse (PUN) is a deletion mutation and thus the presence of an increased frequency of spotting in the offspring of such mice exposed to TCE must result from a back mutation. This study, he said, was clearly positive for a number of known mutagens, including the chemical TCE. Professor MacPhee found Dr Elliott's criticism regarding the use of a dose level considered too high to be essentially irrelevant. A toxic dose level would have killed the melanocytes, negating the appearance of blacker spots in the offspring. In addition, he found the route of administration of no particular relevance when the results were positive in the skin cells of the offspring of the mice to which the material had been administered, regardless of the route of administration. Despite Dr Elliott's criticism with respect to the number of viable offspring from the exposed mice, Professor MacPhee felt there was essentially no difference in that there were 51 control offspring and 41 exposed offspring.

126. With respect to the Bruning study (1997), Professor MacPhee felt the conclusions drawn were modest and reasonable (Ex. R5, p8, para 4). His only criticism related to the conclusion drawn that VHL suppressor gene mutations were more frequent in renal carcinoma patients occupationally exposed to TCE than in renal tumour patients who had not been exposed, were not specific for TCE to this gene as they had not studied any other genes or sequences. Professor MacPhee regarded the Bruning study as an attempt to delineate whether or not there is a signature DNA change or DNA fingerprint which would allow them or their colleagues or future investigators to distinguish between those renal tumour patients who had TCE induced kidney tumours and those who probably did not have TCE induced kidney tumours (Transcript, p307). He saw this as an attempt to develop a diagnostic test , presumably for workers' compensation purposes or the equivalent. In their efforts to find a DNA fingerprint they had in their subsequent report (Brauch et al 1999) demonstrated the presence of double and triple mutations in TCE exposed

renal cancer patients. This mutation has been shown to reside in nucleotide 454. Professor MacPhee was of the opinion that the control group chosen in the Brauch and Bruning experiments was the best that could be achieved, given that the control group by definition must be persons with renal cell carcinomas and no history of TCE exposure.

127. In cross-examination, Professor MacPhee agreed that the VHL gene mutation could be caused by a number of different events or chemicals, that mutations whatever the mutagen have a final common pathway of either base changes or deletion of DNA material and that a comparative sequence analysis would not provide a specific pattern for any mutagen. He was of the opinion that the Brauch data did link TCE with the observed increased incidence of mutations.

128. In cross-examination by Mr Beach, Professor MacPhee dealt with Dr Elliott's criticism of the control in the Schiestl study. He did not agree with the criticism and found the Schiestl results statistically significant. He felt the only control group to be considered was that reported contemporaneously with the study group. He did not consider the possibility of local toxicity of TCE injected intraperitoneally to be relevant, given that the target organ was the offspring of the PUN mice. Professor MacPhee also stated that TCE can induce a weak aneugenic effect in the mouse and that he interpreted Dr Elliott's oral evidence as agreeing with that statement.

129. There then followed what was termed a "hot tub" session in which Dr Elliott and Professor MacPhee discussed various aspects of the scientific reports before the Tribunal, and answered questions submitted by both members of counsel and the Tribunal. First, Dr Elliott addressed the question of whether or not he had stated that TCE was aneugenic. This comment was made with regard to the results of the study of Sujatha and Hegde. Dr Elliott concluded that the findings are consistent in the parameters examined with TCI acting on the cellular protein architecture and inducing changes in the protein spindle apparatus resulting in an aneugenic effect. This, he stated, was his opinion of the study's results but he did not agree with the interpretation.

130. Discussion ensued regarding the Kligerman study and the Duprat and Gradiski studies in relation to micronucleus assay. This discussion was not of assistance to the Tribunal. It related primarily to dosage levels and frequency of administration and the conflicting results in the single and repeated TCE exposures in rats. Dr Elliott concluded that in his view there is no way that TCE is clearly or reproducibly showing an increase in aneugenicity, chromosomal damage or even any reproducible positive result in this assay type (Transcript p334).

131. Professor MacPhee argued that it is not scientifically appropriate to balance positive results with other negative results (transcript, p346). At page 347 of the Transcript Professor MacPhee states: *You have to pay more attention to positive results when you are concerned about human*

safety. Professor MacPhee directed a question to Dr Elliott regarding the interpretation of positive results in light of other negative results, asking "*what would your next experimental step be*?" Dr Elliott's reply was that you would do a further set of appropriate experimental studies. (Transcript p347). Dr Elliott was not aware of any further investigations along these lines.

132. In response to questioning from Mr Beach for the applicant, Professor MacPhee opined that micronucleus studies indicated that some positive results needed further investigation. He discussed the Brauch results and the high incidence of spontaneous mutations in patients with renal cell carcinoma in the VHL suppressor gene. The highest incidence placed on this spontaneous mutation was 60%. The significance of 100% mutation rate in renal cell carcinoma patients exposed to TCE was debated at some length (Transcript p360-363).

133. In answer to a question posed by the Tribunal, Professor MacPhee agreed that the VHL suppressor gene was a marker of renal cell carcinoma, but Dr Elliott felt that this summation of the VHL gene presence blunted specific conclusions being drawn. The Tribunal then asked whether these incidences blunted or magnified the results, to which Professor MacPhee replied that magnifying is as good as any word. (transcript p363). Dr Elliott disagreed with the term magnified and felt that the observation of 100% VHL suppressor gene mutation result was blunted by the existence of a 60% VHL suppressor gene mutation result in the control group.

134. The Tribunal asked questions regarding the methodology of the scientific investigations and the types of experimental animals used, particularly in the Kligerman experiments. Dr Elliott assured the Tribunal that these were standard numbers and certainly the same numbers were used in his own laboratory.

135. Again in answer to a question from the Tribunal, Dr Elliott agreed that any mutations had the potential to be carcinogenic as well as non-carcinogenic; Professor MacPhee agreed with this. On that basis, the Tribunal suggested that any evidence to support a mutation leading to neoplasia should be treated with extreme caution from a regulatory sense. Professor MacPhee essentially agreed with this statement.

136 The Tribunal had the advantage, compared to the Director at the time of her draft report, of several more recent scientific reports regarding mutagenicity of TCE. The Bruning and Brauch reports lend a great deal of weight to the Director's concern that TCE is possibly mutagenic. In particular the Brauch study has identified the point mutation of the VHL suppressor gene at nucleotide 484. This point mutation was found only in renal carcinoma patients exposed to TCE. The full significance of this finding will be subject to further scientific investigation but prima facie appears to be a finding of major scientific significance. The Tribunal finds that the Director's recommendations that trichloroethylene be categorised

as a Category 3 R40 (3 mutagen) is correct and the decision under review with respect to mutagenicity is affirmed.

Conclusion

137. The applicant sought four changes to the draft report in its letter of 1 June 1988 (T5, pp 215-217). The first requested change related to page 130 of the draft report, which dealt with the classification of trichloroethylene in relation to genotoxicity. The applicant wished the draft report to say that trichloroethylene did not meet the Approved Criteria for classification as a Category 3 (R40-M3) substance. We have decided that it did meet the Approved Criteria for such a classification after reviewing the evidence as to mutagenicity above. The decision under review in relation to that requested change must be affirmed.

138. The second requested change related to page 131 of the draft report, which dealt with the classification of trichloroethylene as a Category 2 carcinogen. The applicant sought the substitution of a paragraph saying that trichloroethylene met the approved criteria for classification as Category 3 carcinogen, and shortly stating the basis for such a conclusion. For the reasons we have stated, we believe that the paragraph which the applicant wanted changed was entirely appropriate, and that the respondent's decision as to the second requested change should be affirmed. The challenged paragraph read as follows:-

> *"Trichloroethylene meets the Approved Criteria for classification as a Carcinogen Category 2 (National Occupational Health and Safety Commission (NOHSC), 1994), that 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. Thus the available data provides suspicions of carcinogenic potential in humans (R45)."*

139. The third requested change concerned the last paragraph of section 17.1 on page 184 of the draft report. The original version reads as follows:

> *"The European Union is currently considering the classification of trichloroethylene. Any new information that becomes available as a result of this consideration should be considered in order to determine whether the above classification remains valid."*

The applicant requested that it be changed to read as follows:

> *"The European Union is currently considering the classification of trichloroethylene with respect to carcinogenicity and mutagenicity. Until the results of research studies clearly indicate a different classification is appropriate it is recommended that the current hazard classification Carcinogen: Category 3 R40(3) be maintained."*

140. We have rejected the applicant's contentions as to the carcinogenicity classification of trichloroethylene. We think there is a

significant chance that the European Union's consideration of the classification of the chemical may reveal or highlight new information in relation to carcinogenicity, and that the challenged paragraph in the draft report is therefore quite appropriate. We have therefore decided to affirm the third decision under review.

141. The fourth request by the applicant for a change to the draft report sought the inclusion in the abstract on page 2 thereof of a paragraph in the same terms as the last one we have quoted. As we have reached a contrary conclusion as to the appropriate carcinogenicity category, and see no need to refer to the European Union's current consideration of the appropriate classification of trichloroethylene as to carcinogenicity and mutagenicity in the abstract, we have decided to affirm the fourth decision under review, namely the decision not to include such a paragraph in the abstract.

142. Thus we have decided to affirm all four of the decisions under review. We considered whether it would be more appropriate to set aside the decisions under review and remit the matter to the respondent with recommendations that the draft report be changed to incorporate references to material we have referred to that was published after the draft report was written, and to the studies referred to in paragraph 52 above. Whilst the inclusion of such references in the draft report would have been desirable, we think it preferable to do all we can to ensure that this litigation is brought to an end, and that the process of reclassifying trichloroethylene is completed as soon as possible. We have therefore decided that it is preferable simply to affirm the decisions under review.

I certify that the 142 preceding paragraphs are a true copy of the reasons for the decision herein of Deputy President A M Blow OAM, QC., Professor G A R Johnston AM, FRACI, FTSE, Miss E A Shanahan

Signed:

.....

.....

Personal Assistant

Date/s of Hearing	3,4,5,8,9, November 1999
Date of Decision	31 December 1999
Counsel for the Applicant	Mr J Beach
Solicitors for Applicant	Arthur Robinson & Hedderwicks
Counsel for the Respondent	Mr S Gageler
Solicitor for the Respondent	Australian Government Solicitor

REFERENCES

ACGIH (1992) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, Ohio, American Conference of Governmental Industrial Hygienists.

Adams EM, Spencer HC, Rowe VK, et al. (1951) Vapor toxicity of trichloroethylene determined by experiments on laboratory animals. Arch Ind Hyg Occup Med, **4**: 469-481.

Adler I & et al. (1991) Mouse micronucleus test with known and suspect spindle poisons:results from two laboratories. Mutagenesis, **6**: 47-53.

Allen BC & Fisher JW (1993) Pharmacokinetic modeling of trichloroethylene and trichloroacetic acid in humans. Risk Anal, **13**: 71-86.

Anderson A (1957) Health dangers in industry from exposure to trichloroethylene. Acta Med Scand, **157**(Suppl 323): 7-220.

Anderson C, Sundberg K & Groth O (1986) Animal model for assessment of skin irritancy. Contact Dermatitis, **15**: 143-151.

Anon (1995) Chemical profile: trichloroethylene. Chemical Marketing Reporter(February 6).

Ansell Edmont Industrial (1990) Ansell Edmont chemical resistance guide (5th Ed).

Anttila A, Pukkala E, Sallmen M, et al. (1995) Cancer incidence among Finnish workers exposed to halogenated hydrocarbons. Journal of Occupational and Environmental Medicine, **37**(7): 797-806.

Arai H, Nomiyama H, Saito K, et al. (1988) Health effects of high concentration of TCE exposure for 12 weeks in rats. Sangko-Igaku, **30**: 410-411.

Ashby J, Brady A, Elcombe CR, et al. (1994) Mechanistically-based human assessment of peroxisome proliferator induced hepatocarcinogenesis. Human and Experimental Toxicology, **13**(Supplement 2).

ATSDR (1993) Toxicological profile for trichloroethylene. Atlanta, Georgia, Agency for Toxic Substances and Disesase Registry.

ATSDR (1995) Toxicological profile for trichloroethylene. Atlanta, Georgia, Agency for Toxic Substances and Disease Registry.

Australian Health Ministers' Advisory Council (1997) Standard for the Uniform Scheduling of Drugs and Poisons No. 12. Canberra, Australian Government Publishing Service.

Aviado D, Zakhari S, Simaan J, et al. (1976) Methyl chloroform and trichloroethylene in the environment, Cleveland CRC Press.

Axelson O,Anderson K, et al. (1978) A cohort study on trichloroethylene exposure and cancer mortality. Journal of Occupational Medicine, **20**: 194-196

Axelson O, Selden A, Andersson K, et al. (1994) Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. JOM, **36**(5): 556-562.

Axelson O, Selden A, Andersson K, et al. (1994) Updated and expanded Swedish cohort study on trichloroethylene and cancer risk. JOM, **36**(5): 556-562.

Baden J, Kelley M, Mazze R, et al. (1979) Mutagenicity of inhalation anaesthetics: trichloroethylene, divinyl ether, nitrous oxide and cyclopropane. Br J Anaesth, **15**: 417-421.

Bardodej Z & Vyskocil J (1956) The problem of trichloroethylene in occupational medicine. AMA Arch Ind Health, **13**: 581-592.

Bartsch H, Malaveille C, Barbin A, et al. (1979) Mutagenic and alkylating metabolites of halo-ethylenes, chlorobutadienes and dichlorobutenes produced by rodent or human liver tissues. Arch Toxicol, **41**: 249-277.

Benford DJ & Bridges JW (1986) Xenobiotic metabolism in the lung. In: J. Bridges and L. Chasseaud ed. Progress in drug metabolism. Taylor and Francis Ltd, , **9:** 53-94.

Bernauer U, Birner G, Dekant W, et al. (1996) Biotransformation of trichloroethene: dose-dependent excretion of 2,2,2-trichloro-metabolites and mercapturicm acids in rats and humans after inhalation. Archives of Toxicology, **70**: 338-346.

Best (1994) Calender guide to chemical-resistant Best gloves (2nd ed).

Bhunya SP & Behera BC (1987) Relative genotoxicity of trichloroacetic acid (TCA) as revealed by different cytogenetic assays: bone marrow chromosome aberration, micronucleus and sperm-head abnormality in the mouse. Mutat Res, **188**: 215-221.

Blair A, Hartge P, Stewart PA, McAdams M, et al. (1998) Mortality and cancer incidence of aircraft maintenance workers exposed to trichloroethylene and other organic solvents and chemicals: extended follow up.Occu Environ Med,
55: 161-171

Bloemen LJ & Tomenson J (1995) Increased incidence of renal cell tumours in a cohort of cardboard workers exposed to trichloroethylene. Arch Toxicol, **70**: 129-130.

Bogen KT, Colston BW & Machiccio LK (1992) Dermal absorption of dilute aqueous chloroform, trichloroethylene and tetrachloroethylene in hairless guinea pigs. Fund. Appl. Toxicol, **18**(30-39).

Bonatti S et al. (1992) The analysis of 10 potential spindle poisons for their ability to induce CREST-positive micronuclei in human diploid fibroblasts. Mutagenesis, **7**: 111-114.

Bonnet P, Francin JM, Gradiski D, et al. (1980) Determination de al concentration lethale$_{50}$des principaux hydrocarbures aliphatiques chlores chez le rat. Arch Mal Prof, **41**: 317-321.

Bronzetti G, Corsi C, Cundari E, et al. (1984) Comparative genetic activity in vitro and in vivo of 1,1-dichloroethylene, cis-and trans-1,2-dichloroethylene, trichloroethylene and perchloroethylene. Acta Oncol, **5**: 221-224.

Bronzetti G, Zeiger E & Frezza D (1978) Genetic activity of trichloroethylene in yeast. J Environ Pathol Toxicol, **1**: 411-418.

Bruce WR & Heddle JA (1979) The mutagenic activity of 61 agents as determined by the micronucleus, Salmonella and sperm abnormality assays. Can J Genet Cytol, **21**: 319-334.

Bruckner JV, Davis BD & Blancato JN (1989) Metabolism, toxicity and carcinogenicity of trichloroethylene. Crit Rev in Toxicol, **20**(1): 31-50.

Bruning T, Golka K, Makropoulos V, et al. (1996b) Preexistence of chronic tubular damage in cases of renal cell cancer after long and high exposure to trichloroethylene. Archives of Toxicology, **70**: 259-260.

Bruning T, Vamvakas S, Makropoulos V, et al. (1996a) A case of acute intoxication by trichloroethene: Clinical symptoms, toxicokinetics and renal damage. Arch Pharmacol, **353**(Suppl R109).

Bruning T, Weirich G, Hornauer MA, et al. (1997) Renal cell carcinomas in trichloroethene (TRI) exposed persons are associated with somatic mutations in the von Hippel-Lindau (VHL) tumour suppressor gene. Arch Toxicol, **71**: 332-335.

Buben JA & O'Flaherty EJ (1985) Delineation of the role of metabolism in the in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. Toxicol Appl Pharmacol, **78**: 105-122.

Bull RJ, Sanchez IM, Nelson MA, et al. (1990) Liver tumour induction in B6C3F1 mice by dichloroacetate and trichloroacetate. Toxicology, **63**: 341-358.

Callen DF, Wolf CR & Philpot RM (1980) Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutat Res, **77**: 55-63.

Capellini A & Grisler R (1958) Liver function in workers constantly exposed to trichloroethylene. Med Lav, **49**: 167-172.

Caspary WJ, Langenbach R, Penman BW, et al. (1988) The mutagenic activity of selected compounds at the TK locus: rodent vs human cells. Mutation Research, **196**: 61-81.

Cederberg I (1996). Personal communication.
CEFIC (1986) The occurrence of chlorinated solvents in the environment. Chemistry and Industry, **24**: 861-869.

Cerna M & Kypenova H (1977) Mugagenic activity of chloroethylenes analysed by screening system tests. Mutat Res, **26**: 214-215.

Chang LW, Daniel FB & DeAngelo AB (1992) Analysis of DNA strand breaks induced in rodent liver in vivo, hepatocytes in primary culture, and a human cell line by chlorinated acetic acids and chlorinated acetaldehydes. Environ Mol Mutag, **20**: 277-288.

Commandeur JNM, Boogaard J, Mulder GJ, et al. (1991) Mutagenicity and cytotoxicity of two regioisomeric mercapturic acids and cysteine S-conjugates of trichloroethylene. Arch Toxicol, **65**: 373-380.

Conde-Salazar L, Guimarciens D, Romero LV, et al. (1983) Subcorneal pustular eruption and erythema from occupational exposure to trichloroethylene. Contact Dermatitis, **19**: 235-237.

Costa AK & Ivanetich KM (1984) Chlorinated ethylenes:their metabolism and effect on DNA repair in rat hepatocytes. Carcinogenesis, **5**: 1629-1636.

Cotter LH (1950) Trichloroethylene poisoning. Arch Ind Hyg Occup Med, **1**: 319-322.

Crebelli R, Bignami M, Conti L, et al. (1982) Mutagenicity of trichloroethylene in Salmonella typhimurium TA 100. Ann Ist Super Sanita, **18**: 117-122.

Crebelli R, Conti G, Conti L, et al. (1985) Mutagenicity of trichloroethylene, trichloroethanol and chloral hydrate in Aspergillus nidulans. Mutat Res, **155**: 105-111.

Dalbey W & Bingham E (1978) Metabolism of trichloroethylene by the isolated perfused lung. Toxicol Appl Pharmacol, **43**: 267-277.

Daniel FB, DeAngelo AB, Stober JA, et al. (1992) Hepatocarcinogenicity of chloral hydrate, 2-chloroacetaldehyde and dichloroacetic acid in the male B6C3F1 mouse. Fund Appl Toxicol, **19**: 159-168.

David NJ, Wolman R, Milne FJ, et al. (1989) Acute renal failure due to trichloroethylene poisoning. Br J Ind Med, **46**: 347-349.

Davidson IWF & Beliles RP (1991) Consideration of the target organ toxicity of trichloroethylene in terms of metabolite toxicity and pharmacokinetics. Drug Metab Rev, **23**: 493-599.

De Rosa E, Saia B & Bet E (1971) Epidemiological investigations on workers exposed to trichlorethylene in a tannery. Lav Um, **23**: 240-248.

DeAngelo AB, Daniel FB, McMillan L, et al. (1989) Species and strain sensitivity to the induction of peroxisome proliferation by chloroacetic acid. Toxicol Appl Pharmacol, **101**: 285-298.

Dees C & Travis C (1993) The mitogenic potential of trichloroethylne in B6C3F1 mice. Toxicol Lett, **69**: 129-137.

Degrassi F & Tanzarella C (1988) Immunofluorescent staining of kinetochores in micronuclei: a new assay for the detection of aneuploidy. Mutat Res, **203**: 339-345.

Dekant W, Metzler M & Henschler D (1984) Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. Biochem Pharmacol, **33**: 2021-2027.

Dekant W, Vamvakas S & Berthold K (1986) Bacterial (-lyase mediated cleavage and mutagenicity of cysteine conjugates derived from the nephrocarcinogenic alkenes trichloroethylene, tetrachloroethylene and hexachorobutadiene. Chem Biol Interact, **60**: 31-45.

DeMarini DM, Perry E & Shelton ML (1994) Dichloroacetic acid and related compounds: induction of prophage in E. Coli and mutagenicity and mutation spectra in *Salmonella* TA100. Mutagenesis, **9**: 429-437.

Deutsche Forschungsgemeinschaft (1996) Maximum concentrations at the workplace and biological tolerance values for working materials. Report No 31. Weiheim, VCH.

Dimitrova M, Usheva G & Pavlova S (1974) The work environment's influence on the cardiovascular system. Polycardiographic investigations in workers exposed to trichloroethylene. Int Arch Arbeitsmed, **32**: 145-148.

Dorfmueller MA, Henne SP, York RG, et al. (1979) Evaluation of teratogenicity and behavioural toxicity with inhalation exposure of maternal rats to trichloroethylene. Toxicology, **14**: 153-166.

Douglas et al. (1995) as cited in UK SIAR (1996).

Dow Chemical Company (1993) Neurotoxicological examination of rats exposed to trichloroethylene vapor for 13 weeks . The Dow Chemical Company, Health and Environmental Sciences, The Toxicology Research Laboratory, Midland, MI.

Duprat P, Delsaut L & Gradiski D (1976) Irritant potency of the principle chlorinated aliphatic solvents on the skin and ocular mucous membranes of rabbits. Eur J Toxicol, **3**: 171-177.

Duprat P & Gradiski D (1980) Cytogenetic effect of trichloroethylene in the mouse as evaluated by the micronucleus test. IRCS Med Sci, **8**: 182.

ECETOC (1992) Hepatic peroxisome proliferation. Brussels, European Centre for Ecotoxicology and Toxicology of Chemicals.

ECSA (1990) A comparison of cleaning methods. Aqueous and chlorinated solvents. Brussels, European Chlorinated Solvent Association.

El Ghawabi SM, Mansoor MB & El Gamel M (1973) Chronic trichloroethylene exposure. J Egypt Med Assoc, **56**: 11-12.

Elcombe CR (1985) Species differences in carcinogenicity and peroxisome proliferation due to trichloroethylene. A biochemical human hazard assessment. Arch Toxicol (Suppl 8): 6-17.

Elcombe CR, Rose MS & Pratt IS (1985) Biochemical, histological and ultrastructural changes in rat and mouse liver following administration of trichloroethylene. Possible relevance to species differences in hepatocarcinogenicity. Toxicol Appl Pharmacol, **79**: 365-376.

Ertle T, Henschler D, Muller G, et al. (1972) Metabolism of trichloroethylene in man. I. The significance of trichloroethylene in long-term exposure conditions. Arch Toxicol, **29**: 171-188.

Ettema JH & Zielhuis RL (1975) Effect of alcohol, carbon monoxide and trichloroethylene inhalation on mental capacity. Int Arch Occup Environ Health, **35**: 117-132.

European Chemical News (1995) Swedes suggest tax to prevent perc use. (6-12 March): 21.

European Commission (1994) Technical Guidance Documents in support of the Commission Regulation (EC) No 1488/94 on Risk Assessment for Existing Substances in Accordance with Council Regulation (EEC) No 793/93. Luxembourg, European Commission.

European Commission Directive 93/21/EEC (1993 27 April,) Adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating classification, packaging and labelling of dangerous substances.

Fahrig R (1977) The mammalian spot test (Fellfleckentest) with mice. Arch Toxicol, **38**: 87-98.

Fahrig R, Madle S, Baumann H (1995) Genetic toxicity of trichloroethylene (TCE). Mutation Research, **340**: 1-36

Federal Office of Road Safety (1998) Australian Code for the Transport of Dangerous Goods by Road and Rail (6th ed.). Canberra, Australian Government Publishing Service.

Feingold A & Holaday DA (1977) The pharmacokinetics of metabolism of inhalation anaesthetics. Br J.Anaesth, **49**: 155-162.

Feldman RG (1970) Facial nerve latency studies in man. Effects of trichloroethylene exposure. Electromyography, **10**: 93-100.

Feldman RG, White RF, Eriator II, et al. (1994) Neurotoxic effects of trichloroethylene in drinking water. In: R. Isaacson and K. Jensen ed. The vulnerable brain and environmental risks: vol 3: Toxins in air and water. Plenum Press, New York.

Fernandez JG, Droz PO, Humbert BE, et al. (1977) Trichloroethylene exposure: simulation of uptake, excretion and metabolism using a mathematical model. British Journal of Industrial Medicine, **34**: 43-55.

Fernandez JG, Humbert BE, Droz PO, et al. (1975) Exposition au trichloroethylene. Bilan de l'absorption, de l'excretion et du metabolisme chez des sujets humains. Arch Mal Prof, **36**: 397 (as cited in Lauwerys 1993).

Fiserova-Bergerova V & Pierce JT (1989) Biological monitoring V: dermal absorption. Appl Ind Hyg, **4**(8): F-14-F21.

Fisher JW, Gargas ML & Allen BC (1991) Physiologically based pharmacokinetic modeling with trichloroethylene and its metabolite, trichloroacetic acid, in the rat and mouse. Toxicol Appl Pharmacol, **109**: 183-195.

Flindt-Hansen H & Isager H (1987) Scleroderma after occupational exposure to trichloroethylene and trichloroethane. Acta Derma Venereologica, **67**: 263-264.

Fonzi S, Focardi L & Raddi R (1967) Trichloroethylene as a hepatotoxic substance. Experimental study in chronic poisoning. Lav Um (Suppl 12), **29**: 94-110.

Forkert PG & Birch DW (1989) Pulmonary toxicity of trichloroethylene in mice. Covalent binding and morphological manifestations. Drug Metab Dispos, **17**: 106-113.

Forkert PG, Sylvestre PL & Poland JS (1985) Lung injury induced by trichloroethylene. Toxicology, **34**: 143-160.

Forsberg K & Mansdorf S.Z (1993) *Quick selection guide to chemical protective clothing* (2nd ed), Van Nostrand Reinhold, NY.

Fredrickson M, Bengtsson N-O, Hardell L, et al. (1989) Colon cancer, physical activity and occupational exposures. A case control study. Cancer, **63**: 1838-1842.

Friberg L, Kylin B & Nystrom A (1953) Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyridine-alkali reaction. Acta Pharmacol Toxicol, **9**: 303-312.

Fukuda K, Takemoto K & Tsurata H (1983) Inhalation carcinogenicity of trichloroethylene in mice and rats. Ind Health, **21**: 243-254.

Furnus C et al. (1990) The induction of aneuploidy in cultured Chinese hamster cells by propionaldehyde and chloral hydrate. Mutagenesis, **5**: 323-326.

Galloway SM, Armstrong MJ, Reuben C, et al. (1987) Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluation of 108 chemicals. Environ Mol Mutagen (Suppl 10), **10**: 1-175.

Garabrant DH, Held J, Langholz B, et al. (1998) Mortality of aircraft workers in Southern California. American Journal of Industrial Medicine, **13**: 683-693

Geyer H, Politzki G, Freitag D (1984) Prediction of ecotoxicological behaviour of chemicals: relationship between n-octanol/water partition coefficient and bioaccumulation of organic chemicals by alga Chlorella. Chemosphere,**13**: 269-284 as cited in the UK SIAR (1996).

Goeptar AR, Commandeur JNM, van Ommen B, et al. (1995) Metabolism and kinetics of trichloroethylene in relation to toxicity and carcinogenicity. Relevance of the mercapturic acid pathway. Chem Res Toxicol, **8**: 3-21.

Goldberg ME, Lebowitz MD, Graver EJ, et al. (1990) An association of human congenital cardiac malformations and drinking water contaminants. J Am Coll Cardiac, **16**: 155-164.

Goldsworthy TL & Popp JA (1987) Chlorinated hydrocarbon induced peroxisomal enzyme activity in relation to species and organ carcinogenicity. Toxicol Appl Pharmacol, **89**: 234-244.

Government of Canada (1993) Priority Substances List Assessment Report: Trichloroethylene. Ottawa, Canada, Canada Communication Group.

Gradiski D, Bonnet P, Raoult G, et al. (1978) A comparison of acute pulmonary toxicity of the main chlorinated aliphatic solvents. Arch Mal Prof, **39**: 249-257.

Graovac-Leposavic L, Milosavlfevic Z & Ilic V (1964) Liver function in workers exposed to trichloroethylene. Arh Hig Rada, **15**: 93-97.

Green T (1997) Central Toxicology Laboratory, Formic Acid excretion in rats and mice exposed to trichloroethylene, Report no CTL/R/1312, Cheshire, United Kingdom.

Green T, Dow J, Ellis MK, Foster JR et al (1997a) The role of glutathione conjugation in the development of kidney tumours in rats ecposed to trichloroethylene: Chemico-Biologocal Interactions, **105**: 99-117.
99-117.

Green T, Mainwaring GW & Foster JR (1997b) Trichloroethylene-induced moude lung tumours: Studies of the mode of action and comparisons between tissues. Fundamental and Applied Toxicology, **37**: 125-130.

Green T, Odum J, Nash JA, et al. (1990) Trichloroethylene induced rat kidney tumours: the mechanisms involved and their relevance to humans. Zeneca CTL Report No. CTL/R/1037 (as cited in UK SIAR, 1996).

Green T & Prout MS (1985) Species differences in response to trichloroethylene. II. Biotransformation in rats and mice. Toxicol Appl Pharmacol, **79**: 410-411.

Greim H, Bonse G, Radwan Z, et al. (1975) Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem Pharmacol, **24**: 2013-2017.

Gu ZW, Sele B, Jalbert P, et al. (1981) Induction of sister chromatid exchanges by trichloroethylene and its metabolites. Toxicol Eur Res, **3**: 63-67.

Gudi R & et al. (1992) Assessment of the in vivo aneuploidy/micronucleus assay in bone marrow cells with 16 chemicals. Environ Molec Mutag, **20**: 106-116.

Gun RT, Grygorcewicz C & Nettelbeck TJ (1978) Choice reaction time in workers using trichloroethylene. Med J Aust, **1**: 535-536.

Guyotjeannin C & Van Steenkiste J (1958) Action of trichloroethylene on serum proteins and lipids. Study of 18 employees working in a contaminated atmosphere. Arch Mal Prof, **19**: 489-494.

Haworth S, Lawlor T, Mortelmans K, et al. (1983) Salmonella mutagenicity test results for 250 chemicals. Environ Mutagen (Suppl. 1): 3-142.

Hazardous Substances Data Base (HSDB) (1994) Trichloroethyene

Healy TEJ, Poole TR, Hooper A, (1982) Rat fetal development and maternal exposure to trichloroethylene 100 ppm, Br J Anaesth,**54**: 337-341 as cited in the ATSDR (1993).

Heineman E & et al. (1994) Occupational exposure to chlorinated aliphatic hydrocarbons and risk of astrocytic brain cancer. American Journal of Industrial Medicine, **26**: 155-169.

Henschler D, Eder E, Neudecker T, et al. (1977) Carcinogenicity of trichloroethylene. Fact or artifact? Arch Toxicol, **37**: 233-236.

Henschler D, Elsasser HM, Romen W, et al. (1984) Carcinogenicity study of trichloethylene with and without epoxide stabilisers, in mice. J Cancer Res Clin Oncol, **104**: 149-156.

Henschler D, Romen W, Elsasser HM, et al. (1980) Carcinogenicity study of of trichloroethylene by long term inhalation in 3 animal species. Arch Toxicol, **43**: 237-248.

Henschler D, Vamvakas S, Lammert M, et al. (1995) Increased incidence of renal cell tumors in a cohort of cardboard workers exposed to trichloroethene. Arch Toxicol, **69**: 291-299.

Herbert V, Gerdner A & Colman N (1980) Mutagenicity of dichloroacetate, an ingredient of some formulations of pangamic acid (trade-named vitamin B15). Am J Clin Nutr, **33**: 1179-1182.

Herren-Freund SL, Pereira MA, Khoury MD, et al. (1987) The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. Toxicol Appl Pharmacol, **90**: 183-189.

IARC (1995) Dry cleaning, some chlorinated solvents and other industrial chemicals. In: ed. IARC monographs on the evaluation of carcinogenic risks to humans. International Agency for Research on Cancer, Lyon, **63:** 75-158.

Inoue O, Seiji K, Kawai T, et al. (1989) Relationship between vapor exposure and urinary metabolite excretion among workers exposed to trichloroethylene. Am J Ind Med, **15**: 103-110.

IPCS (International Programme on Chemical Safety) (1985) Trichloroethylene: Environmental Health Criteria 50. Geneva, World Health Organisation.

Irish DD (1963) Aliphatic hydrocarbon solvents. In: F. Patty ed. Industrial Hygiene and Toxicology. Interscience, New York, **:** 1309-1313.

Isaacson LG & Taylor DH (1989) Maternal exposure to 1,1,2-trichloroethylene affects myelin in the hippocampal formation of the developing rat. Brain Res, **488**: 403-407.

Jakobson I, Holmberg B & Ekner A (1986) Venous blood levels of inhaled trichloroethylene in female rats and changes induced by interacting agents. Acta Pharmacol Toxicol, **59**: 135-143.

Kaneko T, Wang PY & Sato A (1994) Enzymes induced by ethanol differently affect the pharmacokinetics of trichloroethylene and 1,1,1 trichloroethane. Occup Environ Med, **51**: 113-119.

Keinfeld M & Tabershaw IR (1954) Trichloroethylene toxicity - report of 5 fatal cases. AMA Arch Ind Hyg Occup Med, **10**: 134-141.

KEMI (1995) Chlorine and chlorine compounds. Use, occurrence and risks - the need for action. Solna, The Swedish National Chemicals Inspectorate.

Kimmerle G & Eben A (1973) Metabolism, excretion and toxicology of trichloroethylene after inhalation. 2. Experimental human exposure. Arch Toxicol, **30**: 127.

Kinkead ER & Wolfe RE (1980) Dermal toxicity of various compounds to female rabbits. Single oral toxicity of various organic compounds. J Am Coll Toxicol, **2**: 712-713.

Kjellstrand P, Holmquist B, Alm P, et al. (1983a) Trichloroethylene: further studies of the effects on body and organ weights and plasma butyrylcholinesterase activity in mice. Acta Pharmacol Toxicol Copenh, **53**: 375-384.

Kjellstrand P, Holmquist B, Mandahl N, et al. (1983b) Effects of continuous trichloroethylene inhalation on different strains of mice. Acta Pharmacol Toxicol Copenh, **53**: 369-374.

Kjellstrand P, Kanje M, Mansson L, et al. (1981) Trichloroethylene: effects on body and organ weights in mice, rats and gerbils. Toxicology, **21**: 105-115.

Kligerman AD, Bryant MF, Doerr CL, et al. (1994) Inhalation studies of the genotoxicity of trichloroethylene to rodents. Mutat Res, **322**: 87-96.

Knadle SA, Green CE, Baugh M, et al. (1990) Trichloroethylene biotransformation in human and rat primary hepatocytes. Toxicol in Vitro, **4**: 537-541.

Koch R, Schlegelmich R & Wolf HU (1988) Genetic effects of chlorinated ethylenes in the yeast Saccharomyces cerevisiae. Mutat Res, **206**: 209-216.

Konietzko H, Elster I, Bengsath A, et al. (1975) EEG variation with controlled exposure to trichloroethylene. Int Arch Occup Environ Health, **35**: 257-264.

Konietzko H & Reill G (1980) The effect of trichloroethylene on some serum enzymes and on the cytoenzymological activity in leucocytes and on the acid base equilibrium. Int Arch Occup Environ Health, **47**: 61-67.

Kostrzewski P, Jakubowski M & Kolacinski Z (1993) Kinetics of trichloroethylene elimination from venous blood after acute inhalation poisoning. J Toxicol Clin Toxicol, **31**: 353-363.

Krost KJ, Pellizzari ED, Walburn SG, et al. 1982. Collection and analysis of hazardous organic emissions. Anal Chem, **54**: 810-817 as cited in ATSDR (1993).

Kylin B, Axell K, Samuel HE, et al. (1967) Effect of inhaled trichloroethylene on the CNS as measured by optokinetic nystagmus. Arch Environ Health, **15**: 48-52.

Laham S (1970) Studies on placental transfer:trichloroethylene. Ind Med Surg, **39**: 46-49.

Land PC, Owen EL & Linde HW (1981) Morphologic changes in mouse spermatoza after exposure to inhalational anesthetics during early spermatogenesis. Anesthesiology, **54**: 53-56.

Landrigan PJ & Kominsky JR (1987) Common source community and industrial exposure to trichloroethylene. Arch Environ Health, **42**: 327-332.

Larson JL & Bull RJ (1992) Species differences in the metabolism of trichloroethylene to the carcinogenic metabolites trichloroacetate and dichloroacetate. Toxicol Appl Pharmacol, **115**: 278-285.

Latif F, Tory K, Gnarra J, et al. (1993) Identification of the von Hippel-lindau disease tumour suppressor gene. Science, **260**: 1317-1320.

Lauwerys RR & Hoet P (1993) Industrial chemical exposure. Guidelines for biological monitoring. Ann Arbor, Lewis Publishers.

Leopardi P et al. (1993) In vivo studies on chemically induced aneuploidy in mouse somatic and germinal cells. Mutat Res, **287**: 119-130.

Leuschner J & Leuschner F (1991) Evaluation of the mutagencicity of chloral hydrate in vitro and in vivo. Arzneim-Forsch/Drug Res, **41**: 1101-1103.

Liang JC & Pacchierotti F (1988) Cytogenic investigations of chemically-induced aneuploidy in mouse spermatocytes. Mutat Res, **201**: 325-335.

Lilis R, Stanescu D, Muica N, et al. (1969) Chronic effects of trichloroethylene exposure. Med Lav, **60**: 595-601.

Lindbohm ML, Taskinen H, Sallmen M, et al. (1990) Spontaneous abortions among women exposed to organic solvents. Am J Ind Med, **17**: 449-463.

Little AD (1990) *Guidelines for the selection of chemical protective clothing, Vol I and II* (3rd ed), ACGIH, Cincinnati, Ohio.

Loprieno N & Abbondandolo A (1980) Comparative mutagenic evaluation of some industrial compounds. In: K. Norpoth and R. Garner ed. Short-term test systems for detecting carcinogens. Springer, Berlin, **:** 333-356.

Lynch AM & Parry JM (1993) The cytochalasin-B micronucleus/kinetochore assay in vitro: studies with 10 suspected aneugens. Mutat Res, **287**: 71-86.

Mackay J, Fox V, Griffiths K, et al. (1995) Trichloroacetic acid: investigation into the mechanism of chromosomal damage in the in vitro human lymphocyte cytogenetic assay and the mouse bone marrow micronucleus test. Carcinogenesis, **16**(5): 1127-1133.

Mailhes J et al. (1988.) Analysis of mouse metaphase II oocytes as an assay for chemically induced aneuploidy. Mutat Res, **198**: 145-152.

Mailhes JB, Aardema MJ & Marchetti F (1993) Investigation of aneuploidy induction in mouse oocytes following exposure to vinblastine-sulfate, pyrimethamine, diethylstlbestrol diphosphate, or chloral hydrate. Environ Mol Mutag, **22**: 107-114.

Makide Y, Tominaga T, Rowland FS. 1979. [Gas Chromatographic analysis of halogenated hydrocarbons in air over Japan.] Chemistry Letters (Chemicals Society of Japan), **4**:355-358.(Japanese) as cited in ATSDR (1993).

Maltoni C, Lefemine G, Cotti G, et al. (1988) Long term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss mice and B6C3F1 mice. Ann New York Acad Sci, **534**: 316-342.

Maltoni C, Leffermine G & Cotti G (1986) Experimental research on trichloroethylene carcinogenesis. In: C. Maltoni and M. Mehlman ed. . Princeton Scientific, Princeton, NJ, **:** 1-393.

Maltoni C & Maioli P (1977) Long term bioassay of carcinogenicity of trichloroethylene: preliminary results. Osp Vita, **4**: 108-110.

Manson JM, Murphy M, Richdale N, et al. (1984) Effects of oral exposure to trichloroethylene on female reproductive function. Toxicology, **32**: 229-242.

Mazzullo M, Bartoli S, Bonora B, et al. (1992) In vivo and in vitro interaction of trichloroethylene with macromolecules from various organs or rat and mouse. Res Commun Chem Pathol Pharmacol, **76**: 192-208.

McConnell G, Ferguson DM & Pearson CR (1975) Chlorinated hydrocarbons and the environment. Endeavour, **34**: 13-18.

McGregor DB, Reynolds DM & Zeiger E (1989) Conditions affecting the mutagenicity of trichloroethylene in *Salmonella*. Environ Mol Mutagen, **13**: 197 - 202.

Metal Finishing Association (1996) Vapour Degreasing. U.K, Environmental Technology Best Practice Programme.

Migliore L & Nieri M (1991) Evaluation of twelve potential aneuploidogenic chemicals by the in vitro human lymphocyte micronucleus assay. Toxicol in vitro, **5**: 325-336.

Miller BM & Adler ID (1992) Aneuploidy induction in mouse spermatocytes. Mutagenesis, **7**: 69-76.

Miller RE & Guengerich FP (1983) Metabolism of trichloroethylene in isolated hepatocytes, microsomes and reconstituted enzyme systems containing cytochrome P-450. Cancer Res, **43**: 1145-1152.

Milman HA, Story DL, Riccio ES, et al. (1988) Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. New York, New York Academy of Sciences.

Mirsalis JC, Tyson CK, Loh EN, et al. (1985) Induction of hepatic cell proliferation and unscheduled DNA synthesis in mouse hepatocytes following in vivo treatment. Carcinogenesis, **6**: 1521-1524.

Mirsalis JC, Tyson CK, Steinmetz KL, et al. (1989) Measurement of unscheduled DNA synthesis and S-phase synthesis in rodent hepatocytes following in-vivo treatment: testing of 24 compounds. Environ Mol Mutat, **14**: 155-164.

Monster AC, Boersma G & Duba WC (1976) Pharmacokinetics of trichloroethylene in volunteers, influence of workload and exposure concentration. Int Arch of Occup Environ Health, **38**: 87-102.

Monster AC, Boersma G & Duba WC (1979) Kinetics of Trichloroethylene in Repeated Exposure of Volunteers. Int Archives of Occup Environ Health, **42**: 283-292.

Morgan RW, Kelsh MA et al. (1998) Mortality of aerospace workers exposed to trichloroethylene. Epidemiology, **9**(4): 424-431.

Moriya M, Ohta T, Watanabe K, et al. (1983) Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res, **116**: 185-216.

Mortelmans K, Haworth S, Lawlor T, et al. (1986) Salmonella mutagenicity tests. II. Results from the testing of 270 chemicals. Environ Mutagen, **8**: 1-119.

Mostofi FK & Price EB (1973) Tumours of the testes; Leydig cell tumours. In: ed. Tumours of the male genital system Fascicle 8. Armed Forces Institute of Pathology, , **:** 86-89.

Muller G, Spassovski M & Henschler D (1972) Trichloroethylene exposure and trichloroethylene metabolites in urine and blood. Arch Toxicol, **29**: 335-340.

Muller G, Spassovski M & Henschler D (1974) Metabolism of trichloroethylene in man. II. Pharmacokinetics of metabolites. Arch Toxicol, **32**: 283-295.

Myhr C & Caspary W (1991) Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: results of 31 coded compounds in the National Toxicology Program. Environmental and Molecular Mutagenesis, **18**: 51-83.

Nagaya T, Ishikawa N, et al (1989) Sister chromatid exchanges in lymphocytes of workers exposed to trichloroethylene. Mutat Res, **222**: 279-282

Nakaaki K, Onishi N, Iida H, et al. (1973) An experimental study on the effect of exposure to trichloroethylene vapour in man. J Sci Labour, **41**: 449-463.

Nakajima T, Okino T, Kurasawa K, et al. (1987) A case of chemical burn, bradycardia, extrasystolic arrhythmia and unconciousness from accidental trichloroethylene exposure. Jpn J Ind Health, **29**: 72-73.

Nakayama H, Kobayashi M, Takahashi M, et al. (1988) Generalized eruption with severe liver dysfunction associated with occupational exposure to trichloroethylene. Contact Dermatitis, **19**: 48-51.

Natarajan AT (1993) An overview of the results of testing of known or suspected aneugens using mammalian cellls in vitro. Mutat Res, **287**: 113-118.

National Cancer Institute (NCI) (1976) Cancer bioassay of trichloroethylene. (National Cancer Institute Carcinogenesis Technical Report Series No 2 - Publication No.76-802), National Cancer Institute.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (1996) Priority Existing Chemical No.4: HCFC-123. Canberra, AGPS.

National Institute for Occupational Safety and Health (NIOSH) (1980) Teratogenic - mutagenic risk of workplace contaminants: trichloroethylene, perchloroethylene, and carbon disulphide, Contract No. 210-77-0047.

National Institute for Occupational Safety and Health (NIOSH) (1987) NIOSH manual of analytical methods. Third edition. Second supplement. Cincinnati, OH: U.S Department of Health and Human Services, Public Health Service, Centers for Disease control and Prevention, NIOSH publication no. 87-117,1003-1-1003-6 as cited in the ATSDR (1993).

National Institute for Occupational Safety and Health (NIOSH) (1989a) Health Hazard Evaluation Report No. HETA 86-380-1957, York International Corporation, Madisonville, Kentucky. Cincinnati, OHIO, NIOSH.

National Institute for Occupational Safety and Health (NIOSH) (1989b) Health Hazard Evaluation Report HETA 88-082-1971, Jostens Incorporated, Princeton, Illinois. Cincinnati, OHIO, NIOSH.

National Institute for Occupational Safety and Health (NIOSH) (1990) Health Hazard Evaluation Report HETA 90-223-2211, Thomson Consumer Electronics, Marion, Indiana. Cincinnati, OHIO, NIOSH.

National Institute for Occupational Safety and Health (NIOSH) (1991) Health Hazard Evaluation Report No. HETA-90-344-2159, A.W. Cash Valve Manufacturing Operation, Decatur, Illinois. Cincinatti, OHIO, NIOSH.

National Institute for Occupational Safety and Health (NIOSH) (1994) NIOSH Manual of Analytical Methods. Cincinnati, OHIO, NIOSH.

National Occupational Health and Safety Commission (NOHSC) (1999) Approved Criteria for Classifying Hazardous Substances. Canberra, Australian Government Publishing Service.

National Occupational Health and Safety Commission (NOHSC) (1994) Control of Workplace Hazardous Substances. Canberra, Australian Government Publishing Service.

National Occupational Health and Safety Commission (NOHSC) (1994) Guidance Note for the Assessment of Health Risks Arising from the use of Hazardous Substances in the Workplace. Canberra, Australian Government Publishing Service.

National Occupational Health and Safety Commission (NOHSC) (1999) List of Designated Hazardous Substances. Sydney, NOHSC.

National Occupational Health and Safety Commission (NOHSC) (1994) National Code of Practice for the Labelling of Workplace Substances. Canberra, Australian Government Publishing Service.

National Occupational Health and Safety Commission (NOHSC) (1994) National Code of Practice for the Preparation of Material Safety Data Sheets. Canberra, Australian Government Publishing Service.

Nelson JL & Zenick H (1986) The effect of trichloroethylene on male sexual behaviour: possible opoid role. Neurobehav Toxicol Teratol, **8**: 441-445.

Nelson MA & Bull RJ (1988) Induction of strand breaks in DNA by trichloroethylene and metabolites in rat and mouse liver in vivo. Toxicol Appl Pharmacol, **94**: 45-54.

Nestmann ER, Chu I, Kowbel DJ, et al. (1980) Short-lived mutagen in Salmonella produced by reaction of trichloroacetic acid and dimethyl sulphoxide. Can J Genet Cytol, **22**: 35-40.

Ni Y-C, Wong T-Y, Kadlubar FF, et al. (1994) Hepatic metabolism of chloral hydrate to free radical(s) and induction of lipid peroxidation. Biochem Biophys Res Comm, **204**: 937-943.

Noland-Gerbac EA, Pfohl RJ, Taylor DH, et al. (1986) 2-Deoxyglucose uptake in the developing rat brain upon pre- and postnatal exposure to trichloroethylene. Neurotoxicology, **7**: 157-164.

Nomiyama K (1971) Estimation of trichloroethylene exposure by biological material. Int Arch Arbeitsmed, **27**: 281-292.

Nomiyama K & Nomiyama H (1971) Metabolism of trichloroethylene in human. Sex differences in urinary excretion of trichloroacetic acid and trichloroethanol. Int Arch Arbeitsmed, **28**: 37-48.

Nomiyama K & Nomiyama H (1977) Dose-response relationship for trichloroethylene in man. Int Arch Occup Environ Health, **39**: 237-248.

Nomura S (1962) Health hazard in workers exposed to trichloroethylene vapour. I. Trichloroethylene poisoning in an electroplating plant. Kumamoto Med J, **15**: 29-37.

Novotna E, David A & Malek B (1979) An epidemiological study of the hepatic tumour incidence in persons working with trichloroethylene. 1. The negative result of retrospective investigation in persons with primary liver cancer. Prac Lek, **31**: 121-123.

Odum J, Foster JR & Green T (1992) A mechanism for the development of Clara cell lesions in the mouse lung after exposure to trichloroethylene. Chem Biol Interactions, **83**: 135-153.

OECD (1993) Occupational and consumer exposure assessments (OECD Environment Monographs No. 70). Paris, France, OECD.

Paddle GM (1983) Incidince of liver cancer and trichloroethylene manufacture: joint study by industry and a cancer register. British Medical Journal, **286**: 846.

Parchman LG & Magee N (1982) Metabolism of 14C-trichloroethylene to 14CO2 and interaction of a metabolite with liver DNA in rats and mice. J Toxicol Environ Health, **9**: 797-813.

Pennarola R, Lamanna P & Castellino N (1966) Pathological findings in experimental trichloroethylene. Folia Med, **49**: 853-864.

Perocco P & Prodi G (1981) DNA damage by haloalkanes in human lymphocytes cultured in vitro. Cancer Lett, **13**: 213-218.

Phoon WH, Chan MOY, Rajan VS, et al. (1984) Stevens-Johnson syndrome associated with occupational exposure to trichloroethylene. Contact Dermatitis, **10**: 270-276.

Prendergast JA, Jones RA, Jenkins LJ, et al. (1967) Effects on experimental animals of long term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1- trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol Appl Pharmacol, **10**: 270-289.

Prout MS, Provan WM & Green T (1985) Species differences in response to trichloroethylene. I . Pharmacokinetics in rats and mice. Toxicology and Applied Pharmacology, **79**: 389-400.

Purchase IFH, Ashby J, Brady A, et al. (1994) Mechanistically-based human assessment of peroxisome proliferator-induced hepatocarcinogenesis. Human and Exp Toxicol, **13**(2).

Radian Corporation (1990) Halogenated solvent cleaners. Emission control technologies and cost analyses. New Jersey, Noyes Data Corporation.

Rapson WH, Nazar MA & Butsky VV (1980) Mutagenicity produced by aqueous chlorination of organic compounds. Bull Environ Contam Toxicol, **24**: 590-596.

Rasmussen K, Brogen CH & Sabroe S (1993) Subclinical affection of liver and kidney function and solvent exposure. Int Arch Occup Environ Health, **64**: 445-448.

Rasmussen RA,. Harsch DE, Sweany PH, et al. 1977. Determination of atmospheric halocarbons by a temperature-programmed gas chromatographic freezeout concentration method. J Air Pollut Control Assoc, **27**: 579-581 as cited in ATSDR (1993)

Rasmussen K, Sabroe S, Wohlert M, et al. (1988) A genotoxic study of metal workers exposed to trichloroethylene. Sperm parameters and chromosome aberrations in lymphocytes. Int Arch Occup Environ Health, **60**: 419-423.

Rebert CS, Boyes WK, Pryor GT, et al. (1993) Combined effects of solvents on the rats auditory system: styrene and trichloroethylene. Int J Psychophysiol, **14**: 49-59.

Reddy JK & Rao MS (1992) Peroxisome proliferation and hepatocarcinogenesis. In: H. Vainio, P. Magee, D. McGregor and A. McMichael ed. Mechanisms of Carcinogenesis in Risk Identification, IARC Publication No. 116. IARC, Lyon, **:** 225-235.

Riccio E, Griffin A & Mortelmans K (1983) A comparative mutagenicity study of volatile halogenated hydrocarbons using different metabolic activation systems. Environ Mutagen, **5**: 472.

Robinson BJ (Updated January 1996) A survey of degreasing operations, 1994. Birmingham, Health and Safety Executive.

Rossi AM, Migliore L, Barale R, et al. (1983) In vivo and in vitro mutagenicity studies of a possible carcinogen, trichloroethylene, and its two stabilizers, epichlorohydrin and 1,2-epoxybutane. Teratogen Carcinogen Mutagen, **3**: 75-87.

Rudd CJ, Mitchell AD & Spalding J (1983) L5178Y mouse lymphoma cell mutagenesis assay of coded chemicals incorporating analyses of the colony size distributions. Environ Mutagen, **5**: 419.

Ruijten MWMM, Verbeck MM & Salle HJA (1991) Nerve function in workers with long-term exposure to trichloroethene. Br J Ind Med, **48**: 87-92.

Russo A & Levis AG (1992a.) Further evidence for the aneuploidogenic properties of chelating agents: induction of micronuclei in mouse male germ cells by EDTA. Environ Mol Mutag, **19**: 125-131.

Russo A & Levis AG (1992b.) Detection of aneuploidy in male germ cells of mice by means of a meiotic micronucleus assay. Mutat Res(281): 187-.

Russo A, Pacchierotti F & Metalli P (1984) Nondisjunction induced in mouse spematogenesis by chloral hydrate, a metabolite of trichloroethylene. Environ Mutagen(6,): 695-703,.

Sagawa K, Nishitani H, Kawai H, et al. (1973) Transverse lesions of the spinal cord after accidental exposure to trichloroethylene. Int Arch Arbeitsmed, **31**: 257-264.

Salvini M, Binaschi S & Riva M (1971) Evaluation of the psychophysiological functions of humans exposed to trichloroethylene. Br J Ind Med, **28**: 293-295.

Sanchez IM & Bull RJ (1990) Early induction of reparative hyperplasia in the liver of B6C3F1 mice treated with dichloroacetate and trichloroacetate. Toxicology, **64**: 33-46.

Sanders VM, Tucker AN, White K, et al. (1982) Humoral and cell-mediated immune status in mice exposed to trichloroethylene in the drinking water. Toxicol Appl Pharmacol, **62**: 385-368.

Sato A & Nakajima T (1978) Differences following skin or inhalation exposure in the absorption and excretion kinetics of trichloroethylene and toluene. Br J Ind Med, **35**: 43-49.

Savolainen H (1981) Pharmacokinetics, pharmacodynamics and aspects of neurotoxic effects of four inhaled aliphatic chlorohydrocarbon solvents as relevant in man. Eur J Drug Metab Pharmacokinet, **6**: 85-90.

Sbrana I, Di Sibio A, Lomi A, et al. (1993) C-Mitosis and numerical chromosome aberration analyses in human lymphocytes: 10 known or suspected spindle poisons. Mutat Res, **287**: 57-70.

Sbrana I, Lascialfari D & Loprieno N (1985) TCE induces micronuclei but not choromosomal aberrations in mouse bone marrow cells. IV ICEM, Stockholm: 163.
Schiestl RH, Aubrecht J, Khogali F, et al. (1997) Carcinogens induce reversion of the mouse pink-eyed unstable mutation. Proc Natl Acad Sci, **94**: 4576-4581.

Schwetz BA, Leong BKJ & Gehring PJ (1975) The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform and methylene chloride on embryonal and fetal development in mice and rats. Toxicol Appl Pharmacol, **32**: 84-96.

Seiji K, Jin C, Watanabe T, et al. (1990) Sister chromatid exchanges in peripheral lymphocytes of workers exposed to benzene, trichloroethylene or tetrachloroethylene, with reference to smoking habits. Int Arch Occup Environ Health, **62**: 171-176.

Shahin MM & Von Borstel RC (1977) Mutagenic and lethal effects of (-benzene hexachloride, dibutyl phthalate and trichloroethylene in Saccharomyces cerevisiae. Mutat Res, **48**: 173-180.

Shelby MD, Erexson GL, Hook GL, et al. (1993) Evaluation of a 3-exposure mouse bone marrow micronucleus protocol. Results with 49 chemicals. Environ Mol Mutagen, **21**: 160-179.

Shelley S, Moore S & Ondrey J (1993) New life for old solvents. Chemical Engineering(June): 63-65.

Sherwood RJ (1976) Ostwald solubility coefficients of some industrially important substances. Br J Ind Med, **33**: 106-107.

Shimada T, Swanson AF, Leber P, et al. (1985) Activities of chlorinated ethane and ethylene compounds in the Salmonella/rat. Microsome mutagenesis and rat hepatocyte/DNA repair assays under vapour phase exposure conditions. Cell Biol Toxicol, **1**: 159-179.

Shindell S & Ulrich S (1985) A cohort study of employees of a manufacturing plant using trichloroethylene. Journal of Occupational Medicine, **27**(8):577-579.

Shipman AJ & Whim BP (1980) Occupational exposure to trichloroethylene in metal cleaning process and to tetrachloroethylene in the drycleaning industry in the U.K. Ann Occup Hyg, **23**: 197-204.

Shirasu Y, Moriya M, Kato K, et al. (1976) Mutagenicity screening of pesticides in the microbial system. Mutat Res, **40**: 19-30.

Siegal J, Jones RA, Coon RA, et al. (1971) Effects on experimental animals of acute, repeated, and continuous inhalation exposures to dichloroactylene mixtures. Toxicol Appl Pharmacol, **18**: 168-174.

Skory Consulting Inc. & Skory LK (1995) Trichloroethylene solvent vapor exposure profile in metal cleaning; Organic vapor monitor (dosimeters) data analysis. Midland, MI.

Slacik-Erben R, Roll R, Franke G, et al. (1980) Trichloroethylene vapours do not produce dominant lethal mutations in male mice. Arch Toxicol, **45**: 37-44.

Smith GF (1970) The investigation of the mental effect of trichloroethylene. Ergonomics, **13**: 580-586.

Smyth HF, Carpanter CP, Weil CS, et al. (1962) Range finding toxicity data: List VI. Am Ind Hyd Assoc J, **23**: 95-107.

Smyth HF, Carpenter CP, Weil CS, et al. (1969) Range finding toxicity data: List VII. Am Ind Hyg Assoc J, **30**: 470-476.

Spirtas R, Stewart PA, Lee JS, et al. (1991) Retrospective cohort mortality study of workers at an aircraft maintenance facility. I Epidemiological results. British Journal of Industrial Medicine, **48**: 515-530.

Standards Association of Australia (1978) AS2161 - 1978: Industrial safety gloves and mittens, SAA, North Sydney.

Standards Association of Australia (1983) AS 2661 Vapour Degreasing Plant - Design, Installation and Operation - Safety Requirements. North Sydney, Standards Association of Australia.

Standards Australia (1995) AS 2865: Safe working in a confined space. Homebush, NSW, Standards Australia.

Standards Australia & Standards New Zealand (1990) AS 3765.1: Clothing for protection against hazardous chemicals: Part 1: Protection against general or specific chemicals. Homebush, NSW, Standards Australia.

Standards Australia & Standards New Zealand (1992) AS/NZS 1337: Eye protectors for industrial applications. Homebush, NSW, Standards Australia.

Standards Australia & Standards New Zealand (1994) AS/NZS 1715: Selection, use and maintenance of respiratory protective devices. Homebush, NSW, Standards Australia.

Standards Australia & Standards New Zealand (1994) AS/NZS 1716: Respiratory protective devices. Homebush, NSW, Standards Association of Australia.

Steward A, Allott PR, Cowles AL, et al. (1973) Solubility coefficients for inhaled anaesthetics for water, oil and biological media. Br J Anaesthesiol, **45**: 282-293.

Stewart RD, Hake CL, LeBurn AJ, et al. (1974a) Biological standards for the industrial worker by breath analysis: trichloroethylene, NIOSH Research Report, Publication No. 74-133.

Stewart RD, Hake CL & Peterson JE (1974b) Degreasers' flush : dermal response to trichloroethylene and ethanol. Arch Environ Health, **29**: 1-5.

Stopps GJ & McLaughlin M (1967) Psychophysiological testing of human subjects exposed to solvent vapours. Am Ind Hyg Assoc J, **28**: 43-50.

Stott WT, Quast JF & Watanabe PG (1982) The pharmacokinetics and macromolecular interactions of trichloroethylene in mice and rats. Toxicol Appl Pharmacol, **62**: 137-151.

Swaen GMH (1995) Increased incidence of renal cell tumours in a cohort of cardboard workers exposed to trichloroethylene. Arch Toxicol, **70**: 127-128.

Szulc-Kuberska J (1972) Selected issues on chronic industrial trichloroethylene intoxication. Folia Med Lodz, **16**: 67-90.

Takamatsu M (1962) Health hazards of workers exposed to trichloroethylene vapour. II. Exposure to trichloroethylene degreasing operations in a communicating machine factory. Kumamoto Med J, **15**: 43-54.

Taskinen H, Anttila A, Lindbohm ML, et al. (1989) Spontaneous abortions and congenital malformations among the wives of men occupationally exposed to organic solvents. Scand J Work Environ Health, **15**: 342-352.

Taylor DH, Lagory KE, Zaccaro DJ, et al. (1985) Effect of trichloroethylene on the exploratory and locomotor activity of rats exposed during development. Sci Total Environ, **47**: 415-420.

Tola S, Vilhunen R, Jarvinen E, et al. (1980) A cohort study on workers exposed to trichloroethylene. Journal of Occupational Medicine, **22**: 737-740.

Tolot F, Viallier J, Roullet A, et al. (1964) Hepatic toxicity of trichloroethylene. Arch Mal Prof, **25**: 9-15.

Triebig G, Reichenbach T & Flugel KA (1978) Biochemical examinations and measurements of the conduction velocity in persons chronically exposed to trichloroethylene. Int Arch Occup Environ Health, **42**: 31-40.

Triebig G, Shaller KH, Erzigkeit H, et al. (1977a) Biochemical investigation and psychological studies of persons exposed to trichloroethylene with regard to non-exposed individuals. Int Arch Occup Environ Health, **38**: 149-162.

Triebig G, Trautner P, Weltle D, et al. (1982) Investigations on neurotoxicity of chemical substances at the workplace. III. Determination of the motor and sensory nerve conduction velocity in persons occupationally exposed to trichloroethylene. Int Arch Occup Environ Health, **51**: 25-34.

Tsuruta H (1978) Percutaneous absorption of trichloroethylene in mice. Ind Health, **16**: 145-148.

Tucker AN, Sanders VM, Barnes DW, et al. (1982) Toxicology of trichloroethylene in the mouse. Toxicol Appl Pharmacol, **62**: 351-357.

U.S. Environmental Protection Agency (USEPA) (1996) Aster Database . National Health and Environmental Effects Research Laboratory, Duluth, Min.

UK Government (1993, July) Risk assessment of existing substances-Guidance produced by a UK Government /Industry Working Group.

United Kingdom (1996) SIDS Initial Assessment Report on Trichloroethylene.

United Nations Environment Programme Industry and Environment Programme Activity Centre (UNEPIE/PAC) (1992) Protecting the ozone layer: Solvents, coatings and adhesives.

US National Toxicology Program (NTP) (1986) Toxicology and carcinogenesis studies of trichloroethylene in Fischer-344/N rats and B6C3F1 mice. NC, NTP, Research Triangle Park.

US National Toxicology Program NTP (1988) NTP technical report on the toxicology and carcinogenesis studies of trichloroethylene in four strains of rats. TR 273. NC, NTP, Research Triangle Park.

US National Toxicology Program NTP (1990) Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No 79-01-6) in Fischer-344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC, NTP.

Vagnarelli P, De Sario A & De Carli L (1990) Aneuploidy induced by chloral hydrate detected in human lymphocytes with the Y 97 probe. Mutagenesis, **5**: 591-592.

Vamvakas S, Bruning, T et al. (1996) Renal cell cancer correlated with occupational exposure to trichloroethylene, as cited in Deutsche Forschungsgemeinschaft (1996) Maximum concentrations at the workplace and biological tolerance values for working materials. Report No 31. Weiheim, VCH

Vamvakas S, Dekant W & Henschler D (1989b) Assessment of unscheduled DNA synthesis in a cultured line of renal epithelial cells exposed to cysteine S-conjugates of haloalkenes and haloalkanes. Mutat Res, **222**: 329-335.

Vamvakas S, Elfarra AA, Dekant W, et al. (1988a) Mutagenicity of amino acid and glutathione S-conjugates in the Ames test. Mutat Res, **206**: 83-90.

Van Duuren BL, Goldschmidt BM, Loewengart G, et al. (1979) Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl Cancer Inst, **63**: 1433-1439.

Vernon RJ & Ferguson RK (1969) Effects of trichloroethylene on visual motor performance. Arch Environ Health, **18**: 894-900.

Vernot EH, MacEwen JD, Haun CC, et al. (1977) Actue toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. Toxocol Appl Pharmacol, **42**: 417-423.

Villaschi S, Giovanetti A, Lombardi CC, et al. (1991) Damage and repair of mouse bronchial epithelium following acute inhalation of trichloroethylene. Exp Lung Research, **15**: 601-614.

Wahlberg JE (1984) Edema inducing effects of solvents following topical administration. Derm Benf Unwelt, **32**: 91-94.

Wallace LA, Pellizzari ED, Hartwell TD, et al. 1986. Total exposure assessment methodology (TEAM) study: Personal exposure, indoor-outdoor relationships, and breath levels of volatile organic compounds in New Jersey. Environment International, **12**: 369-387 as cited in ATSDR (1993).

Walles SAS (1986) Induction of single-strand breaks in DNA of mice buy trichloroethylene and tetrachloroethylene. Toxicol Lett, **31**: 31-35.

Warner JR, Hughes TJ & Claxton LD (1988) Mutagenicity of 16 volatile organic chemicals in a vaporization technique with Salmonella typhimurium TA 100. Environ Mol Mutagen, **11**: 111-112.

Waskell L (1978) A study of the mutagenicity of anaesthetics and their metabolites. Mutat Res, **57**: 141-153.

Watson SC, Foster JR & Elcombe CR (1993) Trichloroacetic acid: species differences in the stimulation of hepatic DNA synthesis. Human Exp Toxicol, **4**: 1-5.

Weiss NS (1996) Cancer in relation to occupational exposure to trichloroethylene. Occupational and Environmental Medicine, **53**:1-5

Wernisch M, Paya K & Palasser A (1991) Cardiac arrest after inhalation of shoemakers glue. Wien Med Wochenschr, **141**: 71-74.

White AE, Takehisa S, Eger EI, et al. (1979) Sister chromatid exchanges induced by inhaled anaesthetics. Anaesthesiology, **50**: 426-430.

Whittaker SG, Zimmerman FK, Dicus B, et al. (1990) Detection of induced mitotic chromosome loss in Saccharomyces cerevisiae - an interlaboratory assessment of 12 chemicals. Mutat Res, **241**: 225-242.

Windemuller FJB & Ettema JH (1978) Effect of combined exposure to trichloroethylene and alcohol on mental capacity. Int Arch Occup Environ Health, **41**: 77-85.

Wolf K & Chestnutt TW (1987) Chlorinated solvents: Market interactions and regulation. Journal of Hazardous Materials, **15**: 137-161.

Woodward-Clyde (1995) 4432 Groundwater Stage 2 Survey ICI Botany Contract C6 Overview Report Parts A-D .

Xu W & Adler I-D (1990) Clastogenic effects of known and suspect spindle poisons studied by chromosome analysis in mouse bone marrow cells. Mutagenesis, **5**: 371-374.

Yoshida M, Fukabori S, Hara K, et al. (1996) Concentrations of trichloroethylene and its metabolites in blood and urine after acute poisoning by ingestion. Hum Exp Toxicol, **15**(3): 254-258.

Zenick H, Blackburn K, Hope E, et al. (1984) Effects of trichloroethylene exposure on male reproductive functions in rats. Toxicology, **31**: 237-250.

Zielinski A (1973) General health state of women professionally exposed to trichloroethylene (Tri) vapours. Med Pr, **24**: 263-271.

Zordan M, Osti M, Pesce M, et al. (1994) Chloral hydrate is recombinogenic in the wing spot test in Drosophila melanogaster. Mutat Res, **322**: 111-116.

Order Form

FOR NICNAS PUBLICATIONS

NICNAS

List of Publications	Quantity	Amount
Handbook for Notifiers @ AUD $55.00 each (incl. GST)		
Australian Inventory of Chemical Substances (AICS) CD ROM @ $242.00 (incl. GST). (2003 version) **Available within Australia only.**		
Copy/s of Full Public Report/s of the following complete assessments. *Include NICNAS reference number/s* ***(no charge)***.		
Full Public Report for Priority Existing Chemical – *Please specify report name* ***(no charge)***.		
	Total	$

All prices include postage and packaging within Australia and by SEAMAIL overseas.
For AIRMAIL please include an additional $50.00 per Handbook and $10.00 each for other NICNAS products.

All orders must be accompanied by prepayment in Australian Dollars. Purchase orders NOT accepted.

Overseas only: Please send by AIRMAIL Yes ◯ No ◯

I enclose a cheque/money order payable to: NICNAS.

Drawn on an Australian bank in Australian Dollars for: $

or: Bankcard / Visacard / Mastercard **only.** Card no.

Signature of card holder Expiry date

☒ Name of card holder

Please initial you complete this section. Please send me a tax invoice Yes/No

Name of recipient Position

Company

Address

Telephone ( ) Fax ( )

Send this order to: NICNAS, Finance
GPO Box 58, Sydney, NSW 2001 Australia

For further information about NICNAS publications please call: Free Call 1800 638 528
Or email info@nicnas.gov.au