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HPV Challenge Program

TEST PLAN

For

CAS# 68411-72-3 Chlorinated C2 Streams

CAS Number:	68411-72-3
Sponsor	The Dow Chemical Company Midland, Michigan
Date of Submission:	2 December 2004
Date of last Update:	2 December 2004

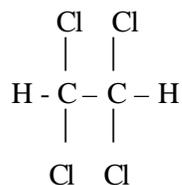
I. JUSTIFICATION FOR SURROGATE CHEMICAL

CAS 68411-72-3 Chlorinated C2 Stream is a compilation of process intermediate streams produced at several manufacturing facilities that consists of chlorinated 2-carbon chemicals. Though somewhat variable, the largest volume components of CAS 68411-72-3 are 1,1,2,2-tetrachloroethane (approximately 64%) and 1,1,2-trichloroethane (approximately 15%). The remaining CAS 68411-72-3 Chlorinated C2 Stream is composed of a number of chlorinated ethanes with no single component present at more than a few percent of the total stream. In general, the overall mammalian and environmental toxicity, with the possible exception of acute oral toxicity, of 1,1,2,2-tetrachloroethane is similar to or in excess of that of 1,1,2-trichloroethane. A previous evaluation of toxicity data as part of the process of setting an internal Dow Chemical Company Industrial Hygiene Guideline for time-weighted occupational exposure to 1,1,2,2-tetrachloroethane established a guideline value (0.1 ppm) which is 100-fold lower than the ACGIH TLV and OSHA PEL for 1,1,2-trichloroethane (10 ppm).

1,1,2,2-Tetrachloroethane will be used as a “surrogate” chemical for defining the toxicity of CAS 68411-72-3 Chlorinated C2 Stream as part of the HPV program based upon its high volume percent of the stream and its mammalian and environmental toxicity. Significantly, 1,1,2,2-tetrachloroethane has also been evaluated previously as part of the OECD SIDS program (<http://www.oecd.org>). It was judged to be “of low priority for further work” at SIAM 15 (October, 2002) indicating the adequacy of its database for coverage of spectrum of OECD SIDS endpoints and lack of significant concern over its toxicological characteristics. Information presented in the present HPV Test Plan and related IUCLID Robust Study Summaries were drawn heavily from the complimentary OECD SIDS documentation.

II IDENTITY**A. Identification of the Surrogate Substance**

CAS Number:	79-34-5
IUPAC Name:	1,1,2,2-Tetrachloroethane
Molecular Formula:	C ₂ H ₂ Cl ₄
Molecular Weight:	167.85
Synonyms:	Ethane, 1,1,2,2- tetrachloro; acetylene tetrachloride; 1,1,2,2-TCE

Figure 1. Structure of the Compound

The compound is a colorless to pale-yellow liquid in the pure or neat state. Because of its structure, 1,1,2,2-TCE is nearly insoluble in water, has a high vapor pressure, and high partition coefficient (log K_{ow}).

B. Purity/Impurities/Additives

As noted, 1,1,2,2-TCE represents approximately 64% of CAS 68411 Chlorinated C2 Stream and will be used as the surrogate chemical for the stream.

C. Physico-Chemical properties**Table 1** Summary of physico-chemical properties

Property	Value
Physical state	colorless to pale-yellow liquid
Melting point	-43.8°C to -36 °C
Boiling point	146.5 °C
Vapour pressure	4.126 hPa to 6.5 hPa at 20° C 7 hPa at 25° C
Water solubility	2.9 g/l at 20° C
Partition coefficient n-octanol/water (log value)	2.39 (measured)

Based on the fugacity model level 1 of Mackay, 1,1,2,2-tetrachloroethane released to the environment will partition mainly into the atmosphere.

III DEVELOPMENT OF ROBUST SUMMARIES AND STUDY SCORING CRITERIA

The Dow Chemical Company has chosen to use the IUCLID (International Uniform Chemical Information Database) format for preparation of robust summaries for the HPV program. Because many of the fields in the IUCLID database program are outside the scope of the HPV program, these fields are typically left blank in the IUCLID robust summary. Scoring of studies from

company files or from the literature for reliability to fulfill the testing requirement for each endpoint used a system similar to that published by Klimisch et al. (1997). Studies were given a score of “1” if the data could be considered valid without restriction based on the completeness of the protocol and adequate details in reporting. Studies were given a score of “2” if the data and study design could be considered scientifically valid to address the endpoint but with restrictions due to lack of various technical or reporting details or deviations from current OECD guidelines. Studies were given a score of “3” if their conduct was not acceptable and “4” if there wasn’t enough information present to assign a reliability rating. However, a study receiving a score of “4” could provide supplementary information that could be used to address the endpoint in a weight of evidence evaluation in the absence of other data.

IV TEST ENDPOINT RESULTS FOR ANALOGUES

Evaluation of the data for 1,1,2,2-TCE leads to the conclusions regarding (1) the quantity of data that currently exists to adequately represent the toxicological and ecological profile of the compound, (2) the concurrence and similarity among the existing data for the various HPV/SIDS endpoints (3) available data from the compound used to adequately represent the various HPV/SIDS endpoints that may not have been subjected to the same level of testing, and (4) utilization of these data to support the conclusion that no further testing is needed for most of the HPV/SIDS endpoints. A summary of the data on each of the HPV/SIDS endpoints for the compound follows.

A. Physical Chemistry

Melting Point

IUCLID 2.1: 1,1,2,2-TCE is a colorless to pale-yellow liquid in the neat or pure state with a melting point of -43.8°C to -36 °C. Because the melting point is well-documented in peer-reviewed literature and databases, **no additional testing is required.**

Boiling Point

IUCLID 2.2: The boiling point for 1,1,2,2-TCE is likewise well-documented. **No additional testing is required.**

Vapor Pressure

IUCLID 2.4: The vapor pressure for 1,1,2,2-TCE has been well-documented in published literature and chemical handbooks. The experimental value is 4.126 hPa to 6.5 hPa at 20° C, and 7 hPa at 25° C. This data is consistent with the physical/chemical nature and suggests a high degree of volatility. **No additional testing is required.**

Partition Coefficient

IUCLID 2.5: The measured value for partition coefficient is 2.39. Such a structure is consistent with low water solubility, and which by definition would be indicative of a high log K_{ow} value. **No additional testing is required.**

Water Solubility

IUCLID 2.6.1: Measured data indicates that 1,1,2,2-TCE is marginally soluble in water (2.9 g/l). The higher log K_{ow} also supports the reported data for water solubility. Sufficient data exist for this endpoint to characterize water solubility for the compound. **No additional testing is required.**

B. Environmental Fate

Photodegradation

IUCLID 3.1.1: Organic substances containing chlorine, if primarily present in the atmospheric compartment and if their lifetime is long enough can reach the stratosphere and decompose through photolysis and other chemical reaction (e.g. with OH°). Chlorine atoms can then participate in the catalytic ozone destruction cycles. The atmospheric lifetime is too short to enable a significant fraction of the compound emitted to reach the stratosphere. **No additional testing is required.**

Stability in Water (Hydrolysis)

IUCLID 3.1.2 Data reported indicate that 1,1,2,2-TCE is expected to hydrolyze under environmental conditions to form trichloroethylene.

In one study, the half-lives at 25 °C and pH 7 and 9 based on a second order elimination reaction was estimated to be 102 days and 1.02 days respectively

(Cooper *et al.*, 1987). In another study, half lives of 575 days at pH 6.05, 36 days at pH 7.01 and 6.6 to 12.8 hours at pH 9 were calculated at 25°C in pure water. The hydrolysis yielded trichlorethylene as the major if not sole product. In pond water sediments the half-life was found to be 29.1 days at 25° C. (Haag and Mill, 1988).

An environmental hydrolysis half-life (25°C, pH 7) of 0.4 year was also reported by Jeffers *et al.* (1989).

Data indicate that 1,1,2,2-TCE will undergo hydrolysis to form trichlorethylene (see corresponding assessment documents for trichloroethylene CAS No 75-01-6 at <http://ecb.jrc.it/esis>) under neutral and alkaline conditions. Hydrolysis increases with increasing pH. At 25°C, half lives of 36 days to 102 days were estimated under neutral pH while half lives from 6.6 hours to 1.02 days were determined under alkaline conditions (pH 9). **No additional testing is required.**

Environmental Transport

IUCLID 3.3.1: Based on the fugacity model level 1 of Mackay, 1,1,2,2-TCE released to the environment will partition mainly into the atmosphere.

1,1,2,2-TCE has an average atmospheric lifetime of 91 days. It has negligible impact on stratospheric ozone and greenhouse effect and minor contribution to the formation of tropospheric ozone. Observed intermediate products formed during the atmospheric oxidation are phosgene, C(=O)ClH and dichloroacetylchloride. Decomposition of phosgene and C(=O)ClH in the atmosphere should lead to the formation of hydrochloric acid and carbon dioxide by hydrolysis in atmospheric water. Dichloroacetylchloride will form hydrochloric acid and dichloroacetic acid which is removed from the atmosphere by rain water. A theoretical distribution of 1,1,2,2-TCE has been calculated at 20°C using the fugacity model level 1 of Mackay with a vapor pressure of 6 hPa and a solubility of 2.9 g/l. Approximately 92.26 % of 1,1,2,2-TCE released into the environment will enter the atmosphere, 7.46% the water compartment, 0.14% soils and 0.14% sediments. 1,1,2,2-TCE that is released in the water will be removed rapidly by volatilization.

Although the values obtained using this model should not be regarded as quantitative, the model results are consistent with the properties of the compound (i.e., low water solubility and high volatility). **No additional testing is required.**

Biodegradation

IUCLID 3.5: Biodegradation is the conversion of a chemical by microorganisms in the environment into its simpler components and ultimately to carbon dioxide and its other constituent molecules. Chemicals are classified as readily biodegradable by the Organization for Economic Development (OECD) guidelines if there is a 70% degradation of dissolved organic carbon within a 10-day period during a typical 28-day laboratory protocol. It is expected to hydrolyze under alkaline conditions and to biodegrade under anaerobic conditions. It is not likely to bioaccumulate and is not expected to adsorb to suspended solids, sediments and soils.

1,1,2,2-TCE is persistent under aerobic conditions. It is not readily biodegradable (0% after 28 days in an OECD 301C test, CSCL, 1992). No significant biodegradation was found in an aerobic degradability test with adaptation utilizing biochemical oxygen demand dilution water containing 5 mg of yeast extract per liter as synthetic medium and 5 ppm and 10 ppm of 1,1,2,2-TCE. The assay utilized a 7-day static incubation at 25°C in the dark followed by three weekly subcultures and employed settled domestic wastewater as the microbial inoculum (Tabak *et al.*, 1981). 1,1,2,2-TCE undergoes degradation under anaerobic conditions. In an anaerobic biodegradability test using a methanogenic laboratory-scale continuous flow fixed-film reactor supplied with 27 µg/l of 1,1,2,2-TCE, 97% steady state removal was achieved after 4 month of operation. The production of 1,1,2-trichloroethane was reported as a result of 1,1,2,2-TCE transformation (Bower *et al.*, 1983).

The rates of disappearance of halogenated ethanes were studied in anoxic sediment-water systems. A half-life of 6.6 days was found for 1,1,2,2-TCE (Jafvert and Wolfe, 1987). Reductive dechlorination or reductive hydrogenolysis is a common transformation of 1,2-carbon chlorinated aliphatics under methanogenic conditions. The production of trichloroethylene and 1,1,2-trichloroethane was reported. The products of abiotic and anaerobic transformations of 1,1,2,2-TCE were determined under methanogenic conditions. 1,1,2,2-TCE degradation started without lag with municipal digester sludge. 1,1,2-trichloroethane, trans-1,2-dichloroethene and cis-1,2-dichloroethene were products of anaerobic transformation while trichloroethylene resulted from abiotic degradation. Trichloroethylene was subsequently further transformed to vinyl chloride and ethene. 1,1,2-Trichloroethane

was reportedly converted to 1,2-dichloroethane, then further degraded to chloroethane and ethane (Chung Chen *et al.*, 1996). **No additional testing is required**

C. Ecotoxicity

Acute Fish Toxicity

IUCLID 4.1: Several acute toxicity studies have been conducted on fish species.

The results of the tests summarized in the following table show that 1,1,2,2-TCE is slightly toxic to freshwater and marine species. **No additional testing is required**

Species	Duration	Results mg/l	Remarks	Methods	Reference	Reliability
<i>Pimephales promelas</i>	72h	LC ₅₀ = 20.4 (20-20.9)	Flow-through, lake water, measured concentrations	US EPA-660/3-75-009, 1975	Ahmad <i>et al.</i> , 1984	1
<i>Oryzias latipes</i>	48h	LC ₅₀ = 31	semi-static test	Japanese Industrial Standard (JIS K 0102-1986-71)	CSCL Japan, 1992	1
<i>Jordanella floridae</i>	96h	LC ₅₀ , semi-static = 26.8 LC50, flow-through = 185 (16.4-20.8)	Flow through and semi-static tests, Dechlorinated Lake Superior water, no aeration nominal conc. for semi-static test, measured conc. for flow-through test.	US EPA-660/3-75-009, 1975	Smith <i>et al.</i> , 1991.	2
<i>Lepomis macrochirus</i>	96h	LC ₅₀ = 20-22	Static test, well water, capped jars, nominal concentrations	US EPA-660/3-75-009, 1975	Buccafusco <i>et al.</i> , 1984	3
<i>Poecilia reticulata</i>	7 days	LC ₅₀ = 36.7	Semi-static test, daily renewal, vessels covered with glass, Unmeasured concentration	Alabaster, JS. And Abram F.S.H. (1964)	Köneman, 1981	2
<i>Cyprinodon variegatus</i> (saltwater)	96h	LC ₅₀ = 12 (4.7-32)	Static test, naturel salt water, open system Nominal concentrations	US EPA-660/3-75-009, 1975	Heitmuller <i>et al.</i> , 1981	3

Aquatic Invertebrates

IUCLID 4.2: The results of the tests conducted for determining the acute toxicity of 1,1,2,2-TCE to invertebrates are summarized in the following table:

Species	Duration	Results mg/l	Remarks	Methods	References	Reliability
<i>Daphnia magna</i>	48h	EC ₅₀ unfed = 23 EC ₅₀ fed = 25 LC ₅₀ unfed, fed = 62,1 LC ₅₀ fed = 57	static test, no renewal, no aeration, stoppered glass containers, measured concentrations.	ASTM (1980)	Ahmad <i>et al.</i> , 1984	1
<i>Daphnia magna</i>	48h	EC ₅₀ = 9.3 (6.8-13)	Static, unaerated conditions, not completely filled closed containers, nominal concentrations	US EPA-660/3-75-009, 1975	Leblanc, 1980	2
<i>Mysidopsis bahia</i> (Marine species)	48h	EC ₅₀ = 9.02	Secondary reference	US EPA-660/3-75-009, 1975	Leblanc, 1984	4

Based on the above studies, 1,1,2,2-TCE can be considered as slightly toxic to freshwater and marine invertebrates. **No additional testing is required.**

Aquatic Plants

IUCLID 4.3: Four toxicity studies employing algae were identified: three on freshwater algae and one on a marine alga. Only one study could be considered as valid with restriction.

Results are given in the following table:

Species	Duration	Results mg/l	Remarks	Methods	References	Reliability
<i>Scenedesmus subspicatus</i>	72h	EC ₅₀ = 47 EC ₁₀ = 9.8	Closed system. measured concentration (at the beginning of the test)	OCDE 201 modified for volatile substance	Behechti <i>et al.</i> , 1995	2
<i>Scenedesmus subspicatus</i>	72h	EC ₅₀ = 76 (31.4-188)	Unmeasured concentrations		EPA, 1978	4
<i>Selenastrum capricornutum</i>	96h	EC ₅₀ = 136	Secondary reference		Leblanc, 1980	4
<i>Skeletonema costatum</i> (Sea water)	96h	EC ₅₀ = 6.44	Secondary reference	US EPA-660/3-75-009, 1975?	Leblanc, 1984	4

No additional testing is required.

D. Toxicological Data

Acute Oral Toxicity

IUCLID 5.1.1: Oral LD₅₀ values for 1,1,2,2-TCE in rats were reported to be between 250 and 800 mg/kg (Smyth *et al.*, 1969; Henschler, 1972 ; Izmerov *et al.*, 1982). **No additional testing is required**

Acute Inhalation Toxicity

IUCLID 5.1.2: Inhalation, LC₅₀ values for 1,1,2,2-TCE of 8.6 mg/l (1200 ppm) and 4.5 mg/l (640 ppm) were reported following a 4-hour exposure in rats (Schmit *et al.*, 1980) and an 8-hour exposure in mice (Pbhkova, 1966), respectively. **No additional testing is required**

Acute Dermal Toxicity

IUCLID 5.1.3: Dermal LD₅₀ values for 1,1,2,2-TCE in rabbits were reported to be 3990 mg/kg (Schmid, 1979) and 4900-8140 mg/kg (Smyth *et al.*, 1969).

No additional testing is required

Skin Irritation

IUCLID 5.2.1: 1,1,2,2-TCE was reported to be irritating to rabbit skin (Smyth *et al.*, 1969). **No additional testing is required.**

Eye Irritation

IUCLID 5.2.2 1,1,2,2-TCE was irritating to eyes (Truhaut *et al.*, 1974). **No additional testing is required**

Repeated-Dose Toxicity

IUCLID 5.4: Numerous studies on repeated exposure toxicity for 1,1,2,2-TCE have been conducted on 1,1,2,2-TCE over the last four decades; however, there are no conventional studies available that allow a clear NOAEL identification and many of these studies are not of guideline quality. However most of the studies gave consistent results allowing target organs to be identification and the establishment of a LOAEL for the inhalation exposure route and possibly for the oral route.

All available data are presented in the following two tables.

Repeated exposure toxicity studies by oral route

Species	Test conditions	Results	Effect level	Reliability	Reference
Rat	5 Fisher 344 males/group, gavage 104 and 208 mg/kg/d for 3 weeks ; no hematology and blood biochemistry ; urinalysis of several enzymes; histopathology of main organs	<u>High dose</u> : all rats died or euthanasied before end of study ; lethargy, diarrhea, breathing difficulties. <u>Low dose</u> : normal growth; normal urinalysis ; liver enlargement and cytoplasmic vacuolisation of hepatocytes ; no changes in kidney, testis and other organs	NOAEL and LOAEL <104 mg/kg/d	2	Butcher, 1996
Rat	50 male or female Osborne-Mendel/group; gavage for 78 weeks , 5d/w; followed by a 32 week observation period ; males : TWA 62 or 108 mg/kg ; females : TWA	<u>High dose</u> : increased mortality; decreased bodyweight ; no increase incidence of non-neoplastic lesions <u>Low dose</u> : decreased	NOAEL and LOAEL <62 (M) and 43 (F) mg/kg/d	2	NCI, 1978

	43 or 76 mg/kg/d; Control : 40males or females; Histopathology on main organs; no blood exams	bodyweight ; no increase incidence of non-neoplastic lesions			
Rat	10 males/group ; gavage for 6 weeks 8 or 20 mg/kg/d; gavage for 27 weeks 3.2 or 8 mg/kg/d; no hematology; blood biochemistry of certain enzymes; histopathology of main organs	<u>High dose</u> : damages reported in liver, kidneys, testes and thyroid; <u>Low dose</u> : minor hepatic effects	NOAEL <3.2 mg/kg/d LOAEL = 3.2 mg/kg/d	3	Gohlke <i>et al</i> , 1977
Mouse	50 male or female B6C3F1 - /group; gavage for 78 weeks , 5d/w; followed by a 12 week observation period; TWA 142 or 284 mg/kg /d Control : 40males or females; Histopathology on main organs; no blood exams	Dose-related increase in mortality ; moderate dose-related decrease in bodyweight ; No incidence increase of non-neoplastic lesions in any organ/tissues examined	NOAEL and LOAEL <142 mg/kg/d	2	NCI, 1978

Repeated exposure toxicity studies by the inhalation route

Species	Test conditions	Results	Effect level	Reliability	Reference
Rat	20-21 male Wistar and Brown Norway/ group; control groups : 10-14 males; whole body exposure ; 5h/d, 5d/w for 13 weeks to concentration fluctuating from 108 to 516 ppm; biochemistry : creatinine, ASAT, ALAT ; urinalysis : proteins; organs examined at necropsy : kidney	- Bodyweight: decreased - Biochemistry : no effect on ASAT, ALAT and creatinine at any time for both strains - Urinalysis : proteinuria was lower in exposed rats of both strains versus their respective controls - Histopathology: minimal glomerulotoxicity in both strains (only visible with electronic microscopy).	NOAEL and LOAEL: <108-516 ppm (742-3545 mg/m ³)	2	Danan <i>et al.</i> , 1983
Rat	110 Sprague Dawley females were divided into one control group and 1 treated groups and exposed whole body by inhalation for 15 weeks to 0 or 560 ppm (single tested concentration), 5-6h/d, 5d/wk. Blood cytology and macroscopic and microscopic examination of liver, kidney, adrenals, ovaries, uterus; Also hepatic DNA neosynthesis	- Transient CNS depressing effects during first exposures. - Bodyweight decreased during the last weeks of exposure - Slight decrease of hematocrit, red and white cells - Hepatotoxicity: increased liver weight, hyperplasia and increased DNA biosynthesis with hepatocellular lesions were seen during the first weeks ; these effects regressed after 19 exposures and disappeared after 39 exposures. - All other organs examined were normal.	NOAEL and LOAEL <560 ppm (3850 mg/m ³)	2	Truffert <i>et al.</i> , 1977
Rat	210 males equally divided in one exposed and one control group ; single dose tested : 13.3 ± 0.24 mg/m ³ (1.94 ppm); whole body exposure 4h/d, 5d/wk for 9 months ; Blood exams comprised: cytology, SGOT, SGPT, BSP excretion, serum albumin, serum globulin, total fat in the liver and kidney, ACTH activity of pituitary gland. SHD, alc Phosphatase and unspecified Esterases. Organ exams: hypophysis, brain, thyroid, thymus, lung, heart, liver, spleen, kidney, adrenals and testes.	- Mortality: no significant difference between treated and control animals. - Bodyweight gain : minimal effect (less than 5% decrease) - Hematology: some increase in leukocyte count after 110 days. No data on WBC were mentioned thereafter. - Clinical biochemistry: serum globulin, fat content of the liver increased in treated animals; the ACTH activity in hypophysis was decreased at interim and final sacrifices (65 % to 13 %). - Organ weights : decrease relative weight of thyroid - Histopathology: mild liver changes; follicular	NOAEL <1.94 ppm (13.3 mg/m ³) LOAEL : Approx. 1.94 ppm (13.3 mg/m ³)	3	Schmidt <i>et al.</i> , 1972

		desquamation in thyroid; no changes in other organs.			
Rat	6 exposed and 2 controls male rats; whole body exposure 2h/d, 2d/wk for 4 weeks at 9000 ppm (single tested concentration). Exams : hemoglobin, blood cells counts; histology of liver and main organs (not specified)	All animals survived; hypermotility followed by CNS depression including almost complete loss of consciousness ; no effect on bodyweight ; tendency to decreased hemoglobin and red blood cell counts; congestion and fatty degeneration of the liver. Congestion of other main organs.	NOAEL and LOAEL <9000 ppm (61830 mg/m ³)	3	Horiuchi <i>et al.</i> , 1962
Mouse	9 male mice whole body exposed to 7000 ppm (single tested concentration) 2h/d, once a week for 4 weeks . Exams : Histology of liver and main organs (not specified)	All nine mice died within the 4 week test period Slight to moderate congestion and fatty degeneration of the liver ; congestion of other organs	NOAEL and LOAEL <7000 ppm (48100 mg/m ³)	3	Horiuchi <i>et al.</i> , 1962
Rabbit	Rabbits exposed to 15 ppm , 3-4 h/d for 7-11 month	Slight effects on liver	NOAEL and LOAEL <15 ppm (100 mg/m ³)	4	Patty, 1994
Rabbit	Rabbits exposed to 100-160 ppm , 8-9 h/d for 4 weeks	No effect ; no typical organ changes were found	NOAEL => 160 ppm (1100 mg/m ³)	4	Patty, 1994
Cats	Cats exposed to 100-160 ppm, 8-9 h/d for 4 weeks	No effect ; no typical organ changes were found	NOAEL >/= 160 ppm (1100 mg/m ³)	4	Patty, 1994
Monkey	A male cynomolgus maccaca was whole body exposed to 1000-4000 ppm , 2h/d, 6d/wk for 9 months Exams: hematology, urinalysis; histology of liver, heart, lung, kidney, pancreas, spleen, testis.	- diarrhea, anorexia; almost complete unconsciousness occurred at 2000-4000 ppm 20min to 1h after exposure to vapors. - Minimal bodyweight changes - Slight increase in white blood cells and decrease of red blood cells and hemoglobin. - Urine no changes in albumin and urobilinogen - Slight to moderate congestion and fatty degeneration of the liver. Congestion of spleen. No changes in other organs.	NOAEL and LOAEL <1000ppm (6870 mg/m ³)	3	Horiuchi <i>et al.</i> , 1962

Data obtained in several species of test animals have identified the liver as the most sensitive target organ of 1,1,2,2-tetrachloroethane on repeated exposure by inhalation or by the oral route. The central nervous system and possibly the hematopoietic

system appear also as target organs but at much higher dose levels. A definitive NOAEL was not established although one old and generally unreliable study in cats and rabbits reported a NOAEL of 160 ppm (1100 mg/m³) which is in contradiction with all other studies (Patty, 1994) and the experience in humans (ATSDR, 1994). Based on a relatively limited study (Schmidt *et al.*, 1972), the inhalation LOAEL in rats is expected to be approximately 2 ppm (14 mg/m³) following exposure for 9 months. The LOAEL by the oral route is expected to be 3 mg/kg/day based on a limited gavage study of over 27 weeks duration (Gohlke *et al.*, 1997). **No additional testing is required.**

Genetic Toxicity: Gene Mutations and Chromosome Aberrations (IUCRID 5.5 and 5.6):

As shown in the Table below, the many gene mutation *in vitro* assays of 1,1,2,2-TCE have given mixed results with positive and negative responses in the presence or absence of metabolic activation often in the same testing systems. A chromosomal segregation assay conducted in yeast was positive; however, a chromosomal aberration assay conducted in Chinese Hamster ovary cells was negative. An increase in Sister Chromatid Exchanges was, however, noted in the latter study. DNA repair assays conducted in bacteria as well as UDS DNA repair assays conducted on rat and mouse hepatocyte primary cultures have all been negative. 1,1,2,2-TCE was reported to bind covalently with DNA in several tissues of rats and mice *in vitro*; however, neoplastic transformation assays utilizing BALB/c 3T3 cultures, were active only when using a special amplification procedure. The significance of the latter finding is unclear.

Genotoxicity and cell transformation *in vitro*

Test system	End point	Result		Reference	Reliability
		- S9	+S9		
<i>Salmonella typhimurium</i> . TA 1535, 1537, 98, 100	Reverse mutations	+	+	Eriksson <i>et al.</i> , 1992	2
<i>Salmonella typhimurium</i> . TA 97, 98, 100, 102	Reverse mutations	+	+	Mersch-Sundermann, 1989	2
<i>Salmonella typhimurium</i> TA 1535, 1537, 98, 100	Reverse mutations	-	-	Milman <i>et al.</i> , 1988	2
<i>Salmonella typhimurium</i> TA 100	Reverse mutations	-	-	Warner <i>et al.</i> , 1988	4
<i>Salmonella typhimurium</i> TA 97, 98, 100, 104	Reverse mutations	+	+	Strobel and Grummt, 1987	2

<i>Salmonella typhimurium</i> TA 1535, 1537, 98, 100	Reverse mutations	-	-	Mitoma <i>et al.</i> , 1984	2
<i>Salmonella typhimurium</i> . TA 1535, 1537, 98, 100	Reverse mutations	-	-	Haworth <i>et al.</i> , 1983	2
<i>Salmonella typhimurium</i> . TA 1535, 1537, 1538,98, 100	Reverse mutations	-	-	Nestman <i>et al.</i> , 1980	2
<i>Salmonella typhimurium</i> TA 1530, 1535, 1538	Reverse mutations	+	NT	Rosenkranz, 1977	4
<i>Salmonella typhimurium</i> TA 1530, 1535, 1538	Reverse mutations	+	NT	Brem <i>et al.</i> , 1974	2
<i>Saccharomyces cerevisiae</i> D7 and XV185-14C	Reverse mutation	-	NT	Nestman and Lee, 1983	2
<i>Salmonella typhimurium</i> BA13 and BAL13	Forward mutation	-	-	Roldan-Arjona <i>et al.</i> , 1991	2
<i>Saccharomyces cerevisiae</i> D7 and D4	Mitotic gene conversion and recombination	+	NT	Callen <i>et al.</i> , 1980	2
<i>Aspergillus nidulans</i> P1 and 35	Chromosome malsegregation	+	NT	Crebelli <i>et al.</i> , 1988	2
Chinese hamster ovary WB1	Chromosome aberration	-	-	Galloway <i>et al.</i> , 1987	2
Chinese hamster ovary WB1	Sister Chromatide Exchanges	+	+	Galloway <i>et al.</i> , 1987	2
<i>Bacillus subtilis</i> H17 and M45	DNA repair damage	-	-	Matsui <i>et al.</i> , 1989	2
<i>Escherichia coli</i> B/r WP2s	DNA repair damage	-	+	DeMarini <i>et al.</i> , 1992	2
<i>Escherichia coli</i> Pol A1-/Pol A+-	DNA repair damage	-	NT	Rosenkranz, 1977	4
<i>Escherichia coli</i> Pol A1-/Pol A+-	DNA repair damage	-	NT	Brem <i>et al.</i> , 1974	2
<i>Escherichia coli</i> ?	DNA repair damage	+?	+?	Upton <i>et al.</i> , 1984	4
<i>Escherichia coli</i> PQ 37	SOS-repair system (SOS Chromotest)	-	-	Mersch-Sundermann <i>et al.</i> , 1989	2
F344 rat hepatocyte primary culture	UDS – DNA repair	-	NT	Williams <i>et al.</i> , 1989	2
Osborne-Mendel rat hepatocyte primary culture	UDS – DNA repair	-	NT	Milman <i>et al.</i> , 1988	2
B6C3F1 mouse hepatocyte primary culture	UDS - DNA repair	-	NT	Milman <i>et al.</i> , 1988	2
Osborne-Mendel rat hepatocyte primary culture	UDS – DNA repair	-	NT	Williams, 1983	2
B6C3F1 mouse hepatocyte primary culture	UDS - DNA repair	-	NT	Williams, 1983	2
Wistar rat liver, kidney, lung, stomach cells	DNA covalent binding	+	NT	Colacci <i>et al.</i> , 1987	2

BALB/c mouse liver, kidney, lung, stomach cells	DNA covalent binding	+	NT	Colacci <i>et al.</i> , 1987	2
BALB/c 3T3 mouse Clone A31	Cell transformation - with amplification	+	+	Colacci <i>et al.</i> , 1993	2
BALB/c 3T3 mouse Clone A31	Cell transformation - without amplification - with amplification	- +	NT NT	Colacci <i>et al.</i> , 1992	2
BALB/c 3T3 mouse Clone A31	Cell transformation - without amplification - with amplification	- +	- +	Colacci <i>et al.</i> , 1990	2
BALB/c 3T3 mouse Clone C1 1-13	Cell transformation - without amplification	-	NT	Milmann <i>et al.</i> , 1988	2
BALB/c 3T3 mouse Clone C1 1-13	Cell transformation - without amplification	-	NT	Tu <i>et al.</i> , 1983 Little AD, 1983	2

1,1,2,2-TCE has also been reported to give mixed results in a variety of *in vivo* genotoxicity assays (see tabulated data below). An ambiguous effect was reported in a rat chromosome aberration study, it failed to induce clastogenic effects in three different studies in *Drosophila* and was reported as negative in a Dominant Lethal Mutation Assay in male rats. It did not induce unscheduled DNA in hepatocytes of mice treated orally although it was shown to have covalently bound with macromolecules, including DNA, from various tissues of mice and rats exposed by the interperitoneal route. In an initiation/promotion assay where gamma-glutamyl-transpeptidase was used as a putative preneoplastic indicator, 1,1,2,2-TCE has displayed both intrinsic initiation and promoting potentials.

Genotoxic and related effects in Animals

Assay	Test conditions	Result	Reference	Reliability
Rat cytogenetic assay	Chromosome aberration determination after 5 days exposure by inhalation to 349 mg/m ³ (50 ppm)	Ambiguous	McGregor, 1980 (quoted in CICAD, 1998)	4
Dominant lethal assay in rat	determination of DL effect after 5 day exposure by inhalation to 349 mg/m ³ (50 ppm)	Negative	McGregor, 1980 (quoted in CICAD, 1998)	4
<i>Drosophila melanogaster</i> eye mosaic assay	Treatment of Leiden Standard larvae by inhalation (500-1000 ppm) Determination of interchromosomal mitotic recombination	Negative	Vogel and Nivard, 1993	2
<i>Drosophila melanogaster</i> Sex linked recessive lethal mutations	Adult male Canton S treated by feeding and injection for testing SLRL at the meiotic and postmeiotic germ cell stage.	Negative	Woodruff <i>et al.</i> , 1985	2
<i>Drosophila melanogaster</i> Sex linked recessive lethal mutations	No data available	Negative	McGregor, 1980(quoted in CICAD, 1998)	4
Mouse hepatocytes Unscheduled DNA Synthesis	Male and female B6C3F1 mice received single gavage at doses of 0, 50, 200, 600 and 1000 mg/kg. UDS determined 2 or 12 h after.	Negative	Mirsalis <i>et al.</i> , 1989	2
Rat and mouse DNA Covalent Binding	Male Wistar rats and BALB/c mice. i.p. single injection of C14 labeled test material. DNA, RNA and protein binding determined in liver, kidney, lung, stomach sampled 22h after treatment	Positive	Colacci <i>et al.</i> , 1987	2
Rat liver Foci Assay	Partly hepatectomised Osborne-Mendel male rats administered 200 mg/kg p.o. / 7 weeks. GGT+ as indicator	Positive	Milman <i>et al.</i> , 1988	2

With the possible exception of the equivocal results for chromosomal aberrations in rats by inhalation (McGregor, 1980 reported by CICAD, 1998), the weight of evidence from *in vivo* and *in vitro* studies suggests that 1,1,2,2-TCE displays a variable degree of genotoxic potential, acting through a mechanism that results in gene conversion and possible chromosomal effects. The potential genotoxic potential of 1,1,2,2-TCE has been well characterized. **No additional testing is required**

Carcinogenicity

IUCLID 5.7: Oral rat and mouse carcinogenicity bioassays of 1,1,2,2-TCE have been conducted by the National Cancer Institute (NCI, 1978).

In the rat study, groups of 50 animals/per sex/dose were fed 62 or 108 mg/kg/day (males) and 43 or 76 mg/kg/day (females) 1,1,2,2-TCE for 78 weeks. No statistically significant excess of neoplastic lesions were observed in both sexes although 2 hepatocellular carcinomas and 1 neoplastic nodule were observed out of 49 males compared *versus* 0/20 males in vehicle controls.

In the mouse study, groups of 50 males and 50 females were administered 142 or 284 mg/kg/day 1,1,2,2-TCE via oral gavage 5 days/week for up to 78 weeks followed by a 12 week holding period. There was a dose related increase in mortality and a slight dose related decrease in bodyweights. Large statistically significant excesses of hepatocellular carcinomas were found in males (6%, 26% and 90% in control, low and high dose group, respectively) and in females (0%, 63% and 91% in control, low and high dose group, respectively). These tumors appeared earlier in mice of the high dose group.

Theiss *et al.*, 1977 conducted a pulmonary tumor response bioassay in Strain A mice which have a high spontaneous incidence of pulmonary adenomas. 1,1,2,2-TCE was injected interperitoneally at 80, 200 or 400 mg/kg/day for 15 to 21 weeks. Lung tumor incidences were increased in treated groups *versus* the control but the differences were not statistically significant. Although the incidence in the high dose group neared statistical significance ($p = 0.059$), the biological significance of this result was limited due to poor survival (5/20 *versus* 15/20 in controls).

Liver tumours induced by some chemicals in mice appear to be of limited relevance to man for the assessment of hazard in human (Hughes *et al.*, 1994). However, the mechanism of liver tumour induction in mice exposed to 1,1,2,2-TCE has not been established. Review of the carcinogenicity and related mechanistic data in mice available on all the potential metabolites of 1,1,2,2-TCE indicate that some of the tumors induced by these metabolites may not be relevant to humans or that humans are less susceptible than rodents (Hughes *et al.*, 1994). This is notably the case for dichloroacetic acid, the primary metabolite of 1,1,2,2-TCE. The toxicity profile of

dichloroacetic acid has been reviewed by ECETOC (1994). **No additional testing is required**

Reproductive Toxicity

IUCLID 5.8: There have been no guideline reproductive toxicity testing of 1,1,2,2-TCE . However, a study evaluating the fertility of exposed males and several repeated dose toxicity studies which have included gonadal histopathological evaluation have provided a relatively thorough evaluation of the potential reproductive toxicity of 1,1,2,2-TCE. The data reported in the following table indicate that this chemical does not selectively affect the reproductive system.

Reproductive toxicity

Species	Test conditions	Results	Effect level	Reliability	Reference
<i>INHALATION</i>					
Rat	<i>One generation study</i> 9 months male parental exposure 4h/d, 5d/wk to 13.3 mg/m ³ (1.94 ppm)	no effect on male fertility no effect on offspring born from exposed father + unexposed mother	NOAEL : > 13.3 mg/m ³ (males)	2	Schmidt <i>et al.</i> , 1972
Rat	<i>Sub-chronic toxicity study</i> Females exposed 15 weeks 560 ppm,(3850 mg/m ³) 5-6h/d, 5d/wk; included gonadal examination.	No effect on female sexual organs.	NOAEL >3850 mg/m ³ (females)	2	Truffert <i>et al.</i> , 1977
Rat	<i>Dominant Lethal assay</i> Males exposed 5 days at 349 mg/m ³ (50 ppm)	Small statistical increase in one type of sperm abnormalities (result considered by authors as being of questionable biological significance)	NOAEL <349 mg/m ³ ?? (males)	4	Mc Gregor, 1980 (quoted in CICAD, 1998)
Rat	<i>Sub-acute toxicity study</i> Males exposed 4 to 10 days at 13.7 mg/m ³ (2 ppm) ; included gonadal examination.	Conflicting results : After 10 days : no effect After 4 days : some atrophy of seminal vesicles, decrease of spermatogenesis	NOAEL - 10 d exp: > 13.7 mg/m ³ - 4 d exp : < 13.7 mg/m ³	3	Golke and Schmidt, 1972
Monkey	<i>Chronic toxicity study</i> One single male cynomolgus maccaca , whole body exposed to 6870 - 27480 mg/m ³ (1000-4000 ppm) , 2h/d, 6d/wk for 9 months; included gonadal examination.	No significant histological changes in testis	NOAEL >27480 mg/m ³ (male)	3	Horiuchi <i>et al.</i> , 1962
<i>ORAL</i>					
Rat	<i>Chronic toxicity study</i> Animals treated up to 108 mg/kg/d (males) and 76 mg/kg/d (females) during 78 weeks; included gonadal examination.	No significant histological changes in male and female sexual organs	NOAEL: > 108 mg/kg/d (males); > 76 mg/kg/d (females)	2	NCI, 1978
Rat	Sub-chronic toxicity study Male rats treated at 3.2, 8 and 20 mg/kg/d during 17 weeks and at 3.2 and 8 mg/kg/d during 27 weeks; included gonadal examination.	At the highest doses : - Testis : High incidence of interstitial edema ; clumped sperm ; epithelial cells present in the tubular lumen ; partial necrosis and totally atrophied tubules , giant cells two-row germinal epithelial cells ; disturbed spermatogenesis - In parallel there were damages in liver, kidney and thyroid gland.	NOAEL : = 3.2 mg/kg/d (males)	3	Golke <i>et al.</i> , 1977
Rat and	Sperm motility and vaginal	Male mice:	NOAEL: 175	2	NTP, 1993

Mouse	cytology evaluation, 10 males and 10 females F344 rats and B6C3F1 mice were exposed via dosed feed for 13 weeks. Doses were 0, 37, 75 and 150 mg/kg feed for rats and 0, 175, 700 and 1400 mg/kg feed for mice. The endpoints include body weight, testicular, epididymal and caudal weights, sperm motility, sperm number/g caudal tissue, and testicular spermatid head count for male and body weight and estrual cyclicity for female animals	<p>↓ terminal body weight at 700 and 1400 mg/kg feed</p> <p>↓ epididymal sperm motility at 1400 mg/kg feed</p> <p>Female mice:</p> <p>↓ terminal body weight at 700 and 1400 mg/kg feed</p> <p>↑ average estrous cycle length at 1400 mg/kg feed</p> <p>Male rats:</p> <p>↓ terminal body weight at 75 and 150 mg/kg feed</p> <p>↓ epididymal sperm motility at all tested doses</p> <p>Female rats:</p> <p>↓ terminal body weight at 75 and 150 mg/kg feed</p> <p>↑ frequency of diestrus stage at 150 mg/kg feed</p>	<p>mg/kg feed for male and female mice</p> <p>LOAEL: 37 mg/kg feed for male rats</p> <p>NOAEL: 37 mg/kg feed for female rats</p>		
Mouse	<i>Chronic toxicity study</i> Males and females treated up to 284 mg/kg/d during 78 weeks; included gonadal examination.	No significant histological changes in male and female sexual organs	NOAEL: > 284 mg/kg/d (males and females)	2	NCI, 1978

Reproductive effects have been observed only in experimental animals exposed to oral or inhalation levels of 1,1,2,2-TCE causing significant decreases in bodyweights and/or other signs of toxicity (mainly liver damage). Furthermore, the data describing adverse findings on reproductive organs were not reproducible at much higher dose levels and longer exposure periods within a study (i.e., lacked dose-response) or were not reproducible. **No additional testing is required.**

Developmental Toxicity

IUCLID 5.9: There are no guideline developmental toxicity studies available on 1,1,2,2-TCE; however, several studies reporting fetotoxicity, only at maternally toxic dose levels, have been reported. No external abnormalities were reported. Decreased fetal bodyweight and/or increased resorptions were reported in range-finding studies in rats and mice exposed via their food during gestation at doses equal or higher than those that induced maternal toxicity (increased mortality or decreased bodyweight gain, respectively) (NTP, 1991a, b) (reliability : 2). The data from these two studies are presented in the following table.

Range finding developmental toxicity studies

Species	Test conditions	Results	Effect level	Reliability	Reference
Rat	8-9 Sprague-Dawley pregnant females/group were exposed via dosed feed at 0, 30, 90, 180, 270 and 360 mg/kg/d from GD4 to GD20. The in-life endpoints included: body weight gain food consumption, clinical signs and mortality. At necropsy on GD20, number of implantation sites, resorptions, dead fetuses and live fetuses, and uterine weight were recorded.	<u>Maternal toxicity:</u> clinical signs at ≥ 270 mg/kg/d, decrease body weight gain at ≥ 90 mg/kg/d, decrease food consumption at all dose levels. <u>Foetotoxicity:</u> decrease fetal weight at ≥ 90 mg/kg/d, total resorptions in 4/9 dams at 360 mg/kg/d, respectively.	NOAEL for maternal and fetal toxicity: 30 mg/kg/d	2	NTP 1991a
Mouse	5-11 CD-1 pregnant females/group were exposed to feed dosed at 0, 0.5, 1.0, 1.5, 2.0 and 3.0% from GD6 to GD15. The in live endpoints include body weight gain food consumption, clinical signs and mortality. At necropsy on GD17, number of implantation sites, resorptions, dead fetuses and live fetuses, and uterine weight were recorded.	<u>Maternal toxicity:</u> clinical signs at $\geq 1.0\%$, maternal mortality at $\geq 1.0\%$, decrease body weight gain at $\geq 1.0\%$, decrease food consumption at $> 1.0\%$, abnormal liver at $> 0.5\%$, <u>Foetotoxicity:</u> total resorptions in 2/8, 1/1 and 1/2 dams at 1.0, 1.5 and 2.0% mg/kg/d, respectively.	NOAEL for maternal toxicity $< 0.5\%$ NOAEL for fetal toxicity = 0.5%	2	NTP, 1991b

Two additional studies of limited value in assessing the potential developmental toxicity of 1,1,2,2-TCE have also been reported. In the first, 1,1,2,2-TCE was administered by the interperitoneal route during gestation in mice of two different strains. There were no effects reported at a dose level of 300 mg/kg. At a dose level of 700 mg/kg some embryotoxic effects (increased post-implantation lost versus controls) and a slight increase in total malformations (7% versus 4% in controls) were found in one strain while no effects were evident in the other strain. No detailed data on the incidence of specific malformations were provided. Fetal bodyweights were similar in controls and all treatment group mice. No maternal data were provided. The authors concluded that the test material was a weakly teratogenic compound by the interperitoneal route (Schmidt 1976). In the second, Schmidt *et al.* (1972) did not report adverse developmental effects in offspring born from unexposed dams mated with male rats previously exposed by inhalation to 13.3 mg/m³ 1,1,2,2-TCE vapor, 2h/day, 5d/week, for 9 months.

While no specific guideline-quality study of developmental toxicity is available, there is no convincing evidence of a developmental toxicity potential of 1,1,2,2-TCE even under extreme dosing conditions in limited studies. Significantly, the OECD SIDS program review of 1,1,2,2-TCE (<http://www.oecd.org>) judged the adequacy of the database for this chemical, including developmental toxicity data, and judged it to be “of low priority for further work” at SIAM 15 (October, 2002). **No additional testing is proposed**

V CONCLUSIONS

A substantial quantity of data currently exist to adequately represent the toxicological and ecological screening profile of 1,1,2,2-TCE. In agreement with the conclusions of the OECD SIDS review of this chemical at SIAM 15 (October, 2002), **it is concluded that no further testing is warranted.**

V REFERENCES

- ACGIH (1991) Documentation of the TLVs and BEIs 6th Edition-ACGIH, Cincinnati, OH, 45240, USA.
- Ahmad, N., Benoit, D., Brooke, L., Call, D., Carlson, A., Defoe, D., Huot, J., Moriarty, A., Richter, J., Shuba, P., Veith, G. and Wallbridge, C. (1984) Aquatic toxicity tests to characterize the hazard of volatile organic chemicals in water: A toxicity data summary Part 1 and 2. n° PB84-141506 of the US Environmental Research Lab.-Duluth, MN.
- Atkinson, R. (1994) Gas phase tropospheric chemistry of organic compounds. J. Phys. Chem. Monography N° 2.
- ATSDR (1994) 1,1,2,2-TETRACHLOROETHANE. US DHHS, PHS, Agency for Toxic Substances and Disease Registry.
- Barrows, M.E. *et al.* (1978) Bioconcentration and elimination of selected water pollutants by the bluegill sunfish (*Lepomis macrochirus*). Exposure Hazard Assess Chem., (Pap. Symp 379-392).
- Behechti, A. *et al.* (1995) Toxicity of chlorinated alkanates on the alga *Scenedesmus subspicatus* in a closed test vessel. Fresenius Envir.Bull.4 : 148-153.
- Blum, D.J.W. and Speece, R.E. (1991) Quantitative structure-activity relationships for chemical toxicity to environmental bacteria. Ecotoxicology and Environmental Safety, 22, 198-224.
- Bouwer, E.J. and McCarty, P.L. (1983) Transformations of 1- and 2-carbon halogenated aliphatic organic compounds under methanogenic conditions. Applied and Environmental Microbiology, 1286-1294.
- Bouwer, E.J. and McCarty, P.L. (1984) Modeling of trace organics biotransformation in the subsurface. Ground Water, 22, 433-440.
- Bouwer, E.J., Wright, J.P. and Cobb, G.D. (1986) Anoxic transformation of trace halogenated aliphatics. Toxic Hazard Wastes, Proc. Mid-Atl Ind Waste Conf, 18th.
- Brem, H., Stein, A.B., and Rosenkantz, H.S. (1974) The mutagenicity and DNA-modifying effect of Haloalkanes. Cancer Res. 34, 2576-2579.
- Bua (1989) 1,1,2,2-TETRACHLOROETHANE. GDCh-Advisory Committee on Existing Chemicals of Environmental relevance (BUA) BUA report N° 29, VCH, Weinheim.
- Buccafusco, R.J. *et al.* (1981) Acute toxicity of priority pollutants to bluegill (*Lepomis macrochirus*). Bull. Environm. Contam. Toxicol., 26, 446-452.
- Bucher, J.R. (1996) NTP Technical Report on Renal Toxicity studies of selected Halogenated Ethanes administered by gavage to F344/N Rats, NTP -Toxicity Report Series N° 45. NIH Publication 96-3935, Feb. 1996, US- DHHS, PHS, NIH.
- Call, D.J. *et al.*, 1985. Fish subchronic toxicity prediction model for industrial organic chemicals that produce narcosis. Environ. Toxicol. Chem., 4, 335-341.

- Callen DF, Wolf CR and Philpot RM, 1980, Cytochrome P450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in *Saccharomyces cerevisiae*. *Mut. Res.* 77, 55-63
- Chiou, C.T. *et al.* (1980) Evaporation of solutes from water. *Environment International*, 3, 231-236.
- Chiou, C.T., Peters, L.J., Freed, V.H. (1979) A physical concept of soil-water equilibria for nonionic organic compounds. *Science*, 206, 831-2.
- Chen, C., Puhakka, J.A., and Ferguson, J.F. (1996) Transformations of 1,1,2,2-tetrachloroethane under methanogenic conditions. *Environ. Sci. Technol.*, 30, 542-547.
- CICAD, (1998) WHO-IPCS 1,1,2,2-tetrachloroethane. World Health Organisation, Geneva.
- Colacci, A. *et al.* (1987) The Covalent Binding of 1,1,2,2-tetrachloroethane to macromolecules of rat and mouse organs. *Teratogenesis, Carcinogenesis and Mutagenesis*, 7, 465-474.
- Colacci, A. *et al.* (1993) Induction of a malignant phenotype in BALB/c 3T3 cells by 1,1,2,2-tetrachloroethane. *Int. J. Oncol.* 2, 937-947.
- Colacci, *et al.* (1990) In vitro transformation of BALB/c 3T3 cells by 1,1,2,2-tetrachloroethane. *Jpn J. Cancer Res.*, 81, 786-792.
- Collacci, A. *et al.* (1992) Initiating activity of 1,1,2,2-tetrachloroethane in two-stage BALB/c 3T3 cell transformation. *Cancer Letters* 64, 145-153.
- Cooper, W.J., Mehran, M. and Joens, J.A. (1987) Abiotic Transformations of Halogenated Organics 1: Elimination Reaction of 1,1,2,2-tetrachloroethane and Formation of 1,1,2-Trichloroethene. *Environ. Sci. Technol.*, 21, 1112-1114.
- Crebelli, R., Benigni, R., Franekic, J., Conti, I. and Carere, A. (1988) Induction of chromosomal malsegregation by halogenated organic solvents in *Aspergillus nidulans*: unspecific or specific mechanism. *Mut. Res.* 201, 401-411.
- CSSL. (1992) Biodegradation and bioaccumulation. Data of existing chemicals. Chemicals Inspection and Testing Institute, Japan, p.2-12.
- Curtis, C. *et al.* (1982) Evaluation of a bacterial bioluminescence bioassay as a method for predicting acute toxicity of organic chemicals to fish. *Aquatic Toxicology and Hazard Assessment, Fifth Conference.* ASTM STP 766, 170-178.
- Danan, M. *et al.* (1983) Glomérulopathies et solvants organiques des graisses: revue de la littérature et étude expérimentale animale avec le tétrachloroéthane 1-1-2-2. *Arch. Mal. Prof.* 44, 235-245.
- DeMarini, D.M. and Brooks, H.G. (1992) Induction of prophage lambda by chlorinated organics: Detection of some single-species/single site carcinogens. *Env. Mol. Mutagenesis*, 19, 98-111.
- Derwent *et al.* *Atmospheric environment* vol.32, N°14/15, pp. 2429-2441.
- Dilling, W.L. *et al.* (1975) Evaporation rates and reactivities of methylene chloride, chloroform, 1,1,1-trichloroethane, trichloroethylene, tetrachloroethylene and other chlorinated compounds in dilute aqueous solutions. *Environ. Sci. Technol.*, 9, 833-838.

- Dilling, W.L., (1977). Interphase transfer processes II: Evaporation rates of chloro methanes, ethanes, ethylenes, propanes and propylenes from dilute aqueous solutions, Comparisons with theoretical predictions. *Environmental Science and Technology*, 11(4), 405-409.
- ECETOC, 1994, Trichloroethylene, Assessment of human carcinogenic hazard. Technical Report N° 60, ECETOC, Brussels, Belgium.
- Eriksson, C. and Brittebo, E.B. (1991) Epithelial binding of 1,1,2,2-tetrachloroethane in the respiratory and alimentary tract. *Arch. Toxicol.*, 65, 10-14.
- Eriksson, *et al.* (1991) A strategy for ranking environmentally occurring chemicals, Part VI: QSARs for the mutagenic effects of halogenated aliphatics. *Acta Chemica Scand.*, 45, 935-944.
- Galloway, S.M. *et al.* (1987) Chromosome Aberrations and Sister Chromatide Exchanges in Chinese Hamster Ovary Cells: Evaluations of 108 Chemicals. *Environ. and Mol. Mutagenesis*, 10, Suppl 10, 1-175.
- Gohlke, R. and Schmidt, P. (1972) Zur subakuten Wirkung geringer Konzentrationen Chlorierter äthane ohne und mit zusätzlicher äthanolbelastung auf Ratten. II Histologische, histochemische und morphometrische Untersuchungen. *Int. Arch. Arbeitsmed.*, 30, 299-312.
- Gohlke, R., Schmidt, P. and Bahmann, H. (1977) 1,1,2,2-Tetrachloroäthan mit Hitzebelastung im Tierexperiment - morphologischer Ergebnisse. *Z. Gesamte Hyg. IHRE Grenzgeb.*, 20, 278-282.
- Haag, W.R. and Mill, T. (1988) Effect of a subsurface sediment on hydrolysis of haloalkanes and epoxides. *Environmental Science and Technology*, 22, 658-663.
- Haider, K. (1980) Degradation of chlorinated aliphatic and aromatic compounds by aerobic and anaerobic soil microorganisms. *Comm. Eur. Communities, Report EUR 6388, Environm. Res. Programme*, 200-204.
- Hallen, R.T. *et al.* (1986) Transformation of chlorinated ethanes and ethenes by anaerobic microorganisms. Extended abstracts, 192th National meeting of the American Chemical Society, Anaheim, CA.
- Halpert, J. and Neal, R.A. (1981) Cytochrome P450 dependant metabolism of 1,1,2,2-tetrachloroethane to dichloroacetic acid *in vitro*. *Biochem. Pharmacol.*, 30, 1355-1368.
- Hawkins, W.E. (1989) Development of carcinogenesis bioassay models: response of small fish species to various classes of carcinogens. Gulf Coast Research Laboratory, Ocean Springs, Mississippi.
- Haworth, S., Lawlor, T., Mortelmans, K., Speck, W. and Zeiger, E. (1983) Salmonella mutagenicity test results for 250 chemicals. *Environ. Mutagenesis, Suppl. 1*, 3-142.
- Heitmuller, P.T. *et al.* (1981) Acute toxicity of 54 industrial chemicals to sheepshead minnows (*Cyprinodon variegatus*). *Bull. Environm. Contam. Toxicol.*, 27, 596-604.
- Henschler, D. (1972) Gesundheitsschädliche Arbeitsstoffe, Toxikologisch-arbeitsmedizinische Begründung von MAK-Werten. Verlag Chemie, Weinheim, (quoted in BUA report N°29).

- Horiuchi, K., Horiguchi, S., Hashimoto, K., Kadowaki, K. and Aratake, K. (1962) Studies on the industrial tetrachloroethane poisoning (2). *Osaka City Medical Journal*, 8, 29-38.
- Hughes, K., Meek, M.E. and Caldwell, I. (1994) 1,1,2,2-tetrachloroethane: Evaluation of Risks to health from environmental exposure in Canada. *Environ. Carcino. and ecotox revs.*, C12, 483-491.
- IARC (1999) "IARC Monographs on the evaluation of carcinogenic risks to humans. "1,1,2,2-tetrachloroethane ", Vol 71, 817-827.
- INRS (1987) Fiche toxicologique 36, *Cah. Notes Doc.*, 126, 47-50.
- IPCC (2000) *Climate Change 2000, The Science of Climate Change, Contribution of Working Group I to the third Assessment Report of the Intergovernmental Panel on Climate Change*. In press.
- Izmerov, N.F., Sanotsky, I.V. and Sidorov, K.K. (1982) *Toxicometric Parameters of Industrial Toxic Chemicals Under Single Exposure*, Moscow, Centre of International Projects, GKNT, 107, 1982 (quoted in BUA report N°29, 1989).
- Jafvert, C.T. and Wolfe, N.L. (1987) Degradation of selected halogenated ethanes in anoxic sediment-water systems. *Environmental Toxicology and Chemistry*, 6, 827-837.
- Jeffers, P.M. *et al.* (1989) Homogeneous hydrolysis rate constants for selected chlorinated methanes, ethanes, ethenes and propanes. *Environ. Sci. technol.*, 23, 965-969.
- Jiang *et al.* (1993) *J.Phys.Chem.*, 97, 5050-5053.
- Kincannon, D.F., Weinert, A., Padorr, R., Stover, E.L. (1983) Predicting treatability of multiple organic priority pollutant wastewaters from single-pollutant- treatability studies. *Proc. Ind. Waste Conf.*, 37, 641-50.
- Kirk-Othmer (1991) *Encyclopedia of Chemical Technology*. 4th ed. Volume 1: New York, NY. John Wiley and Sons, V6 26.
- Koneman, H. (1981) Quantitative structure-activity relationships in fish toxicity studies Part 1: Relationship for 50 industrial pollutants. *Toxicology*, 19(3), 209-221.
- Lauweris, R. (1990) *Toxicologie industrielle et intoxications professionnelles*. Masson Editeur, Paris.
- LeBlanc, G.A. (1984) Interspecies relationships in acute toxicity of chemicals to aquatic organisms. *Environ. Toxicol.Chem.*, 24, 684-691.
- LeBlanc, G.A. (1980) Acute toxicity of Priority Pollutants to Water Flea (*Daphnia Magna*). *Bull. Environm. Contam. Toxicol.*, 24, 684-691.
- Little, A.D. (1983) Cell transformation assays of 11 chlorinated hydrocarbons analogs; Icair Work assignment N° 10. AD Little, Inc Report D-507-10-2A, US EPA Doc 40-8324457, Fiche OTS 0509392.
- Lyman, W.J. *et al.* (1982) *Handbook of chemical property estimation methods*: NY: McGRAW- Hill, pp 15-15 to 15-29.
- Lyman, W.J. *et al.* (1990) *Handbook of chemical property estimation methods*. McGraw-Hill, Inc.

- Matsui, S., Yamamoto, R. and Yamada, H. (1989) The Bacillus Subtilis/microsome REC-assay for the detection of DNA damaging substances which may occur in chlorinated and ozonated waters. *Wat. Sci. Tech.*, 21, 375-887.
- McGregor, D.B. (1980) Tier II Mutagenic screening of 13 NIOSH priority compounds, individual compound report, 1,1,2,2-tetrachloroethane. Report prepared by IRI, Musselburgh, for NIOSH.
- Mersch-Sundermann, V. (1989) Untersuchungen zur Mutagenität organischer Mikrokontaminationen in der Umwelt. II Mitteilung: Die Mutagenität leichtflüchtiger Organohalogene im Salmonella-Mikrosomen-Test (Ames Test) unter Berücksichtigung der Kontaminationen von Grund- und Trinkwässern. *Zentralbl. Bakteriol. Mikrobiol. Hyg. Ser. B* 187, 230-243.
- Mersch-Sundermann, V., Muller, G. and Hofmeister, A. (1989) Untersuchungen zur Mutagenität organischer Mikrokontaminationen in der Umwelt. IV Mitteilung : Die Mutagenität leichtflüchtiger Organohalogen im SOS-Chromotest. *Zentralbl. Hyg. Umweltmed.* 189, 266-271.
- Milman, H. *et al.* (1988) Rat liver foci and in vitro assays to detect initiating and promoting effects of chlorinated ethanes and ethylenes. *Ann. NY Acad. Sci.*, 534, 521-530.
- Mirsalis, J.C. *et al.* (1989) Measuring of Unscheduled DNA Synthesis and S-Phase Synthesis in Rodent Hepatocytes Following *in vivo* treatment: Testing of 24 compounds. *Environ. and Mol. Mutagenesis*, 14, 155-164.
- Mitoma *et al.* (1984) Investigation of the species sensitivity and mechanism of carcinogenicity of halogenated hydrocarbons. SRI project LSU 8280-12, EPA contract 68-01-5079, US EPA /OPTS Public Files Doc. 40-8424225, Fiche OTS 0509408. 1984.
- NCI (1978) Bioassay of 1,1,2,2-tetrachloroethane for possible carcinogenicity. DHEW Publication NIOSH 78-827, Washington DC.
- Nestmann, E.R. and Lee, E.G.H. (1983) Mutagenicity of constituents of pulp and paper mill effluent in growing cells of *Saccharomyces cerevisiae*. *Mut. Res.*, 119, 273-280.
- Nestmann, E.R., Lee, E.G.H., Matula, T.I., Douglas, G.R. and Mueller, J.C. (1980) Mutagenicity of constituents identified in pulp and paper mill effluents using the salmonella/mammalian microsome assay. *Mut. Res.* 79, 203-212.
- Neuhauser, E.F. *et al.* (1985) The toxicity of selected organic chemicals to the earthworm *Eisenia fetida*. *J. ENVIRON. QUAL.*, 14, 383-388.
- Nimitz, J.S. and Skaggs, S.R. (1992) *Env. Sci. Technol.* 26, 739-744.
- NTP (1991a) Range finding studies: developmental toxicity-1,1,2,2-tetrachloroethane when administered via feed in CD Sprague-Dawley rats. Triangle Park Research, NC, US-DHHs, NIH, (NTP-91-RF/DT017).
- NTP (1993) 1,1,2,2-tetrachloroethane. C: C3554. Sperm motility vaginal cytology evaluation in rodents. Triangle Park Research, NC, US-DHHs, NIH, NTP (SMVCE-93-192).
- NTP (1991b) Range finding studies: developmental toxicity-1,1,2,2-tetrachloroethane (repeat) when administered via feed in Swiss CD-1 mice. Triangle Park Research, NC, US-DHHs, NIH, (NTP-91-RF/DT020).

- Olsen *et al.* (2000) *Geophys. Res. Let.*, Vol. 27, N° 10, P; 1475-1478.
- Patty (1994) *Patty's Industrial Hygiene and Toxicology*, 4th Ed., 1994, IIE, 4132-4137.
- Plokhova, E.I. (1966) Toxicity of tetrachloroethane. *Gig Truda i Prof. Zabol.*, 10, 51-52 (quoted in BUA report N° 29, 1989).
- Richter, J.E. *et al.* (1983) Acute and chronic toxicity of some chlorinated benzenes, chlorinated ethanes and tetrachloroethylene to *Daphnia magna*. *Arch. Environ. Contam. Toxicol.*, 12, 679-684.
- Roldan-Arjona, T. *et al.* (1991) An association between mutagenicity of the Ara test of *Salmonella typhimurium* and carcinogenicity in rodents for 16 halogenated aliphatic hydrocarbons. *Mutagenesis* 6, 199-205.
- Rosenkranz, H.S. (1977) Mutagenicity of Halogenated Alkanes and their derivatives. *Env. Health Perspect.* 21, 79-84.
- Schmid, O. (1979) Dermale (perkutane) Toxizität von Arbeitsstoffen Zentralblatt für Arbeitsmedizin, Arbeitsschutz und Prophylaxe, 29, 145-149.
- Schmidt, P., Binnewies, G.R. and Rothe, R. (1972) Zur subakuten Wirkung geringer Konzentrationen Chlorierter äthane ohne und mit zusätzlicher äthanolbelastung auf Ratten. I. Biochemische und toxikometrische Aspekte, insbesondere Befunde bei subakuter und kronischer Einwirkung von 1,1,2,2-Tetrachloräthan. *Int. Arch. Arbeitsmed.*, 30, 283-298.
- Schmidt, R. (1976) Zur embryotoxischen und teratogenen Wirkung von Tetrachloräthan - tierexperimentelle Untersuchungen. *Biol. Rundschau* 14, 220-223.
- Schmit, P., Burk, D., Buerger, A. *et al.* (1980) On the hepatotoxicity of benzene, 1,1,2,2-tetrachloroethane and carbone tetrachloride. *Z. Ges. Hyg. Grenzgeb.*, 26, 167-172 (quoted by ATSDR, 1994).
- Smyth, H.F., Carpenter, C.P., Weil, C.S., Pozzani, U.C., Stiegel, J.A. and Nycum, J. (1969) Range-finding Toxicity Data: List VII. *Am. Ind. Hyg. Assoc. J.*, 30, 470-476.
- Spence, J.W., Hanst, P.L. (1978) *J. Air Pollut. Control Assoc.*, 28.
- Strobel, K. and Grummt, T. (1987) Aliphatic and aromatic halocarbons as potential mutagens in drinking water, III Halogenated ethanes and ethenes. *Toxicological and Environmental Chemistry*, 15, 101-128.
- TABAK, H.H. *et al.* (1981) Biodegradability studies with organic priority pollutant compounds. *J. Water Pollut. Contr. Fed.*, 53, 1503-1518.
- Theiss, J.C., Stoner, G.D., Shimkin, M.B. and Weisburger, E.K. (1977) Test of carcinogenicity of organic contaminants of United States drinking waters by pulmonary response in strain A mouse. *Cancer Res.* 37, 2717-2720.
- Truffert, L., Girard-Wallon, C., Emmerich, E., Neauport, C. and Ripault, J. (1977) Mise en évidence expérimentale précoce de l'hépatotoxicité de certains solvants chlorés par l'étude de la synthèse de l'ADN hépatique. *Arch. Mal. Prof.*, 38, 261-263.
- Truhaut *et al.* (1974) Contribution à l'étude toxicologique du tetrachloro-1,1,1,2-ethane. *Arch. Mal. Prof.*, 35, 593-608.

- Tu, A.S., Murray, T.A., Hatch, K.M., Sivak, A., and Milman, H.A. (1985) *In vitro* transformation of BALB/c-3T3 cells by chlorinated ethanes and ethylenes. *Cancer Letters*, 28, 85-92.
- Upton, A.C. *et al.* (1984) ICPEM Publication N°9. Report of ICPEMC Task Group 5 on the differentiation between genotoxic and non-genotoxic carcinogens. *Mut. Res.* 133, 1-49.
- US EPA (1978) In-depth studies on health and environmental impacts of selected water pollutants: Duluth, Minn., Contract N° 68-01-4646, 9.
- Howard, P.H. *et al.* (1990) Handbook of Environmental Fate and Exposure Data for Organic Chemicals, Lewis Publishers, Vol. II.
- Veight, G.D. *et al.* (1983) Structure-Toxicity Relationships for the Fathead Minnow, *Pimephales promelas*: Narcotic Industrial Chemicals. *Can. J. Fisheries Aquat. Sci.*, 40, 743-748.
- Vogel, E.W. and Nivard, M.J.M. (1993) Performance of 181 chemicals in *Drosophila* assay predominantly monitoring interchromosomal mitotic recombination. *Mutagenesis*, 8, 57-81.
- Walbridge, C.T. *et al.* (1983) Acute toxicity of Ten Chlorinated Aliphatic Hydrocarbons to the Fathead Minnow (*Pimephales promelas*). *Arch. Environ. Contam. Toxicol.*, 12, 661-666.
- Warner, J.R., Hughes, T.J. and Claxton, L.D. (1988) Mutagenicity of 16 volatile organic Chemicals in a vaporization technique with *Salmonella typhimurium* TA 100. *Environ. Mol. Mutagenesis*, 11, Suppl.11, 111.
- Williams, G. (1983) DNA repair tests for 11 chlorinated hydrocarbons analogues to determine potential carcinogenicity. Naylor Dana Institute, Report TR-507-18A, US EPA Doc 40-83224292, Fiche OTS 0509403.
- Williams, G., Mori, H. and McQueen, C. (1989) Structure-activity relationships in the rat hepatocyte DNA-repair test for 300 chemicals. *Mut. Res.* 221, 263-286.
- WMO (1998) Scientific assessment of Ozone Depletion, World Meteorological Organization, Global Ozone Research and Monitoring Project Report N°. 44.
- Woodruff, R.C. *et al.* (1985) Chemical mutagenesis testing in *Drosophila*, Results of 53 coded compounds tested for the NTP. *Environ. Mutagen.*, 7, 677-702.
- Yllner, S. (1971) Metabolism of 1,1,2,2-tetrachloroethane-¹⁴C in the mouse. *Acta Pharmacol. Toxicol.*, 29, 499-512.