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THE DERIVATION OF MAXIMUM PERMISSIBLE CONCENTRATIONS FOR VOLATILE COMPOUNDS IN AIR

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PREFACE

This report contains results of research carried out within the framework of the project 'Setting integrated environmental quality objectives for water, soil and air'. The results have been discussed in the 'Setting integrated environmental quality objectives advisory group'. Members of this group are C.W.M. Bodar (Dutch Health Council), J.H.M. de Bruijn (Ministry of Housing, Physical Planning and Environment), J.H. Canton (National Institute of Public Health and Environmental Protection), C.A.J. Denneman (Ministry of Housing, Physical Planning and Environment), J.W. Everts (Ministry of Transport, Public Works and Water Management, Tidal Waters Division), M.P.M. Janssen (National Institute of Public Health and Environmental Protection), W. Ma (Institute for Forestry and Nature Research), P. Leeuwangh (Winand Staring Centre for Integrated Land, Soil and Water Research), E.J. van de Plassche (National Institute of Public Health and Environmental Protection), P.B.M. Stortelder (National Institute of Inland Water Management), J. Struijs (National Institute of Public Health and Environmental Protection), M. Vossen (National Institute of Inland Water Management), and J. van Wensem (Technical Soil Protection Committee).

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Finally, underlying data and the derivation of MPC's for 2-chloro-1,3-butadiene, 3-chloro-1-propene, 1,1-dichloroethene, 1,2-dichloropropane, 1,3-dichloropropene and 1,1,1-trichloroethane were discussed and adopted in the Toxicology Advisory Group of the National Institute of Public Health and Environmental Protection. Members of the Toxicology Advisory Group were: J. v. Benthem (Laboratory of Carcinogenesis and Mutagenesis), G. Meyer (Laboratory of Toxicology), A.G.A.C. Knaap and F.X.R. v. Leeuwen (both of the Toxicology Advisory Centre).

CONTENTS

SUMMARY

Within the framework of the sub-project 'Volatile compounds' which is part of the project 'Setting integrated environmental quality objectives', *preliminary* Maximum Permissible Concentrations (MPC's) in air have been derived for several volatile compounds. These *preliminary* MPC's have been presented in a previous report by Rademaker et al. (1993). Based on the harmonization of these *preliminary* MPC's in air with those in water and soil, it appeared that the MPC's in the various compartments were in conflict: the occurrence in one compartment of a concentration equal to the MPC, did result in an exceedance of the MPC in another compartment. Based on these intercompartimental harmonization, it is decided to re-evaluate the *preliminary* MPC's in air. This is the subject of the present report.

For 22 volatile compounds an attempt is made to derive a MPC in air. By means of on-line search for recent literature and the examination of original data of studies mentioned in reviews used for deriving *preliminary* MPC's, the available data set is evaluated for each compound to determine whether or not a MPC in air can be derived. For 3-chloro-1-propene, 1,1-dichloroethene, 1,2-dichloropropane, 1,3-dichloropropene and 1,1,1-trichloroethane a MPC in air was derived, while for 2-chloro-1,3-butadiene a *preliminary* MPC was derived. For the remaining 16 compounds essential human toxicological data were lacking. The following MPC's are derived: 7.4 $\mu g/m^3$ for 3-chloro-1-propene, 200 $\mu g/m^3$ for 1,1-dichloroethene, 12.4 $\mu g/m^3$ for 1,2-dichloropropane, 40 $\mu g/m^3$ for 1,3-dichloropropene and 4,820 $\mu g/m^3$ for 1,1,1-trichloroethane. For 2-chloro-1,3-butadiene a *preliminary* MPC was set at 1 $\mu g/m^3$.

SAMENVATTING

In het kader van het project Integrale Normstelling Stoffen voor Water, Bodem en Lucht (INS) zijn binnen het subproject 'Vluchtige Stoffen' voor een aantal stoffen voorlopige Maximaal Toelaatbare Risiconivo's (MTR's) in lucht afgeleid, die beschreven zijn in een eerder rapport (Rademaker et al., 1993). Uit afstemmingsberekeningen van deze *voorlopige* MTR's in lucht met die van water en bodem bleek dat deze risiconivo's voor de drie compartimenten niet met elkaar in overeenstemming zijn: het voorkomen van een concentratie gelijk aan de MTR in het ene compartiment, leidde tot een overschrijding van de MTR in een ander compartiment. Op grond van deze intercompartimentale afstemming is besloten om de *voorlopige* MTR's in de lucht te herevalueren. Dit wordt beschreven in het voorliggende rapport.

Voor 22 vluchtige stoffen is de mogelijkheid onderzocht om een MTR in lucht vast te stellen. Door middel van een on-line zoekactie naar recente literatuur en het bestuderen van de originele literatuur van studies die vermeld worden in reviews welke gebruikt zijn voor de afleiding van voorlopige MTR's, is per stof bekeken of er voldoende gegevens beschikbaar zijn voor het afleiden van een MTR in lucht. Voor 3-chloor-1-propeen, 1,1-dichlooretheen, 1,2-dichloorpropaan, 1,3-dichloorpropeen en 1,1,1-trichloorethaan kon een MTR in lucht afgeleid worden. Voor 2-chloor-1,3-butadiëen werd de *voorlopige* MTR herzien. Voor de overige 16 stoffen ontbreken essentiële humaan toxicologische gegevens. De MTR voor 3-chloor-1-propeen is vastgesteld op 7,4 $\mu g/m^3$, voor 1,1-dichlooretheen op 200 $\mu g/m^3$, voor 1,2-dichloorpropaan op 12,4 $\mu g/m^3$, voor 1,3-dichloorpropeen op 40 $\mu g/m^3$ en voor 1,1,1-trichloorethaan op 4.820 $\mu g/m^3$. Voor 2-chloor-1,3-butadiëen is de *voorlopige* MTR vastgesteld op 1 $\mu g/m^3$.

1. INTRODUCTION

1.1 The project 'Volatile compounds'

The present report is an addendum to Rademaker et al. (1993): "The derivation of *preliminary* maximum permissible concentrations of volatile compounds in air", written within the framework of the project 'Volatile compounds'. This project is part of a larger one titled 'Setting Integrated Environmental Quality Objectives', which aims at deriving integrated environmental quality objectives (i.e. limit and target values) for a great number of compounds in air, water, sediment and soil. In the project 'Volatile Compounds' this is attempted for 46 volatile substances. The approach used in order to derive integrated environmental quality objectives, consists of deriving Maximum Permissible Concentrations (MPC's) for air, water, sediment and soil, followed by harmonization of these MPC's. The derivation of MPC's for water, sediment and soil has been described in Van de Plassche et al. (1993). In an integration report of this subproject, values for these volatile compounds will be derived which can be used to set limit and/or target values for all compartments (Van de Plassche and Bockting, in preparation).

In order to derive MPC's in air, it was decided to use a step-wise approach. First, *preliminary* MPC's have been determined based on information from reviews only. These *preliminary* MPC's have been presented in a previous report (Rademaker et al., 1993). Next step is to investigate whether or not these *preliminary* MPC's in air are coherent with the MPC's for water, sediment and soil. This coherence criterion implies that MPC's for one compartment should be at a level where protection of organisms living in other compartments is ensured: the MPC in one compartment may not lead to exceedance of the MPC in another compartment due to intermedia transport of the substance. The assessment of the coherence of MPC's in the various compartments has been performed according to a procedure by Van de Meent and De Bruijn (in preparation). This procedure will be described in the integration report stated above.
Because most sets of (*preliminary*) MPC's did not meet the coherence criterion, a re-evaluation of the *preliminary* MPC's in air had to be performed. The results are described in the present report. For all compounds the data on which *preliminary* MPC's in air are based, are evaluated and updated by on-line literature search. For compounds with a sufficient toxicological data set MPC's in air will be determined.

1.2 Compounds

The 46 substances of the project 'Volatile compounds' can be divided into two categories:

1. 12 compounds for which limit and/or target values for air have already been set by the Ministry of Housing, Physical Planning and Environment: acrylonitrile, benzene, 1,2-dichloroethane, dichloromethane, ethylene oxide, styrene, tetrachloroethene, tetrachloromethane, toluene, trichloroethene, trichloromethane and vinylchloride. Updating of the data sets of these compounds, showed that re-evaluation of these values was not deemed necessary (Rademaker et al., 1993). Therefore the existing limit and/or target values of these compounds and the respective MPC's for water, sediment and soil will be harmonized in the integration report of the project 'Volatile compounds'.
2. 34 compounds for which no limit and/or target values exist yet in the Netherlands. From this group chlorobenzenes were excluded because a recent evaluation by Slooff et al. (1991) showed the set of inhalation data to be insufficient for deriving a MPC in air. Also xylene-mix, being a mixture of xylene-isomers and ethylbenzene, was excluded from further evaluation. For the remaining 22 compounds of this category (presented in table 2.1.) an attempt is made to derive MPC's in air, by applying the procedure described in Chapter 2.

2. METHODOLOGY

In this section the methodology of deriving MPC's in air will be described. At various instances, the methodology section of the report on *preliminary* MPC's will be referred to (Rademaker et al., 1993).

2.1 Literature search for (eco)toxicological data on volatile compounds

Preliminary MPC's in air were based on information from reviews only (Rademaker et al., 1993). However, in the present report, where MPC's in air are derived which will be used to set integrated environmental quality objectives, consultation of original literature is considered essential. Therefore, the most relevant and critical studies from reviews used for the derivation of *preliminary* MPC's were retrieved. Besides, an on-line search was carried out to complete and up-date the already collected data-set of the compounds. Selected compounds are presented in table 2.1.
The following data bases have been searched: Toxall, CD-ROM-Toxline plus, Biosis, Embase, Medline and IRIS. The search profiles included: CAS-number of the compounds, toxicology (mammals, human), ecotoxicology (insects, birds, plants), inhalatory, inhalation, gas uptake, respiration, respiratory.

Preliminary MPC's in air were derived for ecosystems and humans by Rademaker et al. (1993). The *preliminary* MPC in air for ecosystems was in all cases higher than the one for humans. From the on-line search no relevant ecotoxicological studies could be retrieved to re-evaluate the *preliminary* MPC's for ecosystems. Therefore in the present report the derivation of MPC's in air will be described for humans only.

Table 2.1 : Literature search for volatile compounds

COMPOUND	CASNO.	MOST RECENT REVIEW	ON-LINE START
2-chloro-1,3-butadiene	126-99-8	ACT, 1980	1978
3-chloro-1-propene	107-05-1	IARC, 1985	1983
1,1-dichloroethane	75-34-3	ATSDR, 1990a	1988
1,1-dichloroethene	75-35-4	ATSDR, 1992; IPCS, 1990a	1988
1,2-dichloroethene	540-59-0	ATSDR, 1989b	1987
1,2-dichloropropane	78-87-5	ATSDR, 1989a	1987
1,3-dichloropropane	142-28-9	none	1983
1,3-dichloropropene	542-75-6	ACT, 1993; IPCS, 1990b	1988
2,3-dichloropropene	78-88-6	none	1983
ethylbenzene	100-41-4	ATSDR, 1990b	1988
ethylene	74-85-1	Slooff, 1991a	1989
hexachloroethane	67-72-1	BUA, 1988	1986
2-monochlorotoluene	95-49-8	BUA, 1989a	1987
3-monochlorotoluene	108-41-8	BUA, 1989a	1987
4-monochlorotoluene	106-43-4	BUA, 1989a	1987
pentachloroethane	76-01-7	IARC, 1986b	1984
1,1,2,2-tetrachloroethane	79-34-5	ATSDR, 1989c; BUA, 1989b	1987
1,1,1-trichloroethane	71-55-6	ACT, 1991; Slooff, 1991b	1989
1,1,2-trichloroethane	79-00-5	ATSDR, 1989d	1987
2-xylene	95-47-6	ACT, 1990; ATSDR, 1990c	1988
3-xylene	108-38-3	ATSDR, 1990d	1988
4-xylene	106-42-3	ATSDR, 1990d	1988

2.2 Minimum toxicological data set

In general, for deriving a MPC a complete toxicological profile of the compound has to be known. Conform to recent Integrated Criteria Documents, e.g. on the chlorobenzenes (Slooff et al., 1991) it is decided that for each compound a minimum toxicological data set is required to derive a MPC, containing data on:
- carcinogenicity (inhalation and/or oral) and mutagenicity
- teratogenicity and reproduction (inhalation and/or oral)
- (sub)chronic toxicity data (inhalation)

The exposure route of the study on the most critical effect (principal study)

needs to be inhalatory. From this study the MPC will be derived. Oral studies are only accepted for completing the toxicological profile of a compound on carcinogenicity, teratogenicity and reproduction.
In case one or more elements of the minimum toxicological data set are lacking, no MPC is derived.

2.3 Criteria for studies

Reliability criteria for studies used for deriving MPC's include exposure route, exposure time, exposure schedule and exposure concentration. In accordance with the report on *preliminary* MPC's (Rademaker et al., 1993) studies considered suitable for deriving a MPC are:

A. (Sub-)Chronic toxicity studies with an exposure time of 4 h/d and 5 d/w, or longer. Studies for which no information was available concerning the exposure time, are excluded.
B. Studies in which more than one exposure concentration was used, so a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) could be derived. This aspect should apply to all studies under A to D.
C. Teratogenicity studies. Teratogenic effects were defined as irreversible, structural effects on the foetuses. By definition, effect concentrations at which maternal toxicity occurs, are not included.
D. Reproduction studies, from which an impression can be obtained of the potential of a compound to affect reproduction in males and females. In general this means that the studies should cover the whole reproduction cycle from sexual ripening to growth and development of the following generations.
E. Carcinogenicity and mutagenicity studies, from which an impression of the carcinogenic and mutagenic potential of a compound can be obtained.
F. Case-controlled human studies, in which more than one concentration is tested during a known exposure time. Also human studies should result in a NOAEL or LOAEL.

2.4 Deriving MPC's in air

A MPC is derived only when the minimum toxicological data set is complete. For the extrapolation of MPC's from the available data, two types of compounds should be distinguished. In the first place the non-carcinogenic compounds and the non-genotoxic carcinogens, which require a threshold approach. In the second place the genotoxic carcinogenic compounds for which a non-threshold approach is used. The extrapolation procedure of MPC's for both types of compounds has been described in the report on *preliminary* MPC's (Rademaker et al., 1993). With a few adjustments this procedure will also be used for deriving MPC's. Main difference will be the more flexible application of uncertainty factors (UF) for the threshold approach in the present report.
As the non-threshold extrapolation method was not applied to any of the compounds included (see chapter 4), this procedure will not be described here. The threshold approach used to derive MPC's for the individual compounds is as follows:

1. Correction to continuous exposure: all NOAELs and LOAELs are corrected for continuous exposure (24 h/d; 7d/w) by multiplication with a factor N/7 * M/24, in which N is the number of exposure days per week and M the number of hours per day. These corrected NOAELs/LOAELs are called 'duration corrected values' (DCV's).
2. The lowest DCV's from the data set are selected for further consideration.
3. The original reports of the principal studies are evaluated with respect to aspects like relevance of parameters and animal species and the progression of the various effects in time.
4. A MPC is calculated from the most relevant DCV by applying uncertainty factors. The ones for interspecies (UF=10) and intraspecies variation (UF=10) are used always. The magnitude of other uncertainty factors, for extrapolation from subchronic to chronic exposure or for LOAEL to NOAEL, depends on the information obtained from step 3. Aspects like type of effect (nature, severity and biological significance), specificity of the study, progression of effect in time, duration of the study and extent of available information on the compound determine the uncertainty factor.

3. AVAILABILITY OF DATA

An overview of the availability of the different elements of the minimum toxicological data set for the selected volatile compounds is presented in table 3.1.

For six compounds all elements of the toxicological data set are present: 2-chloro-1,3-butadiene, 3-chloro-1-propene, 1,1-dichloroethene, 1,2-dichloropropane, 1,3-dichloropropene and 1,1,1-trichloroethane. For the remaining compounds no minimum toxicological data set is available. No MPC's can be derived for these compounds. Carcinogenicity data were lacking for six compounds, mutagenicity data for four compounds, teratogenicity studies for seven compounds and reproduction data for fifteen compounds, while (sub)chronic inhalation studies are lacking for nine compounds.

For three out of these fifteen compounds only one additional study will complete the data set. For these compounds, 1,1-dichloroethane, 1,1,2,2-tetrachloroethane and 2-xylene, it concerns reproduction data which are lacking. For 1,1,2,2-tetrachloroethane some data are available, but the studies do not cover the whole reproduction cycle from sexual ripening to growth and development of the following generations. For 1,1,2,2-tetrachloroethane a one generation study on male reproduction parameters is the only study available. As described in Chapter 2 it was decided not to derive MPC's for compounds for which no sufficient data are available concerning effects on reproduction. For 2-chloro-1,3-butadiene and 3-chloro-1-propene reproduction data, although not complete, are considered suitable for obtaining a good impression of the effects of these compounds on reproduction performance.

For twelve compounds studies on more than one element of the minimum toxicological data set are lacking. Two elements are lacking for ethylbenzene, ethylene, hexachloroethane, 3-xylene and 4-xylene. Three elements are lacking for 1,2-dichloropropane, pentachloroethane and 1,1,2-trichloroethane, while for 2-monochlorotoluene four elements are not present. For 1,3-dichloropropane, 3-monochlorotoluene and 4-monochlorotoluene, for which no *preliminary* MPC has been derived, no data were available at all.

Table 3.1 : The minimum toxicological data set for 22 volatile compounds

Compound	CARC	MUT	TERAT	REPRO	TOX ≥90 DAYS	MPC
2-chloro-1,3-butadiene	+	+	+	+	+	yes
3-chloro-1-propene	+	+	+	+	+	yes
1,1-dichloroethane	+	+	+	-	+	no
1,1-dichloroethene	+	+	+	+	+	yes
1,2-dichloroethene	-	+	-	-	+	no
1,2-dichloropropane	+	+	+	+	+	yes
1,3-dichloropropane	-	-	-	-	-	no
1,3-dichloropropene	+	+	+	+	+	yes
2,3-dichloropropene	-	+	-	+	+	no
ethylbenzene	-	+	+	-	+	no
ethylene	+	+	-	-	+	no
hexachloroethane	+	+	+	-	-	no
2-monochlorotoluene	-	-	+	-	-	no
3-monochlorotoluene	-	-	-	-	-	no
4-monochlorotoluene	-	-	-	-	-	no
pentachloroethane	+	+	-	-	-	no
1,1,2,2-tetrachloroethane	+	+	+	-	+	no
1,1,1-trichloroethane	+	+	+	+	+	yes
1,1,2-trichloroethane	+	+	-	-	-	no
2-xylene	+	+	+	-	+	no
3-xylene	+	+	+	-	-	no
4-xylene	+	+	+	-	-	no

4. DERIVATION OF MPC'S FOR VOLATILE COMPOUNDS IN AIR

In this chapter MPC's will be derived for six compounds with a complete toxicological data set. For three more compounds for which only reproduction data were lacking, the *preliminary* MPC derived by Rademaker et al. (1993) will be re-evaluated, based on the examination of original data referred to in reviews and data obtained from on-line search.

4.1 The derivation of MPC's for six volatile compounds

In this section a short description of the toxicological data set will be given for the six individual compounds, followed by the derivation of MPC's. The raw data from which the information in this chapter is extracted, are given in appendix 1. The MPC's are presented in table 5.1.

4.1.1 **2-Chloro-1,3-butadiene** (see appendix 1A)

2-chloro-1,3-butadiene is toxic to mice and harmful to rats after acute inhalation exposure (EC, 1979).
From the scarce inhalatory subchronic data it is concluded that the substance is a depressant of the central nervous system. Effects were observed at duration corrected concentrations of $\geq$ 250 mg/m^3.
The evaluation of the reproductive and teratogenic effects of 2-chloro-1,3-butadiene is complicated by the breakdown into toxic products before use. This more toxic material is damaging to the testis and shows foetotoxicity and embryotoxicity in animals in concentrations as low as 0.15 mg/m^3. No effects were observed at 0.05 mg/m^3. However, no such effects were observed in a study with pure 2-chloro-1,3-butadiene up to a concentration of 77.5 mg/m^3 (DCV: 13 mg/m^3) (Culik et al., 1978).
In workers functional disturbances in spermatogenesis and morphological sperm abnormalities were observed after exposure to low concentrations of impure 2-chloro-1,3-butadiene.
2-Chloro-1,3-butadiene was mutagenic to bacteria and induced sex-linked recessive lethal mutations in *Drosophila melanogaster*. It did not induce mutations in Chinese hamster cells. It induced dominant lethal mutations in mice and rats and chromosomal aberrations *in vivo*.

There is inadequate evidence for the carcinogenicity of 2-chloro-1,3-butadiene to experimental animals. There is inadequate evidence for the carcinogenicity of 2-chloro-1,3-butadiene to humans. The substance was classified in group 3 by IARC (IARC, 1987; see also appendix 3).

From the available data the substance was considered to be genotoxic. Carcinogenicity data were inadequate. A closely related compound, 1,3-butadiene, is mutagenic *in vivo* and carcinogenic in mice after inhalation (NTP, 1991). Based on these data, 2-chloro-1,3-butadiene can not be excluded from being a genotoxic carcinogen, which necessitates a non-threshold approach for deriving a MPC. However, appropriate carcinogenicity data needed for low-dose risk extrapolation are not available.
It was therefore decided to use a pragmatic approach to revise the *preliminary* MPC for 2-chloro-1,3-butadiene. For several other genotoxic carcinogens (acrylonitrile, 1,2-dichloroethane, ethylene oxide and vinylchloride) MPC's, which varied from 3 to 100 $\mu g/m^3$ with an accepted risk of 10^{-6} per year, have been derived previously (Rademaker et al., 1993). Based on this range it is decided to set the *revised preliminary* MPC of 1 $\mu g/m^3$ for 2-chloro-1,3-butadiene.

4.1.2 **3-Chloro-1-propene** (see appendix 1B)

3-Chloro-1-propene is harmful after acute inhalation exposure to mice, rats, rabbits, guinea pigs and cats (EC, 1979).
From the available subchronic studies it is concluded that the liver, kidneys and lungs and the central nervous system are the target organs. In special studies the neurotoxic effects of 3-chloro-1-propene, occurring at lower doses, have been investigated.
Nagano et al., 1991, exposed rats to 31, 155 or 310 mg/m^3 3-chloro-1-propene for 8 h/d, 5 d/w for 34 weeks. Neurotoxicity was observed at the two highest dose levels. The NOAEL in this study was 31 mg/m^3 (DCV: 7.38 mg/m^3).
Reproduction studies have not been carried out. No abnormalities were observed at histopathological examination of the testes from subchronic exposed rats.
No embryotoxic and teratogenic effects were observed in rats and rabbits.
3-Chloro-1-propene was mutagenic to bacteria and yeast. It did not cause chromosome aberrations *in vitro* in mammalian cells.
There is inadequate evidence for the carcinogenicity of 3-chloro-1-propene to experimental animals. In the absence of epidemiological data, no evaluation could be made of the carcinogenicity of 3-chloro-1-propene to humans. The substance was classified in group 3 by IARC (IARC, 1987; see also appendix 3).

In several occupational studies effects on the central nervous systems were observed in workers exposed to a wide range of concentrations of 3-chloro-1-propene for up to 6 years.

Based on the available data 3-chloro-1-propene was considered to be not carcinogenic, which justifies a threshold approach for deriving a MPC.

The neurotoxic effects observed in experimental animals and humans are used as the toxicological endpoint. Because of uncertainties in the human exposure data the MPC is derived by applying an UF of 1000 (interspecies 10, intraspecies 10 and an extra factor 10 for neurotoxic damage in workers observed at relatively low concentrations) to the duration corrected NOAEL of 7.38 mg/m^3, obtained from a 34-week neurotoxicity study in rats. No factor was applied for subchronic toxicity, because it concerns a study on specific effects.

MPC = 7.38 mg/m^3 / 1000 = 7.4 μg/m^3

4.1.3 **1,1-Dichloroethene** (see appendix 1C)

1,1-Dichloroethene is harmful after acute inhalation exposure to rats and hamsters and toxic to mice (EC, 1979).
From the available subchronic and chronic toxicity studies it is concluded that the liver is the target organ. The lowest NOAEL is observed in one of the studies of Prendergast et al. (1967): in monkeys continuously exposed to 0, 20, 61, 101 or 189 mg/m^3 the NOAEL was 20 mg/m^3. At the two highest doses body weight loss, mortality and histopathological changes in the liver were observed. At 61 mg/m^3 the only effect was a decrease in body weight.
At maternal toxic doses embryotoxicity and foetotoxicity were observed after inhalation exposure of 1,1-dichloroethene to pregnant rats and rabbits, no teratogenic effects were found. The substance caused no effect on reproduction performance in rats.
1,1-Dichloroethene is mutagenic to bacteria. It did not cause chromosomal aberrations in mammalian cells *in vitro* neither *in vivo*. DNA damage was observed in mammalian cells both after *in vitro* and *in vivo* administration.
There is limited evidence for the carcinogenicity of 1,1-dichloroethene to experimental animals. There is inadequate evidence for the carcinogenicty of 1,1-dichloroethene to humans. 1,1-Dichloroethene was classified in group 3 by IARC (IARC, 1987; see also appendix 3).

Based on the available data 1,1-dichloroethene was considered to be not carcinogenic, which justifies a threshold approach for deriving a MPC.

The MPC is derived by applying an UF of 100 (interspecies 10, intraspecies 10) to the NOAEL of 20 mg/m^3. No factor is applied for subchronic exposure, because also chronic studies are available, supporting the idea that the effects do not show progression with time:

MPC = 20 mg/m^3 /100 = 200 μg/m^3

4.1.4 **1,2-Dichloropropane** (see appendix 1D)

Based on acute toxicity studies in mice and rats, 1,2-dichloropropane can be classified as harmful (EC, 1979).
From subchronic studies performed by Nitschke (1988) the target organs of 1,2-dichloropropane appeared to be the nasal cavity and the blood. The most critical adverse effect was degeneration of the olfactory epithelium of the nasal cavity in rats. The NOAEL on this effect appeared to be 69.3 mg/m^3 (DCV: 12.4 mg/m^3). 1,2-Dichloropropane did not affect reproduction parameters up to oral concentrations of 250 mg/kg bw. No histopathological effects on reproduction organs were observed after inhalatory exposure. No teratogenic effects were observed up to a concentration of 150 mg/kg bw.
In vitro 1,2-dichloropropane was mutagenic to bacteria and fungi. *In vivo* the compound was not mutagenic to *Drosophila melanogaster.*
For animals limited evidence on carcinogenicity was available. For humans no data were available. 1,2-Dichloropropane was classified by IARC in group 3. (IARC, 1986; 1987; see also appendix 3).

Based on the available data, 1,2-dichloropropane was considered to be not carcinogenic, which justifies a threshold approach for deriving a MPC.

The MPC is derived by applying an UF of 1,000 (interspecies 10, intraspecies 10, subchronic exposure 10) to the duration corrected NOAEL of 12.4 mg/m^3, obtained from a 13-week study in rats.

MPC = 12.4 mg/m^3 / 1000 = 12.4 μg/m^3

4.1.5 **1,3-Dichloropropene** (see appendix 1E)

Based on acute toxicity studies in rats, 1,3-dichloropropene can be classified as harmful (EC, 1979).
Subchronic and chronic toxicity studies indicate that the target organs for 1,3-dichloroethane are the urinary bladder, the uteri of females and the nasal cavity. In longterm studies (Dow Chemical, 1987a; 1987b; Lomax et al., 1989), mice and rats were exposed to concentrations up to 272 mg/m^3. Observed effects were hyperplasia of the urinary bladder, hypertrophy and hyperplasia of the respiratory epithelium, degeneration of the olfactory epithelium, increase in the incidence of benign lungtumors, and hyperplasia and hyperkeratosis in the forestomach. The NOAEL for histopathological changes in the urinary bladder and the nasal cavity, found in mice, was considered to be 21 mg/m^3 (DCV: 4 mg/m^3).
No effects were observed on reproductive parameters in a 2-generation study. 1,3-Dichloropropene was embryotoxic in rats at maternal toxic doses, but not in rabbits. Nor teratogenic effects were observed in rabbits and rats.
Both isomers of 1,3-dichloropropene were mutagenic to bacteria. The addition of glutathione reduced these mutagenic effects. Chromosomal effects were observed *in vitro*. In *Drosophila melanogaster* sex-linked recessive lethal mutations were induced. In vivo, a micronucleus test in mice and a host-mediated assay were negative.
For animals sufficient evidence on carcinogenicity was available. For humans inadequate data were available. 1,3-Dichloropropene was classified by IARC in group 2B. (IARC, 1986; 1987; see also appendix 3). This evaluation was based on oral data. From recent studies in rats and mice 1,3-dichloropropene was concluded to be not carcinogenic via the inhalatory route.

Based on the available data, 1,3-dichloropropene was considered to be not carcinogenic after inhalatory exposure, which justifies a threshold approach for deriving a MPC.

The MPC is derived by applying an UF of 100 (interspecies 10, intraspecies 10) to the duration corrected NOAEL of 4 mg/m^3, obtained from a 2-year mouse study.

MPC = 4 mg/m^3 / 100 = 40 μg/m^3

4.1.6 **1,1,1-Trichloroethane** (see appendix 1F)

Based on the available data in mice and rats, 1,1,1-trichloroethane does not need to be classified as to its acute inhalatory toxicity (EC, 1979).
From several studies the target organs for 1,1,1-trichloroethane appeared to be the liver and brain. In the study by Quast et al. (1988) rats were exposed to 0, 810, 2,700 or 8,100 mg/m^3 for 24 months. In the highest exposure group body weights were increased and very slight hepatic effects were observed. The NOAEL in this study was 2,700 mg/m^3 (DCV: 482 mg/m^3).
1,1,1-Trichloroethane did not affect the reproduction parameters in mice. In rats exposed to 2,700 mg/m^3, no histopathological changes were seen in the testes.
No teratogenic effects were observed in both mice and rats.
1,1,1-Trichloroethane was not mutagenic to bacteria. *In vitro* assays with mammalian cells were negative, except for a chromosomal aberration test in Chinese hamster cells without metabolic activation. 1,1,1-Trichloroethane was negative in the available *in vivo* mammalian tests. A host-mediated assay was negative.
For animals inadequate evidence on carcinogenicity was available. For humans no data were available. 1,1,1-Trichloroethane was classified by IARC in group 3 (IARC, 1979; 1987; see also appendix 3).

Based on the available data, 1,1,1-trichloroethane was considered to be not carcinogenic after inhalatory exposure, which justifies a threshold approach.

The MPC is derived by applying an UF of 100 (interspecies 10, intraspecies 10) to the duration corrected NOAEL of 482 mg/m^3, obtained from a 2-year rat study.

MPC = 482 mg/m^3 / 100 = 4,820 μg/m^3

4.2 Re-evaluation of three preliminary MPC's

For three compounds only data on reproduction were lacking from the minimum toxicological data set. It concerns 1,1-dichloroethane, 1,1,2,2-tetrachloroethane and 2-xylene. For these compounds, *preliminary* MPC's for humans were derived in the report by Rademaker et al. (1993). The data used for deriving *preliminary* MPC's are extracted from this report and summarized here. Furthermore a re-evaluation of the *preliminary* MPC's is performed based on the examination of the original data and on-line literature search.

4.2.1 1,1-Dichloroethane (ethylidene dichloride)

Data from which a *preliminary* MPC was derived:
From subchronic studies in five test animals, corrected NOAELs were obtained varying from 366 to 854 mg/m^3. NOAELs were within the same range for all species. A corrected NOAEL of 7,805 mg/m^3 was found on teratogenicity. For deriving a *preliminary* MPC, the lowest NOAEL of 366 mg/m^3, on haematology and biochemistry in cats, was extrapolated.
A *preliminary* MPC was derived by applying an UF of 1,000 (intraspecies 10, interspecies 10, subchronic 10) to the DCV of 366 mg/m^3.

Preliminary MPC = 366 mg/m^3 / 1,000 = 366 μg/m^3

Conclusion after consulting original data and performing on-line search:
* The original study used for deriving a *preliminary* MPC is examined and did not give rise to an adjustment of the NOAEL. No original data on supporting studies were available.
* No relevant new data were available on-line.
* Although some data on reproduction were available, this information was not complete. Mutagenicity data were inconclusive. The IARC did not classify 1,1-dichloroethane, whereas the EPA classified the compound as a possible human carcinogen (EPA, 1990).

Based on these considerations, it is decided not to derive a MPC. There is no reason for modifying the uncertainty factor of 1,000 used for deriving the *preliminary* MPC.

4.2.2 1,1,2,2-Tetrachloroethane

Data from which a *preliminary* MPC was derived:
Two subchronic studies in rats and rabbits were present, resulting in NOAELs varying from 0.2 to 1 mg/m^3. The sensitivity of both species were comparable. Both studies did not meet the reliability criteria described in section 2.3, because exposure time was only 3-4 h/d. Due to lack of better information and considering the small difference with the set exposure time-limit, the study was accepted for deriving a *preliminary* MPC. The lowest NOAEL of 0.2 mg/m^3, on haematology and biochemistry, was used for extrapolation.
A *preliminary* MPC was derived by applying an UF of 1,000 (intraspecies 10, interspecies 10, subchronic 10) to the DCV of 0.2 mg/m^3.

Preliminary MPC = 0.2 mg/m^3 / 1,000 = 0.2 μg/m^3

Conclusion after consulting original data and performing on-line search:
* No original data were available on the study used for deriving a *preliminary* MPC.
* No supporting new data were found.
* Reproduction data were not available. Limited evidence on carcinogenicity was available for animals. For humans inadequate evidence was available. 1,1,2,2-Tetrachloroethane was classified by IARC in group 3 (IARC, 1979; 1987; see also appendix 3).

Based on these considerations, it is decided not to derive a MPC. There is no reason for modifying the uncertainty factor of 1,000 used for deriving the *preliminary* MPC.

4.2.3 2-Xylene

Data from which a preliminary MPC was derived:
Subchronic studies were performed in four test animals: rats, guinea pigs, monkeys and dogs. NOAELs varied from 337 to 5,075 mg/m^3. The lowest corrected NOAEL of 337 mg/m^3, on growth, (histo)pathology and haematology, was the same for all mentioned animals. This value was used for the extrapolation of a *preliminary* MPC. The compound was considered not teratogenic up to concentrations of 3,000 mg/m^3.

A *preliminary* MPC was derived by applying an UF of 1,000 (intraspecies 10, interspecies 10, subchronic 10) to the DCV of 337 $\mu g/m^3$.

Preliminary MPC = 337 mg/m^3 / 1,000 = 337 $\mu g/m^3$

Conclusion after consulting original data and performing on-line search:

* The original study used for deriving a *preliminary* MPC was examined and did not give rise to an adjustment of the NOAEL.
* On-line data search did not result in new studies.
* Reproduction data were not available. No studies were available supporting the results of the study used for extrapolation. For both animals and humans inadequate evidence on carcinogenicity was available. 2-Xylene was classified by IARC in group 3 (IARC, 1989; see also appendix 3).

Based on these considerations, it is decided not to derive a MPC. There is no reason for modifying the uncertainty factor of 1,000 used for deriving the *preliminary* MPC.

5. CONCLUSIONS

Derivation of MPC's:

MPC's have been derived for 3-chloro-1-propene, 1,1-dichloroethene, 1,2-dichloropropane, 1,3-dichloropropene and 1,1,1-trichloroethane (see table 5.1: MPC's printed in bold). For 2-chloro-1,3-butadiene a *revised preliminary* MPC was derived based on a minimum toxicological data set.

In contrast with the derivation of *preliminary* MPC's, for these MPC's a flexible, compound dependent approach was used in applying uncertainty factors. If subchronic effects were used for extrapolation, and supporting chronic studies were available confirming the fact that the effect is transient or at least not progressing, the UF was set at 1. In most cases this different approach resulted in MPC's differing from the more strictly calculated *preliminary* MPC's.

Table 5.1 : MPC's for six volatile compounds

COMPOUND	**MPC** (in $\mu g/m^3$)	***preliminary*** **MPC** (in $\mu g/m^3$)
2-chloro-1,3-butadiene (chloroprene)	1*	0.008
3-chloro-1-propene (allylchloride)	**7.4**	2
1,1-dichloroethene	**200**	20
1,2-dichloropropane	**12.4**	13
1,3-dichloropropene	**40**	40
1,1,1-trichloroethane	**4,820**	38

*: For 2-chloro-1,3-butadiene no MPC could be determined. The value presented here is a *revised preliminary* MPC.

Reliability of MPC's:

For six compounds MPC's have been derived based on a minimum toxicological data set. For one of these compounds, 2-chloro-1,3-butadiene, it concerned a *revised preliminary* MPC. The size and reliability of this data set and thus the

reliability of the MPC's vary from compound to compound. In case several supporting studies are present to confirm the results of the principal study, the reliability of the derived MPC may be considered higher than when the MPC is based on one study.

Preliminary MPC's:

For 1,1-dichloroethane, 1,1,2,2-tetrachloroethane and 2-xylene no data on reproduction were found. For these compounds a *preliminary* MPC was derived by Rademaker et al. (1993). The data from reviews on which these *preliminary* MPC's were based, and the re-evaluation of the derivation based on original studies and on-line search, are described in chapter 4.2.

In all cases, on-line search did not result in new relevant data. Investigation of original study reports showed that the critical NOAEL/LOAEL, from which a *preliminary* MPC had been derived (Rademaker et al., 1993), still is the most relevant one. This indicates that there is no need for re-evaluation of the *preliminary* MPC's of these compounds. For 1,1,2,2-tetrachloroethane no original data on the most critical study are available. For all three compounds no or only one study is available to support the results of the critical study.

Based on these considerations, it can be concluded that the *preliminary* MPC's for these three compounds will keep their preliminary status.

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APPENDIX 1: PRINCIPAL AND SUPPORTING STUDIES FOR DERIVING MPC'S

CONTENTS:

Appendix 1A. 2-Chloro-1,3-butadiene (chloroprene)

2-Chloro-1,3-butadiene is a very flammable, colourless liquid. It is used in the production of polychloroprene elastomers (IARC, 1979).

Physical chemical properties

Chemical name:	2-chloro-1,3-butadiene
Synonyms:	chloroprene; 2-chlorobutadiene; ß-chloroprene
Structural formula:	$CH_2 = CH - CCl = CH_2$
Cas-#:	126-99-8
Molecular weight:	88.5
Vapour pressure:	39.9 kPa (at 32.8°C)
Odour threshold:	0.4 - 2.0 mg/m^3
Conversion factor:	1 ppm in air = 3.6 mg/m^3

(IARC, 1979; van Gemert and Nettenbreijer, 1977)

Health effects

Animals

Acute toxicity:
In Charles River male rats the LC_{50} for 4-hour exposure was 8,200 mg/m^3. In mice single 8-hour exposures to 2-chloro-1,3-butadiene resulted in a LC_{50} of 591 mg/m^3. Acute toxicity was reviewed by Rademaker et al. (1993).

Subacute and subchronic toxicity:
No recent inhalation studies have been carried out. In rats and hamsters repeated exposure to 2-chloro-1,3-butadiene for 6 h/d, 5 d/w for 4 weeks resulted in a slight decrease in body weight and behavioural effects in rats, and in slight irritation and restlessness in hamsters at the lowest dose of 1400 mg/m^3 (DCV: 250 mg/m^3) (IARC 1979). Rats exposed for 13 weeks to 300 mg/m^3 (DCV: 100 mg/m^3) showed no adverse effects. Rats exposed to 200 or 1200 mg/m^3 (DCV: 65 or 400 mg/m^3) for 5 months showed an increased mortality at the highest dose. In the same dose group CNS depression occurred, body weight

was decreased and slight blood changes were observed (Nyström, 1948).

Reproduction:
The ovarian function was tested in female rats, which were exposed to 30 mg/m^3 for 5 h/d, 6 d/w for 6 months and mated with untreated males at the end of the exposure period. The duration of the oestrus was significantly increased and the anoestrus duration significantly decreased in treated females compared to controls. In unexposed second and third generation offspring, descended from exposed females, these small changes were also observed. Fertility was comparable to controls in each generation (Draper, 1991).
Sanotskii (1976) studied the gonadotrophic effects of 2-chloro-1,3-butadiene in rats exposed continuously to 0.05, 0.15 or 1.69 mg/m^3 for 4.5 months. Functional and morphological changes in spermatogenesis were observed in rats at 0.15 and 1.69 mg/m^3. In mice continuously exposed for 2 months to 0, 0.06, 0.32 or 3.5 mg/m^3 a dose related increase in the number of tubules with desquamating germinal epithelium was observed at the two highest dose levels.
Since in this Russian study the methods used to prepare and generate the concentration of 2-chloro-1,3-butadiene were not specified and effect concentrations were very low (< 1 ppm), the probable formation of reactive breakdown products in the testsubstance before use (Nyström, 1948) might be the origin of the observed effects. Because of this and because the present occupational threshold limit value for 2-chloro-1,3-butadiene in the USA is 77.5 mg/m^3, the studies by Culik et al. (1978) were performed to examine the effects of pure 2-chloro-1,3-butadiene.
Male reproduction was not impaired when male rats were exposed to 77.5 mg/m^3 (DVC: 13 mg/m^3) 4 h/d for 22 days and bred with untreated females for 8 consecutive weeks (Culik et al., 1978).
In a 2-generation reproduction study male and female rats were exposed to 0, 36, 112 or 360 mg/m^3 2-chloro-1,3-butadiene, 6 h/d and 5 d/w for 13 weeks and then mated with unexposed animals. F_1 pups were exposed to the same dose as their treated parent for 10 weeks from 4 weeks of age. No effects were observed on F_0 fertility, intrauterine mortality or litters size as well as postnatal mortality and general condition of the F_1 generation. In the F_1 generation from females exposed to 360 mg/m^3 (DCV: 64 mg/m^3) bodyweight was decreased from birth to 4 weeks of age (Draper, 1991).

Teratogenicity:
Pregnant rats were exposed to 0, 3.6, 36 or 90 mg/m^3 2-chloro-1,3-butadiene for 4 h/d from day 1-12 of gestation or from day 3-20 of gestation. No maternal, embryotoxic or teratogenic effects were observed (Culik et al., 1978).

Pregnant rats were exposed from day 4-16 of gestation to 0, 36, 90, 270 or 630 mg/m^3 for 6 h/d. Maternal toxicity was observed at 270 and 630 mg/m^3. At the two highest dose groups the number of live fetuses, empty uterus weight and foetal weight were decreased. No visceral or skeletal malformations were observed. The NOAEL for embryotoxicity/foetotoxicity is 90 mg/m^3 (DCV: 23 mg/m^3) (Draper, 1991).

Mutagenicity:
2-Chloro-1,3-butadiene was mutagenic in *Salmonella typhimurium* and induced recessive lethal mutations in *Drosophila melanogaster*. 2-Chloro-1,3-butadiene vapour did not induce gene mutations in V79 Chinese hamster cells. It caused chromosome aberrations *in vitro* in bone marrow cells and spleen lymphocytes of rats. 2-Chloro-1,3-butadiene was positive in dominant lethal assays with mice and rats (Van Went & Canton, 1984; IARC, 1979).

Carcinogenicity:
No carcinogenic effects were observed in studies with rats after oral, subcutaneous or intratracheal exposures. The tumour incidence was not enhanced in mice after dermal application of 2-chloro-1,3-butadiene. IARC considered the studies to be not appropriate for evaluation of the carcinogenicity (IARC, 1979).

Humans

Functional disturbances in spermatogenesis and morphological abnormalities of sperm were observed among Russian workers exposed to 2-chloro-1,3-butadiene at concentrations several times higher than the Russian highest permissible concentration of 2 mg/m^3, set in 1940 (Sanotskii, 1976).
In another study with exposed workers, an increase in chromosome aberrations of peripheral lymphocytes, abnormal sperm morphology and motility were observed. In the wives of exposed workers a threefold increase in abortion frequency was observed. Note: possibly the workers were not exclusively exposed to 2-chloro-1,3-butadiene (Van Went and Canton, 1984).
Occupational exposure to 2-chloro-1,3-butadiene was related in one study to an excess of lung and skin cancers, but in other studies no increase in lung cancers or other types of cancer was reported among 2-chloro-1, 3-butadiene exposed workers. One case report describes the occurrence of an angiosarcoma of the liver in a worker extensively exposed to formulated polychloropropene (IARC, 1979).

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Appendix 1B. 3-Chloro-1-propene (allylchloride)

3-Chloro-1-propene is a colourless liquid with a pungent garlic-like odour. It is used as an intermediate in the manufacturing of epichlorohydrin, glycerol, allyl alcohol, diallyl phtalate, fine chemicals and pharmaceuticals (IARC, 1985).

Physical chemical properties

Chemical name:	3-chloro-1-propene
Synonyms:	allylchloride;
	1-chloro-2-propene;
	2-propenyl chloride
Structural formula:	$CH_2 = CH - CH_2Cl$
Cas-#:	107-05-1
Molecular weight:	76.5
Vapour pressure:	39.5 kPa (at 20°C)
Odour threshold:	1.5 mg/m^3
Conversion factor:	1 ppm in air = 3.1 mg/m^3

(IARC, 1985; Torkelson and Rowe, 1981)

Health effects

Animals

Acute toxicity:
The LC_{50}-values for 2-hour exposure to 3-chloro-1-propene were determined in mice, rats, rabbits, guinea pigs and cats. They varied from 5,800 mg/m^3 to 22,500 mg/m^3, with the guinea pig being the most susceptible species (Lu et al., 1982).
4-Hour LC_{50}-values were reported to be 6,678 mg/m^3 for both mice and rats. Acute toxicity was reviewed by Rademaker et al. (1993).

Subacute and subchronic toxicity:
Studies have been carried out in mice, rats, rabbits and cats with exposures varying from 5 weeks to 6 months. Results were reviewed by Rademaker et al. (1993). The target organs were liver, kidneys and lungs and the central nervous system (see also special studies).
In a limited study Torkelson et al. (1959) exposed groups of rats, guinea pigs,

rabbits and dogs to 0 (air exposed), 0'(unexposed) or 9 mg/m^3 3-chloro-1-propene (DCV: 2 mg/m^3), 7 h/d and 5 d/w for 6 months. Half of the number of rats was kept for a 2 month recovery period. No compound related effects were observed on mortality, behaviour, growth, haematology, macroscopy, organ weight and histopathology. The slight central lobular degeneration observed in livers of female rats was reversible within 2 months. In a limited pilot study with rats and rabbits exposed to 25 mg/m^3 (DCV: 5 mg/m^3) for 35 days, following the protocol described above, adverse effects on liver and kidneys were observed in both species (Torkelson et al., 1959).
In a limited study with rabbits and cats exposed to 0 or 206 mg/m^3 3-chloro-1-propene, for 6 h/d and 6 d/w during 3 months (DCV: 0 and 44 mg/m^3) histopathological changes in the liver, kidney and lungs were observed in both species. Peripheral neuropathy was reported in rabbits. Exposure according to the same protocol of rabbits and rats to 17.5 mg/m^3 (DCV: 4 mg/m^3) for 5 months, did not result in adverse effects (Lu et al., 1982; He et al., 1985).
When groups of male and female mice and rats were exposed for 6h/d and 5d/w to 0, 3.1, 9.3, 31 or 62 mg/m^3 (DCV: 0, 0.6, 2, 6 or 11 mg/m^3) 3-chloro-1-propene for 3 months no effects were observed on clinical observations, body weight, haematology, clinical chemistry, urinalysis, organ weights, macroscopy and histopathology (Quast et al., 1982a). In a follow-up experiment mice and rats were exposed to 0, 155, 310 or 775 mg/m^3, according to the same protocol. Slight tubular degeneration was observed in the kidneys of high dose rats. Both the mid and high dose rats exhibited a slight increase in the cytoplasmic granularity and eosinophilic staining of the cortical epithelial cells when compared with the control rats. The NOAEL in this study was 155 mg/m^3 (DCV: 27 mg/m^3) (Quast et al., 1982b).

Reproduction:
Reproduction studies have not been carried out with 3-chloro-1-propene. However effects on male gonads have been examined *in vitro* as well as *in vivo*.
No effects on testosterone production were observed in cultured testes of foetal rats exposed to 3-chloro-1-propene (Warren, 1985).
No histopathological effects were observed on the testes after subchronic exposure of rats to concentrations varying from 9.3 to 775 mg/m^3 3-chloro-1-propene (Torkelson et al., 1959; Quast et al., 1982a, 1982b).
In a Russian study (Guseinov, 1982) male rats were exposed to 0, 0.29, 1.1 or 3.1 mg/m^3 (DCV: 0.03, 0.13 and 0.37 mg/m^3) 3-chloro-1-propene, for 4 h/d and 5 d/w for 4 months. Gonads were histologically assessed and sperm motility tests were carried out. At the mid and high dose groups histological changes and decreased sperm motility time were observed. At the lowest concentration only a

slight reduction in sperm motility time was seen.

Teratogenicity:
Maternal toxicity but no embryotoxicity was observed in a developmental screening test (modified Chernoff/Kavlock) with mice (Hardin, 1987; Hardin et al., 1987).
In a Russian study maternal and embryotoxic effects were seen in rats exposed for 4 h/d during pregnancy to 3.1 mg/m^3, but not in rats exposed to 0.29 mg/m^3 (Alizade et al., 1982).
No embryotoxic and teratogenic effects were observed in rats and rabbits exposed to concentrations up to 930 mg/m^3 (DCV: 273 mg/m^3) 3-chloro-1-propene for 7 h/d from day 6-15 or 6-18 of gestation, respectively (John et al., 1983).

Mutagenicity:
Mutagenicity assays in *Salmonella typhimurium* were positive, with and without metabolic activation. The mutagenic activity greatly decreased in the presence of an exogenous activating system. 3-Chloro-1-propene induced gene conversions in *Saccharomyces cerevisiae* but did not cause mutations in *Aspergillus nidulans*. The compound did not induce chromosome aberrations in rat liver cells. 3-Chloro-1-propene induced unscheduled DNA synthesis in HeLa cells (EPA, 1991; IARC, 1985).

Carcinogenicity:
Studies were carried out in mice and rats (gavage, dermal and i.p.). The oral mice and rat studies were not appropriate to evaluate because of high mortality in exposed animals (tumour development did not attribute to mortality) (NCI, 1977). Following i.p. administration, a slight increase in the incidence of lung adenomas was observed in mice. After repeated dermal administration of 3-chloro-1-propene, no skin tumours were observed in mice (IARC, 1985).

Special studies:
In a 4-month Russian study (with a 1-month recovery period) Guseinov (1983) studied the neurotoxicological effects of 3-chloro-1-propene in rats. The animals were exposed to 0.3, 1.1 or 3.1 mg/m^3 3-chloro-1-propene for 4 h/d and 5 d/w. At the highest dose body weight was reduced and the unconditioned reflex activity and cumulative threshold index (as a measure for CNS activity) were affected, while at 1.1 mg/m^3 (DCV: 0.13 mg/m^3) only a slight reversible reduction in unconditioned reflex activity was observed (Guseinov, 1983).
In a more reliable well performed study neurotoxicity was studied in rats

exposed to 0, 31, 155 or 310 mg/m^3 3-chloro-1-propene for 8 h/d, 5 d/w for 34 weeks. Nerve conduction velocities of the tail nerve and the width of landing foot-spread were determined at a 4-day interval period. A significant reduction of motor and sensory nerve conduction velocities and nerve action potentials were observed at 310 and 155 (less severe) mg/m^3 after 28 weeks when also clinical signs of neuropathy (i.e. weakness of hindlimbs and significantly extended landing foot-spreads) were seen. Motor distal latency was retarded in high dose rats during the last week of the study. The NOAEL for neurotoxicity in this study was 31 mg/m^3 (DCV: 7.38 mg/m^3) (Nagano et al., 1991).

Humans

Eye irritation was observed in 50% of the people exposed to a concentration of 155-310 mg/m^3. Nasal irritation and pulmonary discomfort were reported after exposure to 3-chloro-1-propene of about 77.5 mg/m^3 for 5 minutes (NIOSH).
Workers exposed to concentrations of 3-chloro-1-propene ranging from 3.1 to 350.3 mg/m^3 for 16 months developed liver damage, which was shown to be reversible after cessation of exposure (Hausler and Lenich, 1968).
Motor and sensory neurotoxic damage of the distal parts of the extremities was reported in workers exposed for 2.5 months to 6 years to concentrations varying from 2.6 - 6650 mg/m^3, with a mean concentration of 2966 mg/m^3. Another group of workers exposed to a range of 0.2 - 25.1 mg/m^3 for 1 to 4.5 years showed similar but less marked effects. No time-weighed average of the range of exposure concentrations was available. No significant dysfunction of liver, kidney or other organs was found (He et al., 1985).
Kasimova (1978) reported neurotoxic effects and an increased urinary excretion of noradrenaline, increased blood acetylcholine with a decreased cholinesterase activity in workers exposed to 6.4 - 140 mg/m^3 for 1 to > 5 years.

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Appendix 1C. 1,1-Dichloroethene (vinylidene chloride)

1,1-Dichloroethene is a volatile, colourless liquid which polymerizes readily and has a mild, sweet odour. It is used as a chemical intermediate in the manufacture of polyvinylidene copolymers for films and coatings (IARC, 1979; RECT, 1988).

Physical chemical properties

Chemical name:	1,1-dichloroethene
Synonyms:	vinylidene chloride; 1,1-dichloroethylene; VDC; 1,1-DCE
Structural formula:	$CH_2 = CCl_2$
Cas-#:	75-35-4
Molecular weight:	96.9
Vapour pressure:	78.6 kPa (at 25°C)
Odour threshold:	2000 - 5500 mg/m^3
Conversion factor:	1 ppm in air = 4 mg/m^3

(IARC, 1979)

Health effects

Animals

Acute toxicity:
Single 4-hour exposures to 1,1-dichloroethene vapours resulted in LC_{50} values of 460-820 mg/m^3 in mice, 12,800 - 41,200 mg/m^3 in rats and 6,640 mg/m^3 in hamsters (Rademaker et al., 1993).

(Sub)Chronic toxicity:
90-Day toxicity studies have been carried out in different species. These studies were reviewed by Rademaker et al. (1993).
Groups of rats, guinea pigs, rabbits, dogs and monkeys were continuously exposed for 90 days to 0, 20, 61, 101 or 189 mg/m^3 (Prendergast et al., 1967). No effects were observed on clinical signs, body weight and haematological and biochemical parameters. Mortality rates were significantly increased and body

weight was decreased in guinea pigs and monkeys exposed to 61, 101 or 189 mg/m^3. At histopathology focal necrosis, lymfocyte infiltration, hemosiderin metamorphosis and fatty metamorphosis were observed in the liver of high dose dogs and rats and in monkeys at the two highest dose levels. In high dose rats also hypertrophy of the tubular epithelium of the kidney was seen. The NOAEL in this study is 20 mg/m^3.
Hepatocellular fatty changes were observed in the midzonal region of the hepatic centre of rats exposed to 100 mg/m^3 (DCV: 18 mg/m^3) up to 18 months, in a 24-month toxicity and oncogenicity study. The observed changes were not progressing in time from 6 to 12 to 18 months and had disappeared after 24 months (Quast et al., 1986).

Reproduction:
In a 3-generation study in which rats received 0, 50, 100 or 200 mg/l 1,1-dichloroethene in their drinking water, survival was comparable in six sets of litters over three generations in control and exposed groups. The reproductive capacity was not affected (Nitschke et al, 1983).

Teratogenicity:
Pregnant rats and rabbits were administered 80-640 mg/m^3 (DCV 23-187 mg/m^3) for 7 h/d from day 6-15 or 6-18 of gestation, respectively. Embryotoxicity and foetotoxicity were observed at maternal toxic doses (rats: 320 mg/m^3 and rabbits: 640 mg/m^3) but teratogenic effects were not seen in neither rats or rabbits (Murray et al. 1979).

Mutagenicity:
Concentrations of 1,1-dichloroethene in air were mutagenic to *Salmonella typhimurium* with metabolic activation. Reverse mutations were induced in *Escherichia coli* with metabolic activation. 1,1-Dichloroethene was not mutagenic for V79 cells exposed to vapour *in vitro*, nor did it produce chromosomal aberrations *in vitro* in cultured Chinese hamster lung cells without metabolic activation. 1,1-Dichloroethene did not produce chromosomal aberrations in bone marrow cells of ICR mice given a single or i.p. treatment *in vivo*. 1,1-Dichloroethene was negative in a dominant lethal test in mice and rats. DNA alkylation and subsequent repair, which were specific to liver and kidney, were observed in mice and rats treated with 1,1-dichloroethene *in vivo*. The compound induced unscheduled DNA synthesis in isolated hepatocytes from phenobarbital-induced rats. (EPA, 1989; IARC, 1979; 1986; Short et al., 1977).

Carcinogenicity:
Studies were conducted with mice, rats and hamster. Negative results were obtained in oral studies with mice and rats and in inhalation studies with rats and hamsters (IARC, 1986).
Mice were exposed to 0 or 220 mg/m^3 for 6 h/d, 5 d/w for 12 months. In both treated males and females the incidence of hemangiosarcomas of the liver was marginally increased. Inflammatory, degenerative and mitotic changes occurred in the liver (Lee et al. 1977).
In another study with mice a treatment related increase in the incidence of kidney adenocarcinomas was observed in males (EPA, 1989).

Humans

Acute exposure to high concentrations (> 15,880 mg/m^3) of 1,1-dichloroethene in air results in CNS depression and narcosis. Repeated exposure to low concentrations is associated with liver and renal dysfunction (IARC 1986).
Skin contact with 1,1-dichloroethene causes irritation and eye contact causes conjunctivitis and transient corneal injury (IARC, 1986).
Two limited cohort studies were carried out in humans. The limitations of both studies did not permit an assessment of the carcinogenicity of 1,1-dichloroethene to humans (IARC, 1986).

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Appendix 1D. 1,2-Dichloropropane

1,2-Dichloropropane is a volatile colourless liquid, which is used as an insecticidal soil fumigant. The compound is also used as an industrial solvent for oil, fats, resins, waxes and rubber (ATSDR, 1989).

Physical and chemical properties

Chemical name:	1,2-dichloropropane
Synonyms:	propylene dichloride; propylene chloride; 2,3 dichloropropane; 1,2-D
Structural formula:	CH_3-CHCl-CH_2Cl
CAS-#:	78-87-5
Molecular weight:	112.99
Vapour pressure:	6.6 kPa (at 25°C)
Odour threshold:	1.2 mg/m^3
Conversion factor:	1 ppm in air = 4.8 mg/m^3

(ATSDR, 1989)

Health effects

Animals

Acute toxicity:
In mice and rats exposed for 8 to 10 hours, LC_{50}'s were found varying from 2,285 to 14,420 mg/m^3 (Rademaker et al., 1993).

Subacute and subchronic toxicity:
Subchronic toxicity studies were performed in mice, rats and rabbits by Nitschke (1988). Groups of B6C3F1 mice and F344 rats were exposed to 0, 69.3, 231 or 693 mg/m^3 (DCV: 0, 12.4, 41 and 123 mg/m^3, respectively) for 13 weeks, 5d/w and 6h/d. Groups of rabbits were exposed to 0, 693, 2,310 or 4,621 mg/m^3 (DCV: 0, 123, 410 and 825 mg/m^3) according to the same regimen. No effects were observed on mortality, clinical signs of toxicity, behaviour, haematology, clinical chemistry, urinalysis and macroscopic examination. In rabbits exposed to 693 mg/m^3 (DCV: 123 mg/m^3) red blood cell counts were decreased. Male rats

of the 693 mg/m^3 group showed reduced body weight. In the male rats exposed to 693 mg/m^3 slight inflammation of the larynx was seen. Very slight to slight degeneration of the olfactory mucosa in the nasal cavity in male and female rats of the 231 and 693 mg/m^3 groups was observed. In the same rats very slight to slight hyperplasia of the respiratory epithelium of the nasal cavity were observed. In only a few rats exposed to 69.3 mg/m^3 marginal hyperplasia was observed.
The effects on the olfactory mucosa were considered to have more toxicological relevance. The NOAEL on these effects found in rats is considered to be 69.3 mg/m^3 (DCV: 12.4 mg/m^3).
In a subacute pilot study of 2 weeks by Nitschke and Johnson (1983) rats were exposed to 0, 462, 1,386 or 4,621 mg/m^3 (DCV: 0, 74, 223 and 740 mg/m^3) for 6 h/d and 4.5 d/w. In rats exposed to 462 and 1,386 mg/m^3 slight to moderate degeneration of the nasal olfactory epithelium was observed, while severe degeneration was observed in the 4,621 mg/m^3 group.

Reproduction:
In a 2-generation rat study no effects were found on reproduction parameters up to concentrations of 100 mg/kg bw (EPA, 1991).
In a 10-week inhalation study with D-D, a formulation containing 55% 1,3-dichloropropene and 25% 1,2-dichloropropane, no adverse effects were observed on the fertility and reproductive performance of male and female rats (Linnet et al., 1988).
90-Day exposure to 1,2-dichloropropane at a relatively high dose of 500 mg/kg bw resulted in testicular degeneration and reduced sperm production, while these effects were not present at a dose of 250 mg/kg bw (ATSDR, 1989).

Teratogenicity:
1,2-Dichloropropane, administered to rabbits, caused foetal toxicity at a maternally toxic dose: delayed skeletal ossification of the skull bones. No teratogenic effects were found at doses of 125 mg/kg bw in rats and 150 mg/kg bw in rabbits. (ATSDR, 1989; EPA, 1991).

Mutagenicity:
1,2-Dichloropropane was mutagenic to *Salmonella typhimurium*. It induced mutations in *Aspergillus nidulans*. The compound was not mutagenic to *Streptomyces coelicolor*. No sex-linked recessive lethal mutations were induced in *Drosophila melanogaster* treated by injection or inhalation. (IARC, 1986).

Carcinogenicity:
Carcinogenicity was tested in mice and rats via oral exposure. In mice,

administered 125 or 250 mg/kg bw for 103 weeks, 5 d/w, a dose-related increase of hepatocellular tumours (combined adenomas and carcinomas) was observed. In rats, administered 62, 125 or 250 mg/kg bw, inconclusive results were obtained with females (poor survival). There was no effect on the tumour incidences in male rats. (IARC, 1986 and 1987).

Humans

Acute and repeated exposure of humans to unknown concentrations caused renal failure, acute liver damage, haemolytic anemia, disturbed coagulation and respiratory irritation. These effects could be reversed aftere cesssation of exposure (EPA, 1991).
Two cases of allergic dermatitis were attributed to 1,2-dichloropropane in workers in the plastics industry (EPA, 1991).
There were no data available on the carcinogenicity of 1,2-dichloropropane to humans (IARC, 1986 and 1987).

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Appendix 1E. 1,3-Dichloropropene

1,3-Dichloropropene is a chloroform-like, light coloured liquid with a sharp, sweet, penetrating and irritating odour, which is used as a soil fumigant (IARC, 1986).

Physical and chemical properties

Chemical name:	1,3-dichloropropene
Synonyms:	chloroallyl chloride; chloropropenyl chloride; DCP; 1,3-dichloropropylene
Structural formula:	$CHCl=CH-CH_2Cl$
CAS-#:	542-75-6; cis: 10061-01-5; trans: 10061-02-6
Molecular weight:	110.97
Vapour pressure:	cis: 5.7 kPa; trans: 4.5 kPa (at 25°C)
Conversion factor:	1 ppm in air = 4.5 mg/m^3

(IARC, 1986)

Health effects

Animals

Acute toxicity:
In rats exposed for 4 hours, LC_{50}'s were found varying from 2,700 to 3,310 mg/m^3 1,3-dichloropropene (Rademaker et al., 1993).

(Sub)chronic toxicity:
Subchronic and chronic studies were performed in mice, rats, guinea pigs, rabbits and dogs. These studies were reviewed by Rademaker et al. (1993).
In two studies (Dow Chemical, 1987a and 1987b), rats and mice were exposed for 5 d/w and 6 h/d to 22.7, 90.8 or 272.4 mg/m^3 Telone, containing >92% 1,3-dichloropropene (50% cis; 43% trans) for 2 years. DCV's were 4, 16 and 49 mg/m^3. No effects were observed on mortality, behaviour and urinalysis. Effects in mice exposed to 272 mg/m^3 Telone were decreased body weights, haematological changes, increased relative brain weights, decreased relative heart and kidney weights, hyperplasia of the non-glandular stomach, benign lung

tumours, uterine nodules, decreased vacuolation of the liver, dilatation and hypercellularity of the larynx and chronic inflammation of the urinary bladder. In both male and female mice exposed to 272 and 90.8 mg/m^3, hyperplasia of the epithelium of the urinary bladder and degeneration of the olfactory epithelium were observed. In rats exposed to 272 mg/m^3 1,3-dichloropropene, decreased total protein and albumin concentrations, degeneration of the olfactory epithelium and fibrosis of the underlying mucosa, and a slightly increased incidence of primary benign subcutaneous fibromas were observed. In females exposed to 272 mg/m^3 and 90.8 mg/m^3, a roughened opaque surface of the urinary bladder was seen. The NOAEL in mice and rats was considered to be 22.7 mg/m^3 (DCV: 4 mg/m^3).
Lomax et al. (1989) exposed mice and rats to 0, 21, 84 and 251 mg/m^3 1,3-dichloropropene (49.5% cis; 42.6% trans) for 2 years, 5 d/w and 6 h/d. Duration corrected values were 0, 4, 15 and 45 mg/m^3, respectively. No effects were observed on clinical signs of toxicity, mortality, haematology, clinical chemistry and histopathological changes in the major organs, including the respiratory tract. In male and female mice, exposed to 251 mg/m^3, body weights were decreased. In mice exposed to 84 and 251 mg/m^3, exposure-related changes were seen in the urinary bladder and the nasal tissue. Effects: hyperplasia of the urinary bladders, hypertrophy and hyperplasia of the respiratory epithelium and/or degeneration of the olfactory epithelium. In male mice of the 251 mg/m^3 group, an increase in the incidence of benign lung tumors (bronchioloalveolar adenomas) and hyperplasia and hyperkeratosis in the forestomach were reported. In rats exposed to 251 mg/m^3 1,3-dichloropropene, body weights were decreased and degeneration of the olfactory epithelium was observed.
The NOAEL found in mice for hypertrophy and hyperplasia of the nasal respiratory epithelium and for epithelial hyperplasia and inflammation of the urinary bladder, is considered to be 21 mg/m^3 (DCV: 4 mg/m^3).

Reproduction:
In a 2-generation reproduction study, rats were exposed for 6h/d and 5 d/w to 0, 45, 136 and 409 mg/m^3 Telone (containing >92% 1,3-dichloropropene). No effects were found on reproductive parameters up to the highest concentration of 409 mg/m^3 (DCV: 73 mg/m^3) (ACT, 1993).

Teratogenicity:
Rats were exposed to 0, 91, 272 or 545 mg/m^3 1,3-dichloropropene from day 6-15 of gestation. Embryotoxic effects were observed at maternal toxic doses. No teratogenic effects were found. After exposure of pregnant rabbits to the same concentrations during gestation day 5-18 maternal toxicity was observed at the

two highest concentrations, but no embryotoxicity or teratogenic effect were seen. (WHO, 1990; ACT, 1993).

Mutagenicity:
Both the cis- and the trans-isomer of 1,3-dichloropropene were mutagenic to *Escherichia coli*, *Salmonella typhimurium* TA1535 and TA100, but not to strains TA1537 and TA98. The addition of glutathione reduced the mutagenic effects of 1,3-dichloropropene on *Salmonella* TA100 and TA1535. In cultured hamster ovary cells chromosomal aberrations were observed in presence of metabolic activation. The incidence of sister chromatid exchanges was significantly increased in cultured hamster cells. Sex-linked recessive lethal mutations were induced in *Drosophila melanogaster*. *In vivo*, a micronucleus test in CD-1 mice and a host-mediated assay were negative. (IARC, 1986; ACT, 1993).

Carcinogenicity:
Carcinogenicity was tested in mice and rats (oral and inhalatory).
Inhalation studies in mice and rats were available in which animals were exposed for 2 years. No increase in malignant tumours was observed at any concentration (Dow Chemical, 1987a; 1987b; Lomax et al., 1989; Stott et al., 1988).
In the oral studies (NTP, 1985), 1,3-dichloropropene was administered to mice and rats by gavage. The survival of control male mice was very low, which made this study inadequate for evaluation. In female mice, 1,3-dichloropropene produced dose-related increases in the incidences of malignant tumours of the urinary bladder and forestomach. In the rat study, an increase in the incidence of malignant forestomach tumours was observed only in males of the highest dose group. It should be noted, that in both oral studies a testcompound was used containing 1% epichlorohydrin, which is carcinogenic to experimental animals and has been shown to produce forestomach tumours in rats. (IARC, 1986).
Subcutaneous administration in mice resulted in inconclusive results.

<u>Humans</u>

Accidental exposure of humans to 1,3-dichloropropene caused headache, chest discomfort, mucous membrane irritation, dizziness, nausea and vomiting. Two years after exposure, headache, chest discomfort and malaise were still reported in 50% of the exposed people.
Common eye and skin injuries associated with 1,3-dichloropropene exposure were conjunctivitis and burns.
In workers exposed to 4.5 mg/m^3 1,3-dichloropropene (time-weighed-average), sperm counts and percentages of normal sperm were normal.

Two cases of malignant histiocytic lymphoma were reported in firemen previously treated for acute syptoms after exposure to 1,3-dichloropropene. (IARC, 1986).

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Appendix 1F. 1,1,1-Trichloroethane

1,1,1-Trichloroethane is a volatile colourless liquid, which is used as a solvent for adhesives, and in metal degreasing, pesticides, printing inks, among other uses. The compound is also extensively used in household products (ATSDR, 1990).

Physical and chemical properties

Chemical name:	1,1,1-trichloroethane
Synonyms:	chloroethene; chlorotene; methylchloroform; methyltrichloromethane; trichloromethylmethane
Structural formula:	CCl_3-CH_3
CAS-#:	71-55-6
Molecular weight:	133.4
Vapour pressure:	16.4 kPa (at 25°C)
Odour threshold:	650 mg/m^3
Conversion factor:	1 ppm in air = 5.4 mg/m^3

(ATSDR, 1990; IARC, 1979)

Health effects

Animals

Acute toxicity:
In mice and rats, exposed to 1,1,1-trichloroethane for 6 to 7 hours, LC_{50}'s were found varying from 55,000 to 77,000 mg/m^3 (ATSDR, 1990).

(Sub-)Chronic toxicity:
Studies were performed in mice, rats, rabbits, guinea pigs, gerbils, dogs and monkeys (cited in: Rademaker et al., 1993).
In a well performed study, Quast et al. (1988) exposed groups of rats and mice to 0, 810, 2,700 or 8,100 mg/m^3 1,1,1-trichloroethane, for 24 months, 5 d/w and 6 h/d. Duration corrected values were 145, 482 and 1,446 mg/m^3. In mice no adverse exposure-related effects were observed in any exposure group. In rats no effects were observed on mortality, clinical signs of toxicity, haematology,

urinalysis, clinical chemistry, organ weights and gross pathology. The body weights of female rats exposed to 8,100 mg/m^3 were decreased throughout the study. Very slight hepatic effects (accentuation of the lobular pattern, hepatocytes in the portal region smaller, with altered cytoplasmic staining) were seen in the liver of 8,100 mg/m^3 exposed male and female rats necropsied at 6, 12 and 18 months.
The NOAEL found in rats was considered to be 2,700 mg/m^3 (DCV: 482 mg/m^3).

Reproduction:
In a 2-generation study with mice, no effects were observed on reproduction parameters up to an oral dose of 1,000 mg/kg bw (Lane et al., 1982).
In male rats exposed for 6 months to 2,700 mg/m^3 (DCV: 563 mg/m^3), no histopathological effects were observed on the testes (Torkelson et al., 1958).

Teratogenicity:
Mice and rats were exposed to 4,700 mg/m^3, 7 h/d during gestation day 6-15. No maternal, embryonal or foetal toxicity was observed. No teratogenic effects were observed in both mice and rats (Schwetz et al., 1975).

Mutagenicity:
Ames tests with *Salmonella typhimurium* and *Escherichia coli* were negative. 1,1,1-Trichloroethane did not induce gene mutations in *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*. A chromosomal aberration test in Chinese hamster cells without metabolic activation was positive. A gene mutation test in L5178Y mouse lymphoma cells was negative without metabolic activation. 1,1,1-Trichloroethane did not induce SCE in Chinese hamster cells. No sex-linked recessive lethals were induced in *Drosophila*. No chromosomal abnormalities were found in bone marrow of rats inhalatory exposed for 52 weeks to 1,1,1-trichloroethane. Micronucleus tests in mice were negative. No dominant lethals were observed in mice orally exposed.
A host-mediated assay with *Saccharomyces cerevisiae* in mice was negative. DNA damage/repair tests in *Escherichia coli* or *Bacillus subtilis* were mainly negative. No unscheduled DNA synthesis was induced in rats and mouse hepatocytes and in HeLa cells. DNA repair tests in rat hepatocytes were negative.
(WHO, 1992; EPA, 1990).

Carcinogenicity:
Inhalation and oral studies were performed in mice and rats. Inhalatory exposure of mice and rats to DCV's of 145, 482 and 1,446 mg/m^3, for two years, did not

cause an increase in tumour incidence (Quast et al., 1988). In male mice, administered 2,807 and 5,615 mg/kg bw for 78 weeks, liver tumours were observed. In rats, administered 750 and 1,500 mg/kg bw for 78 weeks, no treatment related tumour response was seen (IARC, 1979).

Special studies:
In two 3-month studies the effects of 1,1,1-trichloroethane on the biochemistry of the central nervous system of gerbils were examined (Rosengren et al., 1985; Karlsson, 1987). The animals were exposed to 0, 380, 1,134 or 5,400 mg/m^3. No effects were seen on brain weight and total protein. In different brain areas of exposed animals DNA concentrations were significantly decreased. Also effects were observed on the astroglial cell population in the cerebral cortex at the two highest concentrations. The interpretation and significance of these effects are unclear. There is no indication for a specific neurotoxic effect at the concentrations used in this study.

Humans

Acute inhalatory exposure of humans caused mild eye irritation, nervous system effects, cardiac arrythmia, mild liver effects, unconsciousness and decreased blood pressure. The effects of long-term exposure are not known.
Exposure of the skin of volunteers caused reversible effects: mild irritation to burning sensations. (ATDSR, 1990; WHO, 1992).
There were no data available on the carcinogenicity of 1,1,1-trichloroethane to humans.

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APPENDIX 2: ABBREVIATIONS

CE	=	continuous exposure (24 h/d and 7 d/w)
CNS	=	central nervous system
DCV	=	duration corrected value (in mg/m^3)
LC_{50}	=	concentration which is lethal for 50% of the test animals
LOAEL	=	lowest observed adverse effect level (in mg/m^3)
MPC	=	maximum permissible concentration (in $\mu g/m^3$ or mg/m^3)
NOAEL	=	no observed adverse effect level (in mg/m^3)
SCE	=	sister chromatid exchange
UF	=	uncertainty factor

APPENDIX 3: IARC CLASSIFICATION

The IARC categorization reflects the strength of the evidence of carcinogenicity of an agent, derived from studies in humans and in experimental animals and from other relevant data.

Group 1: The agent is carcinogenic to humans.

This category is used only when there is sufficient evidence of carcinogenicity in humans.

Group 2A: The agent is probably carcinogenic to humans.

This category is used only when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Exceptionally, an agent may be classified into this category solely on the basis of limited evidence of carcinogenicity in humans or of sufficient evidence of carcinogenicity in experimental animals strengthened by supporting evidence from other relevant data.

Group 2B: The agent is possibly carcinogenic to humans.

This category is generally used for agents for which there is limited evidence in humans in the absence of sufficient evidence in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in humans or when human data are nonexistent but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence or no data in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data, may be placed in this group.

Group 3: The agent is not classifiable as to its carcinogenicity to humans.

Agents are placed in this category when they do not fall into any other group.

Group 4: The agent is probably not carcinogenic.

This category is used for agents for which there is evidence suggesting lack of carcinogenicity in humans together with evidence suggesting lack of carcinogenicity in experimental animals. In some circumstances, agents for which there is inadequate evidence of or no data on carcinogenicity in humans but evidence suggesting lack of carcinogenicity in experimental animals, consistently and strongly supported by a broad range of other relevant data, may be classified in this group.

Reference: IARC (1987) IARC monographs on the evaluation of carcinogenic risks to humans, Overall evaluation of carcinogenicity: An updating of IARC monographs volumes 1 to 41. Suppl.7.