# SUBSTANCE EVALUATION REPORT

**Public Name:** tetrachloroethylene

**EC Number(s):** 204-825-9

**CAS Number(s):** 127-18-4

**Submitting Member State Competent Authority:**

*Latvian Environment, Geology and Meteorology Centre,*
*Maskavas iela 165,*
*Riga, LV-1019, Latvia*
*+37167032600, lvgmc@lvgmc.lv, www.lvgmc.lv*

**Year of evaluation (as given in the CoRAP):** 2013

**VERSION NUMBER:** *1.0* **DATE:** *03.03.2014.*

| **Conclusions of the most recent evaluation step*** | Tick relevant box(es) |
|---|---|
| Concern not clarified; Need to request further information from the Registrant(s) with the draft decision | |
| Concern clarified; No need of further risk management measures | X |
| Concern clarified; Need for risk management measures; RMO analysis to be performed | |
| Other: [*please specify*] | |

**Include details in the executive summary*

# DISCLAIMER

The report has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the report. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the report are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

# Executive summary

## Grounds for concern

It was suspected that the substance is a potential PBT with wide and dispersive uses. While the substance is not available in consumer products, there is the possibility of high exposure at the workplace. The substance has been assessed under the Existing Substances Regulation (EC) No. 793/93. The conclusion was that the 'B' criterion has not been met.
However, taking into consideration the harmonised classification (see Section 3.1), the market volume (see Section 2.1), and marginal case regarding bioaccumulation criterion, it was advised to further investigate use and exposure pattern of tetrachloroethylene.

## Procedure

- Evaluation was based on data submitted by the Registrant.

## Conclusions

- Taking into consideration the PBT criteria detailed in Annex XIII of REACH and information submitted by the Registrant, tetrachoroethylene meets the criteria for persistence (P and vP), but does not meet the criteria for bioaccumulation (B or vB) and toxicity (T).

- According to the eMSCA evaluation of human health hazards, tetrachloroethylene meets the criteria for classification as skin irritant [Skin Irrit. Category 2, H315 (Xi, R38)] and eye irritant [Eye Irrit. Category 2, H319 (Xi, R36)] as well as skin sensitizer capable of causing an allergic skin reaction [Skin. Sens. 1B, H317 (R43)], as possible carcinogen [Carc. Category 2, H351 (Carc. Cat. 3, R40).

- Exposure via oral route is considered as negligible as the bioaccumulation potential of this substance is very low.

- 20 ppm (138 mg/$m^3$) is regarded as the NOAEL (DNEL, OEL) for human repeated dose toxicity by inhalation route expressed as an 8 hours TWA value (SCOEL). The proposed DNEL for worker long-term systemic exposure via the dermal route is 39.4 mg/kg bw/day (Chemical Safety Report, 2010). According to information obtained in ECETOC TRA v2 modeling for 7 possible usages of the substance as well as for its manufacture, the highest long term Risk Characterization Ratio for combined routs (inhalation + dermal) is estimated to be 0.89 not causing concerns with respect to workers' health.

# CONTENTS

# TABLES

# 1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

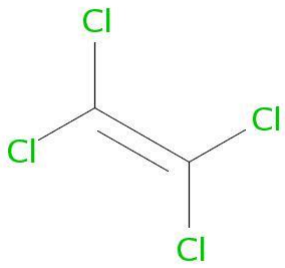
In line with the Guidance for identification and naming of substances under REACH the tetrachloroethylene is organic, a mono constituent substance.

## 1.1 Name and other identifiers of the substance

**Table 1: Substance identity**

| | |
|---|---|
| **Public Name:** | tetrachloroethylene |
| **EC number:** | 204-825-9 |
| **EC name:** | tetrachloroethylene |
| **CAS number (in the EC inventory):** | 127-18-4 |
| **CAS number:** | 127-18-4 |
| **CAS name:** | tetrachloroethene |
| **IUPAC name:** | tetrachloroethene |
| **Index number in Annex VI of the CLP Regulation** | 602-028-00-4 |
| **Molecular formula:** | $C_2Cl_4$ |
| **Molecular weight range:** | 165.85 g/mol |
| **Synonyms:** | perchloroethene, perchloroethylene, Perc, PCE |

**Structural formula:**



## 1.2 Composition of the substance

Information is stated in confidential Annex.

**Name:**

**Description:**

**Degree of purity:**

**Table 2: Constituents**

| Constituents | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| *Name and EC number* | | | |

**Table 3: Impurities**

| Impurities | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| *Name and EC number* | | | |

**Table 4: Additives**

| Additives | Typical concentration | Concentration range | Remarks |
|---|---|---|---|
| *Name and EC number* | | | |

## 1.3 Physico-chemical properties

**Table 5: Overview of physicochemical properties as reported in the registration dossiers**

| Property | Value | Remarks provided by the registrant(s) |
|---|---|---|
| Physical state at 20°C and 101.3 kPa | *Liquid* | The substance is a colourless liquid. |
| Melting/freezing point | -22°C | Data from handbook. |
| Boiling point | 121,4°Cat 101.325 kPa | Data from handbook. |
| Vapour pressure | 2.5 kPa at 25°C | Data from handbook. |
| Surface tension | Other justification | In accordance with column 2 of REACH Annex VII, the study is not required, as the surface tension is not expected based on the substance structure; neither it is the desirable substance property. |
| | 32.1 mN/m at 20°C | As supported information submitted publication. |
| Water solubility | 150 mg/l at 25°C | Data from handbook. |
| Partition coefficient n-octanol/water (log value) | 2.53 at 23°C | Published in a peer-reviewed article. |
| Flash point | The substance is non-flammable. | Data from handbook. |
| Flammability | Study scientifically unjustified | In accordance with section 1 of REACH Annex XI, this study is scientifically unjustified, as the substance has no flash point. |
| Explosive properties | Other justification | In accordance with column 2 of REACH Annex VII, the study is not required, no chemical groups associated with explosive properties present in the molecule. |
| Self ignition temperature | - | - |
| Oxidising properties | Other justification | In accordance with column 2 of REACH Annex VII, the study is not required, on the basis on chemicals structure: no halogen atoms chemically bonded to oxygen or nitrogen. |
| Granulometry | Other justification | In accordance with column 2 of REACH Annex VII, the study is not required: the substance is marketed or used in a non solid or granular form. |
| Stability in organic solvents and identity of relevant degradation products | Other justification | In accordance with column 1 of REACH Annex IX, the study is not required, as the stability of the substance is not considered to be critical. |
| Dissociation constant | Study technically not feasible | In accordance with section 2 of REACH Annex XI, technically not possible to conduct the study taking into account the properties of the substance: the substance does not contain chemical groups which can dissociate. |
| Viscosity | 0.844 mPa ·s at 25°C (dynamic) | Data from handbook. |
| Auto flammability | The substance does not have an autoignition temperature. | Data from handbook. |
| Reactivity towards container material | - | - |

| Property | Value | Remarks provided by the registrant(s) |
|---|---|---|
| Thermal stability | - | - |
| Solubility in organic solvents/fat solubility | *Solubility in* diethyl ether fully miscible.<br>Solubility in ethanol fully miscible.<br>Solubility in chloroform fully miscible.<br>Solubility in benzene fully miscible. | Data from handbook. |
| Density | 1.61 g/cm³ at 25°C | Data from handbook. |

# 2 MANUFACTURE AND USES

## 2.1 Quantities

Information is stated in confidential Annex.

### 2.1.1 Manufacturing processes

Not relevant for this evaluation.

## 2.2 Identified uses

Tetrachloroethylene is a solvent used in organic synthesis. It is used also in dry cleaning operations. It may be used in a mixture with other chlorocarbons as degreasing agent in automotive and other metalworking industries. It may be a part of paint strippers and spot removers composition.

### 2.2.1 Uses by workers in industrial settings

Not relevant for this evaluation.

### 2.2.2 Use by professional workers

Not relevant for this evaluation.

### 2.2.3 Uses by consumers

Not relevant for this evaluation.

## 2.3 Uses advised against

### 2.3.1 Uses by workers in industrial settings advised against

Not relevant for this evaluation.

### 2.3.2 Use by professional workers advised against

Not relevant for this evaluation.

### 2.3.3 Uses by consumers advised against

Not relevant for this evaluation.

# 3 CLASSIFICATION AND LABELLING

## 3.1 Harmonised Classification in Annex VI of the CLP Regulation

Table 3.1. of Annex VI of Regulation (EC) No 1272/2008 (CLP Regulation)

Index No. 206-028-00-4

| Classification | | Labelling | | |
|---|---|---|---|---|
| **Hazard Class and Category Code(s)** | **Hazard statement Code(s)** | **Pictogram, Signal Word Code(s)** | **Hazard statement Code(s)** | **Suppl. Hazard statement code(s)** |
| Carc. 2<br>Aquatic Chronic 2 | H351<br>H411 | GHS08<br>GHS09<br>Wng | H351<br>H411 | |

H351: Suspected of causing cancer.
H411: Toxic to aquatic life with long lasting effects.

Table 3.2. of Annex I of Directive 67/548/EEC (DSD)

Index No. 206-028-00-4

| Classification | Risk phrases | Safety phrases | Identication(s) of danger |
|---|---|---|---|
| Carc. Cat. 3; R40<br>N; R51-53 | 40<br>51/53 | 2-23-36/37-61 | Xn<br>N |

R40: Limited evidence of a carcinogenic effect.

R51/53: Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

## 3.2 Self classification

The registrant follows the harmonised classification in section 3.1 and in addition includes the following self classifications:

According to CLP : Skin Irrit. 2 H315: Causes skin irritation.
Skin Sens. 1B H317: May cause an allergic skin reaction.
STOT Single Exp. 3 H336: May cause drowsiness or dizziness.

According to 67/548/EEC: Xi; R38: Irritating to skin.

R43: May cause sensitisation by skin contact.

R67: Vapours may cause drowsiness and dizziness.

In addition to the harmonised and self classification given above, is the following classification notified to the Classification and Labelling Inventory:

Eye Irrit. 2; H319: Causes serious eye irritation.

# 4 ENVIRONMENTAL FATE PROPERTIES

## 4.1 Degradation

### 4.1.1 Abiotic degradation

#### 4.1.1.1 Hydrolysis

One key study with reliability "2" (Dilling WL, Tefertiller NB, Kallos GJ, 1975) and 2 supporting studies, first with reliability "2" (Jeffers PM, Ward LM, Woytowitch LM, Wolfe NL, 1989) and second with reliability "4" (ECETOC, 1999), on assessment of tetrachloroethylene hydrolysis are provided by the registrant.

In accordance with submitted studies (Dilling et al 1975; Jeffers PM, et al 1989; ECETOC, 1999) degradation of tetrachloroethylene by hydrolysis is very slow.

The half- life of tetrachloroethylene is reported:

- $t_{1/2}$ = 8.8 million years at pH 7 and 25 °C, (pseudo-)first order (= DT50) (Dilling WL et al, 1975),
- $t_{1/2}$ = 990 million years at pH 7 and 25 °C (Jeffers PM et al, 1989).

Wherewith, hydrolysis is not expected to be an important removal process for tetrachloroethylene.

#### 4.1.1.2 Phototransformation/photolysis

##### 4.1.1.2.1 Phototransformation in air

One key study with reliability "2" (US EPA, AOPWIN, 2000) and 1 supporting study with reliability "2" (EU RAR, 2005) on assessment of tetrachloroethylene phototransformation in air are provided by registrant.

Tetrachloroethylene undergoes reactions with hydroxyl radicals in the atmosphere. Using the calculation method (US EPA, AOPWIN, 2000), the half-life of tetrachloroethylene is calculated 50 days (test conditions $25^{o}$C; 12 h day; $OH^{-}$ radical concentration 1.5E6 OH/$cm^{3}$). Tetrachloroethylene also reacts with ozone, nitrate radicals and hydroperoxy radicals, chlorine atoms in the atmosphere.

During the laboratories studies the following main degradation products of tetrachloroethylene are identified: phosgene, trichloroacetyl chloride, hydrogen chloride, carbon dioxide and carbon

monoxide, at the same time also detected such as carbon tetrachloride, dichloroacetyl chloride and chloroform (ECETOC, 1999; EU RAR 2005).

#### 4.1.1.2.2 Phototransformation in water

One key study with reliability "2" (Dilling WL et al, 1975) and 1 study, first with reliability "4" (ECETOC, 1999) on assessment of tetrachloroethylene phototransformation in water are provided by the registrant.

Dilling LW et al., (1975) reported that tetrachloroethylene in water degraded by 75-76% in the direct sunlight and 59-65% after one year in the dark. The experiment was done in outdoor conditions.

Hence, photolysis is not likely to be a significant removal process for tetrachloroethylene.

#### 4.1.1.2.3 Phototransformation in soil

Not relevant for this evaluation.

## 4.1.2 Biodegradation

### 4.1.2.1 Biodegradation in water

#### 4.1.2.1.1 Estimated data

Not relevant for this evaluation.

#### 4.1.2.1.2 Screening tests

One key study with reliability "2" (Mudder TI, Musterman JL, 1982), 10 supporting studies with reliability "2" (Fathepure BZ, Nengu JP, Boyd SA, 1987; CSCL, 1992; Kästner M, 1991; Liang LN, Grbic -Galic D, 1993; Vogel TM, McCarty PL, 1985; Tabak HH, Quave SA, Mashni CI, Barth EF, 1981; DiStefano TD, Gosset JM, Zinder SH, 1992; Freedman DL, Gosset JM, 1989; Holliger C, Schraa G, Stams AJM, Zehnder AJB, 1993; DiStefano TD, Gossett JM, Zinder SH, 1991) and 1 further supporting study with assigned reliability "2" (EU RAR, 2005) on assessment of tetrachloroethylene biodegradation in water (screening test) are submitted.

In the key study the modified shake flask closed bottle biodegradation test was performed. Tetrachloroethylene was not biodegraded in a shake-flask, closed bottle biodegradation procedure after a 21 day acclimation period (adaptive transfer after 48 or 72 h) both with and without lactose. No biodegradation was observed in a river die-away study after a 21-day acclimation period without co-metabolite.

One supported study based on the OECD guideline 301 C (Ready Biodegradability: Modified MITI Test (I)) (CSCL, 1992) was provided. In activated sludge test 11% of tetrachloroethylene degraded after 28 days ($O_2$ consumption). Hence, tetrachloroethylene based on the test results is considered as not readily biodegradable.

In the study by Tabak et al. (1981) a static-culture, flask screening procedure method based upon BOD was used. Gradual biodegradation with adaptation was observed. Tetrachloroethylene (initial concentration 5 mg/l) losses were 45 % after the initial incubation period, 54% after the first subculture, 69 % after the second subculture and 87 % after the third subculture; losses due to volatilisation were 23 %. In the experiment using tetrachloroethylene at an initial concentration of 10 mg/l losses were 30 % after the initial incubation period, 41 % after the first subculture, 67 % after the second subculture and 84 % after the third subculture; losses due to volatilisation were 16 %. The tests show that tetrachloroethylene may undergo primary degradation, the rate of degradation is increasing with adaptation of the micro-organisms. (EU RAR, 2005).

A number of studies have been reported on the biodegradation of tetrachloroethylene in anaerobic conditions:

- 80 % of degradation after 50 days. In co-culture with methanogenic bacteria the dechlorination rate increases to > 99 % depletion in 7 days. (Fathepure BZ, Nengu JP, Boyd SA, 1987; Fathepure BZ, Boyd SA, 1988);
- 99 % of degradation after 10 days (0% degradation after 4 days, 1% - after 6 days, 4% after 8 days). The samples were anaerobically pre-incubated. (Kästner M, 1991);
- 23-51 % of degradation after 7 days. Degradation of tetrachloroethylene occurs under methanogenic conditions using aquifer material derived from contaminated soil. (Liang LN, Grbic -Galic D, 1993);
- > 98 % of degradation after 2 days. Study was done using a continuous-flow fixed-film methanogenic column. (Vogel TM, McCarty PL, 1985);
- > 99 % of degradation after 2 days reported in degradation study with tetrachloroethylene using a methanol-tetrachloroethylene methanogenic culture. (DiStefano TD, Gosset JM, Zinder SH, 1991);
- > 99 % of degradation after 5 days. Study was performed using adapted micro-organisms from a wastewater treatment plant. The main degradation product detected was ethene with traces of trichloroethylene and dichloroethene. (Freedman DL, Gosset JM, 1989);
- > 99 % of degradation after 5 days. In DiStefano et al., 1992 the same culture and tetrachloroethylene concentrations were used as described in DiStefano et al., 1991. (DiStefano TD, Gosset JM, Zinder SH, 1992);
- > 99 % of degradation after 54 days. Holliger C, Schraa G, Starms AJM, Zehnder AJB (1993) isolated a bacterium capable of growing on tetrachloroethylene from an inoculum derived from anaerobic sediment and anaerobic granular sludge. It was detected that the main degradation product was ethane with traces of cis-1,2,-dichloroethane, trichloroethylene, vinyl chloride and ethene.

#### 4.1.2.1.3 Simulation tests (water and sediments)

One key study with reliability “2” (Parsons F, Lage GB, 1985) and 1 supporting study with reliability “2” (De Bruin WP, Kotterman MJJ, Posthumus MA, Schraa G, Zehnder AJB, 1992) on assessment of tetrachloroethylene biodegradation in water are provided.

Parsons F et al., (1985) reported that tetrachloroethylene was transformed in microcosms composed of aquifer materials (anaerobic condition). In the study natural sediments were collected from uncontaminated sites in the Everglades. Bacterial cultures from groundwater taken from a trichloroethylene spill site were used. These cultures were composed of mixed populations of aquatic or soil microorganisms. Transformation products were detected using gas chromatography.

A maximum concentration of cis 1,2-dichloroethylene 3190 ± 1480 µg/l and trichloroethene 217.7 µg/l was observed after 7-8 weeks of incubation.

At anaerobic conditions tetrachloroethylene degraded more than 95 % after 5 days of study to ethane and ethene as indicated in the supporting study by de Bruin WP et al., (1992).

#### 4.1.2.1.4 Summary and discussion of biodegradation in water and sediment

*Screeining tests*

A number of studies have been reported on the biodegradation of tetrachloroethylene in aerobic and anaerobic test conditions. It was concluded that tetrachloroethylene is not readily biodegradable under the stringent conditions of a modified shake flask closed bottle biodegradation test (test performed in accordance to OECD guideline 301 C).

At the same time tetrachloroethylene undergoes anaerobic biodegradation by a process of reductive dechlorination. Also in anaerobic biodegradation studies with presence of bacterial culture and other substrates such as methanol, biodegradation of tetrachloroethylene was observed. The main degradation products are ethene and ethane.

*Simulation tests*

Under anaerobic test conditions tetrachloroethylene was degraded in water and sediment to ethene and then to ethane. In the process of reductive dechlorination under anaerobic conditions tetrachloroethylene was found to be dechlorinated stepwise via trichloroethylene, cis-1,2-dichloroethene, and vinyl chloride to ethene.

### 4.1.2.2 Biodegradation in soil

1 key study (Pavlostathis SG, Zhuang P, 1993) as well as 3 supporting studies (Zhuang P, Pavlostathis SG, 1995; Ninomiya K, Saki M, Ohba E, Kashiwagi N, 1994; Phelps TJ, Niedzielski JJ, Malachowsky KJ, Schram RM, Herbes SE, 1991 and Enzien MV, Picardal F, Hazen TC, Arnold RG, Fliermans CB, 1994) on biodegradation of tetrachloroethylene in soil have been provided. All of them are considered to be of acceptable reliability of "2".

In the key study reductive dechlorination of tetrachloroethylene using static microcosms packed with contaminated soil was studied under anaerobic conditions.

The half-life (DT50) was determined:

- 578 days (microcosm with nitrate amendment)
- 193 days (microcosm with sulphate amendment)
- 533 days (microcosm with nitrate plus electron donor amendment)
- > 38.5 days (microcosm with sulphate plus electron donor amendment, microcosm with electron donor amendment; microcosm with electron donors vitamins and trace element amendment).

The degradation of tetrachloroethylene was indicated as 99 % after 332 days. Trichloroethylene and cis-1,2-dichloroethylene were observed as the degradation products under both sulphate reducing and methanogenic conditions.

Zhuang et al. (1995) studied the effect of temperature, pH and electron donor concentration on the reductive dechlorination of tetrachloroethylene under anaerobic conditions. It was concluded that dechlorination increased up to 35ºC and then decreased as the temperature rose above 45ºC. The

maximum level of dechlorination was observed at pH 7. The effect of varying the electron donor concentration on dechlorination was studied using the methanogenic culture amended with different amounts of acetate. The rate of dechlorination increased rapidly with initial increases in acetate concentration and then slowed with subsequent increases in the acetate concentration.

In the supporting study Phelps et al. (1991) reported a 60% decrease in concentrations of tetrachloroethylene within 21 days in an aerobic packed-column. Similar results were obtained by Enzien et al. (1994) who reported a 90% removal of tetrachloroethylene from a soil column held under bulk aerobic conditions. In both cases it was speculated that the decrease may have been due to the presence of anaerobic niches within the column bed, though no specific evidence of anaerobic biodegradation was found.

In study done by Ninomiya K et al. (1994) a 100% dehalogenation of tetrachloroethylene was observed after seven days of experiment under anaerobic test conditions. Microcosms were prepared from aquifer solids and distilled water spiked with 3 μmol tetrachloroethylene. The microcosms were then incubated in the dark for 10 days.

Based upon the provided information tetrachloroethylene undergoes anaerobic degradation. The process by which the degradation occurs is reductive dechlorination.

### 4.1.3 Summary and discussion on degradation

*Hydrolysis*

Hydrolysis is not expected to be an important removal process for tetrachloroethylene. As the half-lives in the range from 8.8 months to several million years have been reported (Dilling et al., 1975; Jeffers et al 1989).

*Phototransformation in air*

Tetrachloroethylene undergoes reactions with hydroxyl radicals in the atmosphere. The half-life of tetrachloroethylene is calculated to 50 days (US EPA, AOPWIN, 2000).

*Phototransformation in water*

Dilling LW et al, (1975) reported that tetrachloroethylene in water degraded by 75-76% in the direct sunlight and 59-65% after one year in the dark. Hence, photolysis is not likely to be a significant removal process for tetrachloroethylene.

*Biodegradation in water and soil*

A number of studies have been reported on the biodegradation of tetrachloroethylene in aerobic and anaerobic test conditions. It was concluded that tetrachloroethylene is not readily biodegradable under the stringent conditions of a modified shake flask closed bottle biodegradation test (test performed in accordance OECD guideline 301 C).

At the same time tetrachloroethylene undergoes anaerobic biodegradation which is supported by simulation and screening tests.

## 4.2 Environmental distribution

### 4.2.1 Adsorption/desorption

The registrant provided the following explanation for data waiving: "*In accordance with column 2 of REACH Annex VIII, the adsorption/desorption study does not need to be conducted as the substance can be expected to have a low potential for adsorption (log Kow < 3)". Registrant* supported the adsorption/desorption data by information from EU RAR, 2005. The available measured values range from 40.7 to 525. Therefore, the registrant decided to calculate the Koc value from the octanol-water partitioning coefficient (log Kow = 2.53) to 141 L/kg (log value is 2.18).

### 4.2.2 Volatilisation

The Henry's Law constant for tetrachloroethylene and the air-water partitioning coefficient are calculated as 2,110 Pa.$m^3$/mol and 0.893 $m^3/m^3$ respectively using EUSES with a vapour pressure of 1,900 Pa and a water solubility of 149 mg/l at 20$^o$C.

### 4.2.3 Distribution modelling

Not relevant for this evaluation.

### 4.2.4 Summary and discussion of environmental distribution

The Koc value calculated from the octanol-water partitioning coefficient (log Kow = 2.53) is 141 L/kg (log value is 2.18).

The Henry's Law constant is 2,110 Pa. $m^3$/mol at 20$^o$C.

## 4.3 Bioaccumulation

### 4.3.1 Aquatic bioaccumulation

One key study with reliability "2" (Barrows ME, Petrocelli SR, Macek KJ, Carroll JJ, 1980) and 4 supporting studies with reliability "2" (Wang X, Harada S, Watanabe M, Koshikawa H, Sato K, Kimura T, 1996; Neely WB, Blau GE, 1974; Data of existing chemicals based on the CSCL Japan: biodegradation and bioaccumulation, 1992; Wang X, Harada S, Watanabe M, Koshikawa H, Sato K, Kimura T, 1996) on assessment of tetrachloroethylene bioaccumulation in aquatic/sediment are provided.

In the key study (Barrows ME, et al. 1980) Bluegill *Lepomis macrochirus* (a freshwater fish) was exposed to 3.43 µg/l tetrachloroethylene for 21 days at 16°C in a closed, flow-through system. The concentration of tetrachloroethylene (as 14C-label) was monitored to steady state in water and fish. Bioconcentration factor (BCF) was 49 based on whole body w.w.

In supporting studies also the BCF were calculated:

- BCF is 312 for marine algae *Heterosigma akashiwo* (Wang X, et al. 1996);
- BCF is 40 for freshwater *Oncorhynchus mykiss* (Neely WB, et al. 1974);
- BCF 25.8 – 77.1 for *Cyprinus carpio* in accordance with OECD Guideline 305 C (Bioaccumulation: Test for the Degree of Bioconcentration in Fish) (CSCL, 1992);
- BCF 101 for marine algae *Skeletonema costatum*. (Wang X, et al. 1996).

Taking into account the data no significant bioaccumulation of tetrachloroethylene in fish is expected. The BCF of tetrachloroethylene in marine algae is 312 for *Heterosigma akashiwo* and 101 for *Skeletonema costatum*.

The log $K_{ow}$ value for tetrachloroethylene is below 3, indicating a low potential for bioaccumulation. The BCF for fish is calculated as 28.2 by the Technical Guidance Document method.

### 4.3.2 Terrestrial bioaccumulation

Not relevant for this evaluation.

### 4.3.3 Summary and discussion of bioaccumulation

In a number of studies the BCF for fish is calculated, the values ranged from 49 to 77.1. Taking into account the data no significant bioaccumulation of tetrachloroethylene in fish is expected. The log $K_{ow}$ value for tetrachloroethylene is below 3, indicating a low potential for bioaccumulation.

## 4.4 Secondary poisoning

Not relevant for this evaluation.

# 5 HUMAN HEALTH HAZARD ASSESSMENT

## 5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

### 5.1.1 Non-human information

Not relevant for this evaluation.

### 5.1.2 Human information

Not relevant for this evaluation.

### 5.1.3 Summary and discussion on toxicokinetics

Not relevant for this evaluation.

## 5.2 Acute toxicity

### 5.2.1 Non-human information

#### 5.2.1.1 Acute toxicity: oral

Not relevant for this evaluation.

#### 5.2.1.2 Acute toxicity: inhalation

Not relevant for this evaluation.

#### 5.2.1.3 Acute toxicity: dermal

Not relevant for this evaluation.

#### 5.2.1.4 Acute toxicity: other routes

Not relevant for this evaluation.

### 5.2.2 Human information

Not relevant for this evaluation.

### 5.2.3 Summary and discussion of acute toxicity

Not relevant for this evaluation.

## 5.3 Irritation

### 5.3.1 Skin

One key study with reliability "1" on assessment of rabbits skin irritation is provided based on OECD guideline No. 404 (Van Beek, 1990, unpublished report). Two groups of 3 New Zealand White rabbits were treated with a substance of > 99.95 % purity stabilized with ionol (concentration 10 mg/l). 0.5 ml of the test material was applied as an occlusive coverage on a shaved skin for 4 hours. After exposure the test material was washed up with a warm water and soap. Skin reactions were scored by the method of Draize (1944) at 1, 24, 48, 72 hours, 9 and 16 days after the exposure.

Well-defined erythema was observed 24, 48, 72 hours after the application (mean score "4") which was not fully reversed at day 16. Other skin reactions (oedema – mean score 1.7-1.9, ischemic necrosis, incrustation, scaliness) were from slight to moderate at different time points.

According to CLP criteria (mean value of ≥2,3 - ≤4,0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal) the substance shall be classified as Skin Irrit. Category 2, H315: causes skin irritation.

Besides, a numerous human investigations cited in the Chemical Safety Report (2010) confirm that tetrachloroethylene is irritating (but not corrosive) to the skin (Redmond and Schappert, 1987; Morgan, 1969; Ling and Lindsay, 1971; Meyer, 1973; Hake and Stewart, 1977; Metz et al, 1982; Stewart and Dodd, 1964).

### 5.3.2 Eye

One supporting study with poorly reported data (assigned reliability "4") on eye irritation potential of rabbits is provided (Duprat et all., 1976). In this study 0.1 ml of undiluted tetrachloroethylene was applied giving rise to a mild catarrhal conjunctivitis in rabbits. The total score for eye irritation was only 4 on a scale of 0‑110 but the scoring system is not detailed. The conclusion was made that this result does not trigger classification for eye irritation. The Registrant gave the statement that: "*In accordance with section 1.1 and 1.2 of REACH Annex XI, further testing does not appear scientifically necessary. The available animal study (limited reported, not performed in accordance with currently regulatory guidelines) in combination with the human data on eye irritation are considered sufficient to cover the endpoint eye irritation*". However, taking into account the properties of the substance as a skin irritant such conclusion is not justified. Besides, it is stated in the Chemical Safety Report (2010) that slight and transient eye irritation which developed within the first two hours of exposure and subsided before the end of the 7-hour exposure has been reported by human volunteers at about 100 ppm (690 mg/m$^3$) (Stewart et al., 1970). In addition, according to the study with human volunteers performed by Rowe VK et al., 1952, the vapour concentration of tetrachloroethylene which will cause minimal irritation of the eyes in the unacclimated individual lies between 100 and 200 ppm, but 280 ppm causes a burning sensation in the eyes. Higher concentrations are provoking even more serious eye irritation effects.

Based on weight of evidence from human data, the evaluating MSCA suggests classification as Eye irrit. category 2.

### 5.3.3 Respiratory tract

One supporting study with limited information on study conditions but with assigned reliability "2" on irritation potential of respiratory tract using male rats is provided (Janssen PJM, 1990). 25 minutes long exposure by inhalation route (single exposure) applying concentration 10000 ppm (69000 mg/m$^3$) of the substance did not cause respiratory irritation.

In addition, according to Chemical Safety Report (2010), mild nasal irritation was reported by human volunteers exposed at 216 ppm (1490 mg/m$^3$) for 2 hours but not at 106 ppm (731 mg/m$^3$) for 1 hour (Rowe et al., 1952) and at 100 ppm (690 mg/m$^3$) for 7 hours (Stewart et al., 1970). Given the very mild and transient nature of the nasal irritation reported in the two human volunteer studies available and the complete absence of signs of respiratory tract irritation in animals, tetrachloroethylene is not considered to be a respiratory tract irritant.

### 5.3.4 Summary and discussion of irritation

One key study of high reliability performed according to OECD guideline No. 404 on skin irritation of New Zealand White rabbits triggers the classification as Skin Irrit. Category 2, H315: causes skin irritation, due to clearly expressed erythema in all rabbits tested and not completely reversed on day 16. Besides, a numerous human investigations support that tetrachloroethylene is irritating but not corrosive to the skin.

As regards eye irritation, no proper information is provided. The statement by the Registrant that the available supporting negative study on eye irritation of rabbits which was declared of being of poor quality due to reporting deficiency is enough to state that further testing is not scientifically necessary seems to be not acceptable. In addition, some signs of human eye irritation caused by the substance are reported. Minimal irritation of the eyes in the unacclimated individual lies between 100 and 200 ppm, but higher concentrations of tetrachloroethylene are provoking even more serious eye irritation effects. According to CLP criteria, skin irritant substances may be considered as leading to eye irritation (Category 2) as well (3.3.2.3). Based on weight of evidence from human data, the eMSCA suggests classification as Eye irrit. category 2 (causes eye irritation).

With respect to respiratory tract irritation one supporting study with reliability "2" using high concentration of tetrachloroethylene (10000 ppm) for short period (25 min.) by inhalation exposure gave no indication of irritation in rats. Taking into account that experiments on acute inhalation toxicity have shown the LC50 level for rats to be 4100-5000 ppm (6-8 hours exposure) (European Union Risk Assessment Report, Final draft human health report, 2008) the lack of respiratory tract irritation seems to be proved. Additionally, human data have shown only very mild and transient nature of the nasal irritation caused by tetrachloroethylene at 216 ppm (1490 mg/m$^3$) for 2 hours.

## 5.4 Corrosivity

Not relevant for this evaluation.

## 5.5 Sensitisation

### 5.5.1 Skin

No human information is available, but one animal key study with reliability "1" on assessment of contact hypersensitivity to tetrachloroethylene in the mouse (local lymph node assay) provided based on the OECD guideline No. 429 (NOTOX, 2010, unpublished report). Female mice, CBA/J strain, inbred were treated with a substance of 99.6 % purity. Three experimental groups of five mice were used applying the test substance concentrations of 5, 25 or 100% w/w on three consecutive days (25 µL/ear) by open application on the ears. For the control group the vehicle alone was administered (Acetone/Olive oil (4:1 v/v)).

Three days after the last exposure, all animals were injected with 3H-methyl thymidine and after five hours the draining (auricular) lymph nodes were excised and pooled for each animal. After precipitating the DNA of the lymph node cells, radioactivity measurements were performed. The activity was expressed as the number of Disintegrations Per Minute (DPM) and a stimulation index (SI) was subsequently calculated for each dose group. The SI is the ratio of the DPM/group compared to DPM/vehicle control group. If the results indicate a SI $\geq$ 3, the test substance may be regarded as a skin sensitizer according to OECD guideline No. 429.

Besides, Alpha- Hexylcinnamaldehyde was used as a positive control proving the applicability of the testing system.

The SI values calculated for the substance concentrations 5, 25 and 100 % were 0.9, 1.4 and 4.3 respectively. The estimated test substance concentration that will give a SI=3 was calculated to be of 66.4 % (so called EC3 value). Tetrachloroethylene can be regarded as a skin sensitiser.

According to the Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP), tetrachloroethylene should be classified as skin sensitizer (Category 1B) and labelled as H317: May cause an allergic skin reaction because there are positive results from an appropriate animal test as well as EC3 > 2 % and hence the CLP criteria taking into account the Second ATP to CLP are fulfilled.

The Registrant's proposal to classify the substance as skin sensitiser Category 1B is justified.

### 5.5.2 Respiratory system

No information is provided and the Registrant gives the following explanation: "*In accordance with section 1 and 2 of REACH Annex XI, given the widespread and extensive nature of exposure to tetrachloroethylene via work activities and consumer products, the lack of reports of skin and respiratory sensitisation indicates that the potential of tetrachloroethylene to cause these conditions is negligible (if it exists at all) and as tetrachloroethylene does not possess any structural alerts for sensitisation, the conductance of a study is scientifically unjustified*". However, this statement seems to be not fully justified as the skin sensitisation is proved (see chapter 5.5.1). Nevertheless, data on respiratory tract irritation (see chapter 5.3.3) are negative, therefore it can be concluded that tetrachloroethylene is not a respiratory system sensitizer. As it is stated in the Chemical Safety Report (2010) concerning some asthma like symptoms observed in the human studies on respiratory tract irritation, it is unlikely that the underlying mechanism is immunologically-mediated.

### 5.5.3 Summary and discussion on sensitisation

Only one key study according to OECD guideline No. 429 on the assessment of contact hypersensitivity to tetrachloroethylene in the mouse done by local lymph node assay provided (NOTOX, 2010, unpublished report). For 100 % substance the assessed SI value 4.3 was exceeding the guideline skin sensitiser`s limit value SI=3. Besides, the interpolated EC3 value was 66.4 % allowing classify the substance as Category 1B, H317: May cause an allergic skin reaction.

Based on sensitising properties with respect to skin, the statement provided by Registrant "*...the lack of reports of skin and respiratory sensitisation indicates that the potential of tetrachloroethylene to cause these conditions is negligible...*" as a reason for no submission of information on respiratory system sensitisation seems not to be justified but, on the other hand, the negative data on respiratory tract irritation provide necessary evidence concerning no classification.

## 5.6 Repeated dose toxicity

### 5.6.1 Non-human information

#### 5.6.1.1 Repeated dose toxicity: oral

According to CLP criteria, Category 2 for specific target organ toxicity-repeated exposure can be attributed "*on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations*". The guidance dose for Category 2 by oral route in experiments with rats is equal or less than 100 mg/kg bw/day.

One carcinogenicity key study assessed with reliability "2" on B6C3F1 mice concerning exposure by oral route is provided (Weisburger, 1977). Duration of exposure was 78 weeks, followed by a 12-week observation period but the frequency of treatment - five consecutive days per week during which the animals received by gavage 390 and 770 mg/kg bw/day (females) and 540 and 1070 mg/kg bw/day (males), all of them as the time-weighted average doses. The calculated LOAEL value was 390 mg/kg bw/day for females and 540 mg/kg bw/day for males based on kidney lesions-degeneration of the proximal convoluted tubules with cloudy swelling, fatty degeneration and necrosis.

Additionally, supporting study assessed with reliability "2" on Osborne-Mendel rats (Weisburger, 1977) gave the LOAEL value of 470 mg/kg bw/day both for males and females. However, it must be noted that the dose range applied was limited. Besides, in a number of other studies on rats and mice by oral exposure (summarized in the European Union Risk Assessment Report: Tetrachloroethylene, Final draft human health report for publication, 2008 and marked as a supportive study with reliability "2") no significant effects were observed at dosage equal to or below 100 mg/kg bw/day.

Taking into account the CLP criteria, tetrachloroethylene shall not be classified as repeated dose toxicant by oral route.

#### 5.6.1.2 Repeated dose toxicity: inhalation

According to CLP criteria, Category 2 for specific target organ toxicity-repeated exposure can be attributed "*on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations*". The guidance concentration range for Category 2 by inhalation route in experiments with rats is $0,2 < C \leq 1,0$ mg/litre/6h/day (vapour). Following, the upper borderline value for classification or non-classification is ~145 ppm.

In the carcinogenicity study (marked as the key study in the registration dossier but supportive study in the IUCLID file) with reliability "2" on Fischer 344 rats (National Toxicology Programme, 1986) during 103 weeks exposure period (6 hours per day, 5 days per week) the calculated LOAEC value was 200 ppm based on renal lesions - tubular cell karyomegaly and cytomegaly. Similar results have been obtained in a number of studies summarized under European Union Risk Assessment Report: Tetrachloroethylene, Final draft human health report for publication, 2008) marked as supporting study and assessed with reliability "2". For example, in the two-generation reproduction study (Tinston, 1995) no significant effects were found in comparison with controls in the livers of Wistar rats (the F0 parents) exposed to 1000 ppm tetrachloroethylene for 6 hours/day, 5 days/week for a total of about 14 to 17 weeks.

Non-classification for repeated dose toxicity by inhalation route is justified based on the weight of evidence, however, the carcinogenicity key study on B6C3F1 mice provided (National Toxicology Programme, 1986) has proposed the LOAEC value 100 ppm based on both liver lesions (degeneration, characterized by hepatocellular necrosis, cytoplasmic vacuolation, inflammatory infiltration and regenerative foci) and kidney damage (tubular cell karyomegaly, nephrosis and casts) as well as on congestion of the lungs.

#### 5.6.1.3 Repeated dose toxicity: dermal

According to CLP criteria, Category 2 for specific target organ toxicity-repeated exposure can be attributed "*on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations*". The guidance dose for Category 2 by dermal route in experiments with rats or rabbits is $20 < C \leq 200$ mg/kg bw/day.

No information is provided in the registration dossier, the registrant explains that "*in accordance with column 2 of REACH Annex IX-X, testing shall be performed using the most appropriate route of administration. Testing by the inhalation route is appropriate if exposure of humans is likely to occur via inhalation; this is the main route of exposure to tetrachloroethylene (...) Therefore, no study for the dermal route is needed*".

Indeed, Kezic et al. (2000) and Riihimäki & Pfäffli (1978) estimated a dermal uptake of only 0.3% and 1%, respectively, of the respiratory uptake. Poet et al. (2002), in a comparative study, concluded that the permeability coefficient (KP) for humans is much lower than for rats. However, these figures do not consider the de-greasing properties of tetrachloroethylene, when brought as a liquid to the skin. After de-greasing, the skin is rendered much more permeable for tetrachloroethylene (Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene, 2009).

#### 5.6.1.4 Repeated dose toxicity: other routes

No information provided

Rather many worker health surveys and studies, mainly within the dry-cleaners, specifically investigating potential effects on the liver, kidney, nervous system and colour vision have not shown convincing health effects at the exposure range up to 67 ppm (462 mg/m$^3$) as a mean 8h TWA by inhalation route for a prolonged time span up to 6 – 10 years (Scientific Committee on Occupational Exposure Limits (SCOEL), 2008; marked as the key study and generally assessed with reliability "2"). The critical organs subject to effects of tetrachloroethylene are kidney, liver and central nervous system. Following, 20 ppm (138 mg/m$^3$) can be regarded as the NOAEL for human repeated dose toxicity by inhalation route expressed as an 8 hours TWA value.

Regarding oral or dermal exposure, no human data are available.

### 5.6.2 Human information

Not relevant for this evaluation.

### 5.6.3 Summary and discussion of repeated dose toxicity

According to CLP criteria, Category 2 for specific target organ toxicity-repeated exposure can be attributed "*on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations*". The guidance dose for Category 2 by oral route in experiments with rats is equal or less than 100 mg/kg bw/day and by inhalation route in experiments with rats the upper borderline value for classification or non-classification is ~145 ppm (vapour).

The calculated LOAEL value for mice by oral exposure was 390 mg/kg bw/day (Weisburger, 1977). Besides, in the number of other studies on rats and mice no significant effects were observed at dosage equal to or below 100 mg/kg bw/day. With respect to inhalation route, the calculated LOAEC value for rats was 200 ppm.

No animal data on repeated dose toxicity by dermal route are provided. However, the most relevant exposure route for human health appears to be the inhalation route.

From worker health surveys and studies the value of 20 ppm (138 mg/m$^3$) can be regarded as the NOAEL for human repeated dose toxicity by inhalation route expressed as an 8 hours TWA value applicable in the occupational environment according to SCOEL.

Regarding oral or dermal exposure, no human data are available, but in order to arrive at a long-term value for the dermal route for workers, the Chemical Safety Report (2010) proposes extrapolation from the inhalation long-term value 138 mg/m3 of the SCOEL:

138 mg/m3* [100/50] (a) * 10 m3(b) / 70 kg (c) =39.4 mg/kg bw/day

(a) correction for absorption;

(b) 8-hour respiratory volume for workers

(c) body weight for workers

Generally, no classification for repeated dose toxicity is justified as well as reasoning for calculation of a long-term value for the dermal route for workers is acceptable.

## 5.7 Mutagenicity

## 5.7.1 Non-human information

### 5.7.1.1 In vitro data

4 key studies (National Toxicology Programme, 1986; Connor et al, 1985; Kringstad et al, 1981; Vamvakas et al, 1989) on bacterial reverse mutation assay (Ames test) using different Salmonella typhimurium strains (TA 100, TA 98 TA 1535, TA 1537, etc.), 1 key study on in vitro mammalian chromosome aberration test (using Chinese hamster ovary cells) as well as 1 key study on mammalian cell gene mutation assay (using mouse lymphoma L5178Y cells) – both from National Toxicology Programme, 1986, have been provided. All assays were carried out with and without metabolic activation system (S9, liver homogenate from Aroclor-induced male Sprague-Dawley rats or others).

None of thestudies was performed according to OECD guidelines but all of them are considered to be of acceptable reliability of "2" and similar to respective OECD guidelines No 471 (Bacterial Reverse Mutation Assay), No 473 (In vitro Mammalian Chromosome Aberration Test) or No 476 (In vitro Mammalian Cell Gene Mutation Test).

The reported test substance purity was > 99 % applying generally up to 333 μg per plate in Ames test) and up to 136.3 μg/ml in cell cultures for mammalian chromosome aberration test. As regards the mammalian cell gene mutation assay, tetrachloroethylene concentrations used (up to 100 nl/ml with metabolic activation system and up to 150 nl/ml without metabolic activation system) were generally toxic to the cells, as indicated by inhibition of growth. Parallel positive controls were usually carried out using for example sodium azidefor, cisplatin and methylmethanesulfonate,

All tests gave negative results with respect to genotoxicity proving that the substance is not a mutagen. No classification for mutagenicity is justified.

### 5.7.1.2 In vivo data

4 key studies concerning in vivo data are provided: 2 studies on chromosome aberration in rats (Beliles et al, 1980; Rampy et al, 1978), 1 study on micronucleus assay in mice (Murakami et al, 1995) and 1 study on gene mutation in rats (Potter et al, 1996). Differing study patterns and exposure periods have been applied – intraperitoneal administration of the test substance in micronucleus assay, inhalation in chromosome aberration studies and oral gavage in gene mutation assessment.

None of the studies was performed according to OECD guidelines but all of them are considered to be of acceptable reliability of "2" and similar to respective OECD guidelines.

The substance did not induce micronuclei in mouse peripheral blood reticulocytes up to 2000 mg per kg (Murakami et al, 1995), no chromosome or chromatid aberrations were found in rats in prolonged inhalation study up to 600 ppm for 6 hours a day, 5 days a week, for 12 months followed by an observation period which extended through the rats' life-time (Rampy et al, 1978) as well as tetrachloroethylene did not increase the number of DNA strand breaks relative to vehicle control in gene mutation assessment in rats using the daily dietary dose of 1000 mg/kg of the substance for 7 days (Potter et al, 1996).

Slight increases in bone marrow cells with chromosomal aberrations (breaks, deletions and fragments) and increase in poliploid cells in the rat males were found in acute and repeated inhalation study up to dose of 500 ppm (Beliles et al, 1980). But it is stated by the Registrant that the relevance of the findings to tetrachloroethylene is limited by the low purity of the test sample used (purity - 91.43 %). Besides, the substance was not considered clastogenic for female rats.

No classification for mutagenicity is justified.

## 5.7.2 Human information

One supporting study with reliability "2" on genetic toxicity potential of tetrachloroethylene in relation to dry-cleaning workers is provided (Toraason et al., 2003). 18 dry-cleaning workers and 20 laundry workers used as controls were investigated. All participants were women under the age of 70 who had worked in the dry-cleaning or laundry industry for at least 1 year. Race, smoking status and age have been taken into account. Leukocyte 8-OHdG was statistically significantly reduced in dry-cleaners (mean of 8.1±3.6 ng/mg dG) compared to laundry workers (mean of 16.0±7.3 ng/mg dG) revealing seemingly the potential impact of increased repair of oxidative DNA damage. In contrast, urinary levels of 8-epi-PGF or 8-OHdG did not differ among launderers and dry-cleaners showing no signs of oxidative stress caused by tetrachloroethylene which should enhance the 8-epi-PGF or 8-OHdG levels. Hence, mutagenicity potential in humans caused by the substance is not proved.

## 5.7.3 Summary and discussion of mutagenicity

Both in vitro (4 Ames test studies, 1 mammalian chromosome aberration test study, 1 mammalian cell gene mutation assay) and in vivo studies (1 study on chromosome aberration, 1 study on micronucleus assay, 1 study on gene mutation) gave no indication about mutagenicity of tetrachloroethylene. Slight increases in bone marrow cells with chromosomal aberrations and increase in poliploid cells merely in the rat males found in one other in vivo study is not convincing in relation to the test substance as the purity of the sample was insufficient (91.43 %).

With respect to humans, no clear mutagenicity potential is shown in a supporting study on dry-cleaning workers exposed to tetrachloroethylene compared to a control group - laundry workers not exposed to the substance.

In general, no classification for mutagenicity is justified.

## 5.8 Carcinogenicity

## 5.8.1 Non-human information

### 5.8.1.1 Carcinogenicity: oral

One supporting study generally assessed with reliability "2" concerning carcinogenicity of tetrachloroethylene by oral route is provided (Weisburger, 1977: in European Union Risk Assessment Report, Final draft human health report, 2008). The study has been conducted involving tests in Osborne-Mendel rats and B6C3F1 mice. Groups of 50 male and 50 female animals of each species received by gavage 2 dosages, 5 days/week for 78 weeks. This dosing period was followed

by an observation period of 32 weeks for rats and 12 weeks for mice. Groups of 20 animals of each sex were used for untreated control and vehicle (corn oil) control groups. Complicated dosage scheme with differing doses in the time was applied but the time-weighted average doses were about 470 and 950 mg/kg/day for rats and a more or less the same for mice.

Tetrachloroethylene was clearly carcinogenic following oral administration in mice, producing significantly increased incidences of hepatocellular carcinoma in both males and females. Hepatocellular carcinomas were found in 2/17 untreated and 2/20 vehicle control, 32/49 low dose and 27/48 high dose males. The figures for females were 2/20, 0/20, 19/48 and 19/48 respectively. In its turn, the results of the assay in rats do not allow a proper evaluation of carcinogenic potential due to the large number of early deaths occurring in the treated groups.

Another study mentioned by the Registrant and involving Sprague-Dawley rats dosed by oral gavage with 500 mg/kg/day of the tetrachloroethylene in olive oil once daily on 4-5 days per week, for 104 weeks (Maltoni et al, 1986) did not result in an increase in benign and/or malignant tumors in rats of both sexes.

#### 5.8.1.2 Carcinogenicity: inhalation

Two key studies concerning carcinogenicity of tetrachloroethylene by inhalation route are provided (National Toxicology Programme, 1986). Both of them were qualified as studies similar to OECD Guideline No 451 (Carcinogenicity Studies) and assessed with reliability "2". In the studies both sexes of mice strains B6C3F1 and Fischer 344 rats have been applied testing the substance of high analytical purity (99.9 %). Tetrachloroethylene was vaporized at 100ºC-110ºC, diluted with air, and introduced into the exposure chambers with mice at concentrations 100 ppm and 200 ppm in one study and 200 ppm and 400 ppm in another study with rats. Frequency of exposure in both cases was 6 hours per day, 5 days per week during 103 weeks. 50 animals per sex and per dose were tested including control group not treated. Signs of general toxicity (minimal to mild hepatic leukocytic infiltration, centilobular necrosis, bile stasis, mitotic alteration) were reported from preliminary studies within the concentration range 200-1600 ppm because the dosage which was chosen for the main studies seems to be justified.

Necropsy was performed on all animals. During necropsy, all organs and tissues were examined for grossly visible lesions.

In the study with mice clear evidence for carcinogenicity was provided by the increased incidence of hepatocellular carcinoma obtained in both males (7/49 at 0 ppm; 25/49 at 100 ppm; 26/50 at 200 ppm) and females (1/48; 13/50; 36/50, accordingly). Mean body weights and weight gain of dosed and control groups were comparable throughout the study. Therefore, the LOAEC of 100 ppm for carcinogenicity is suggested.

With respect to experiment with rats a slight and not statistically significant increase in renal tubular cell carcinomas of males was found at higher dose 400 ppm (2/50) which is not a convincing evidence, however, it is remarked by the Registrant that large historical control data are not showing incidences of this type of tumor at all. Based on these data, the LOAEC of 200 ppm is suggested. Besides, not statistically significant influence of tetrachloroethylene on incidences of different tumors and neoplastic changes in brain, testis, respiratory tract and other organs is found.

#### 5.8.1.3 Carcinogenicity: dermal

One supporting study generally assessed with reliability "2" concerning carcinogenicity of tetrachloroethylene by dermal route is provided (Van Duuren et al, 1979: in European Union Risk

Assessment Report, Final draft human health report, 2008). Nevertheless, limitations of experimental design and reporting deficiencies are mentioned by the Registrant.

Groups of 30 female Swiss mice received applications of tetrachloroethylene (each of 18 or 54 mg, in acetone), 3 times/week on shaved skin. The duration of the dosing is not clearly specified. No skin tumors have been reported in the high dose group, in 30 acetone-treated controls or in 100 untreated control mice. Thus the test produced no convincing evidence of any carcinogenic potential for tetrachloroethylene by the dermal route.

### 5.8.2 Human information

A summary of results of a few epidemiological studies examining cancer mortality and incidence among dry-cleaners and certain other groups of workers exposed particularly to tetrachloroethylene has been mentioned in the Chemical Safety Report (2010). The general conclusion is that the evidence shows no increased risk of cancer in humans resulting from exposure to tetrachloroethylene. However, IARC has stated in 1995 that there is evidence for consistently positive associations between exposure to tetrachloroethylene and the risks for oesophageal and cervical cancer and non-Hodgkin's lymphoma confirmed further by some other studies. Nevertheless, is stressed that confounding factors cannot be excluded and the total numbers in the cohort studies combined are relatively small. But a recent study found no association between dry-cleaning work and cancer of the oesophagus and cervix in Denmark, Finland, Norway and Sweden (Lynge et al., 2006). In general, the epidemiologic study results are inconsistent and contradictory not allowing making a clear conclusion on carcinogenic potential of tetrachloroethylene for humans.

### 5.8.3 Summary and discussion of carcinogenicity

Both 2 key studies by inhalation route and one supporting study by oral route gave clear indication about increase in hepatocellular carcinoma in mice (B6C3F1) observed in both sexes and generally reflecting the dose-related patterns. On the contrary, there is no convincing evidence about carcinogenic potential of tetrachloroethylene in rats (Fischer 344, Osborne-Mendel, Sprague-Dawley) neither by inhalation route, nor by oral route.

As regards human data, the epidemiological study results are too inconsistent and contradictory to make a clear conclusion about the carcinogenic potential of tetrachloroethylene for humans, especially in the light of a most recent research done by Lynge et al., 2006.

According to CLP criteria, the placing of a substance in the Category 2 (suspected of causing cancer) can be done on the basis of limited evidence obtained from animal studies (mice), but which is not sufficiently convincing to place the substance in Category 1A or 1B due to lack of convincing human data and due to unconvincing data on rats. Besides, the substance does not have mutagenic properties (see chapter 5.7). The corresponding classification according to DSD is Carc. Cat. 3, R40. (*Remark: this hazard class is under harmonised classification and included in Annex VI, of Regulation (EC) No 1272/2008).*

The provided data are counted as sufficient to justify the mentioned classification with regard to carcinogenicity.

Additionally, it is underlined in the Chemical Safety Report (2010) that in relation to human health the kidney tumours seen in male rats exposed to 400 ppm (2760 mg/m3) tetrachloroethylene for 2 years cannot be neglected. The most plausible mechanism of action involves the additional contribution over and above chronic nephrotoxicity of the genotoxic and cytotoxic activity of the

reactive metabolite of the glutathione conjugation/beta-lyase pathway. However, as the potential genotoxicity of this metabolite is only expressed under conditions of sustained renal toxicity and associated increased cell proliferation, the threshold for renal toxicity is considered an appropriate starting point for DNEL derivation. Therefore, the exposure level which is considered without any effects in humans 20 ppm (138 mg/m$^3$) (expressed as 8 hours TWA value) for repeated dose toxicity is considered also to be protective against carcinogenic effects.

## 5.9 Toxicity for reproduction

### 5.9.1 Effects on fertility

#### 5.9.1.1 Non-human information

One key study on effects of tetrachloroethylene on fertility is provided (Tinston DJ, 1995). The mentioned two-generation study on Wistar rats by exposure through inhalation route was carried out according to EPA Guideline OTS 798.4700 (Reproduction and Fertility Effects) and was assessed as being of reliability "1".

The experimental atmosphere was generated by evaporating liquid tetrachloroethylene (99.9 % purity) in a heat exchanger warmed to approximately 60°C. Clean dry air was passed through the generation equipment and the vapour/air mixture was then passed into the exposure chamber. The animals were treated at 100, 300 or 1000 ppm 6 hours/day, 5 days/week for 11 weeks before mating; daily during the mating period of up to 21 days and continued at 7 days/week until sacrifice for the males and until day 20 of gestation for the females. Starting with the day 7 the dams constituting F1 generation and selected as the parents of F2 generation were exposed to similar treatment scheme at least 11 weeks before mating. 24 male and 24 female rats per sex and per dose have been tested.

The investigations carried out on parents included clinical observations, body weight, food consumption, fertility (indicated by the success of the mating), length of gestation, precoital interval, organ (testes, liver and kidney) weights, necropsy and histopathology of certain tissues. Fertility was established by the success of each mating. The criterion for a successful mating was the production of a viable litter - a litter in which at least one pup was found alive at day 1.

NOAEL for paternal toxicity is estimated to be 100 ppm as some paternal toxicity (hair loss, pale appearance, increased breathing rate, etc.) was observed at 300 ppm but the highest dose tested (1000 ppm) caused depression of the CNS expressed as reduced activity and reduced response to sound.

With regard to fertility, no effects on it, as well as on mating performance is revealed compared to untreated control group - even at the highest dose 1000 ppm. Therefore, the NOAEL for effects on fertility is estimated to be 1000 ppm. Some observed effects on development in F1 and F2 (reductions in litter size and pup survival at 1000 ppm, and pup body weight at 1000 and 300 ppm) are considered likely to be the non-specific consequences of maternal toxicity.

Two other studies on rats or New Zealand white rabbits (Beliles RP et al., 1980; Tepe SJ et al., 1980) with reliability "2" indicated that tetrachloroethylene does not trigger effects on fertility and/or on mating performance by inhalation route at the substance concentration 500 - 1000 ppm.

According to CLP criteria, substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other

information, of an adverse effect on sexual function and fertility. Besides, such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. Hence, non classification of tetrachloroethylene for reproductive toxicity is justified.

#### 5.9.1.2 Human information

It is stated in the Chemical Safety Report (2010) that no firm conclusions can be made from human data regarding fertility and reproductive performance but details are not provided.

## 5.9.2 Developmental toxicity

#### 5.9.2.1 Non-human information

One key study on effects of tetrachloroethylene on development is provided (Carney et al, 2006). The mentioned study on Crl:CD (SD) rats by exposure through inhalation route was carried out according to OECD Guideline 414 (Prenatal Developmental Toxicity Study) and was assessed as being of reliability "1".

Animals were whole body exposed in 0.75 $m^3$ exposure chambers at 75, 250 and 600 ppm (purity of the substance > 99 %) with the frequency 6 hours/day, 7 days/week during gestation day 6-19. 22 females per dose were tested.

Animals were evaluated for clinical signs, body weight and feed consumption. Maternal necropsies were performed on gestation day 20. All fetuses and placentae were dissected from the uterus and weighed individually. Each fetus and placenta was externally examined and any abnormalities were recorded.

NOEC for maternal toxicity is estimated to be 250 ppm based on slight, but statistically significant reductions in body weight gain and feed consumption during the first 3 days of exposure. In its turn, NOEC for developmental toxicity is estimated to be 250 ppm, too, taking into account reduced gravid uterus, placental and foetal body weights, and decreased ossification of thoracic vertebral centra at 600 ppm. All these effects have been related to maternal toxicity. Fetal and placental weights at 65 ppm were similar to control values of untreated animals. The resorption rate was low in all groups, there were no treatment-related effects on litter size or group mean sex ratio.

Other supporting studies` summaries generally assessed with reliability "2" (European Union Risk Assessment Report, 2008) on Swiss Webster and NMR1 mice, SD and Long Evans Rats as well as on New Zealand White rabbits by inhalation rout indicated that inhalation exposure to tetrachloroethylene cannot cause foetal malformations at concentrations ranging from 65 to 1000 ppm, however, majority of them were carried out using only one single concentration level.

According to CLP criteria, substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development. Besides, such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. Hence, non classification of tetrachloroethylene for reproductive toxicity is justified.

#### 5.9.2.2 Human information

In the Chemical Safety Report (2010) it is stated that there is no convincing evidence that tetrachloroethylene causes developmental toxicity in humans, however, concern has been raised regarding the risk of spontaneous abortion, particularly, in dry-cleaning workers. An investigation conducted in the form of a retrospective epidemiological study of a cohort of dry-cleaners has shown no significant difference in the risk of spontaneous abortion between the control group (laundry workers not exposed to tetrachloroethylene) and dry-cleaning workers (Doyle et al., 1997). Also it is stressed that previous evidence for a positive association with tetrachloroethylene exposure is derived mainly from two case-control studies (Windham et al., 1991; Kyyronen et al., 1989), both of which involve small numbers and may be subject to various criticisms, including the fact that they failed to take into account known work-related risk factors for spontaneous abortion such as strenuous work, prolonged standing, bending down, shift-work and high workload.

### 5.9.3 Summary and discussion of reproductive toxicity

Neither one key study in rats as well as 2 supportive studies in rats and rabbits with respect to fertility effects, nor one key study in rats and a summary of supportive studies on effects of tetrachloroethylene on development (rats, mice, rabbits) by inhalation route gave convincing evidence concerning toxicity for reproduction. The NOAEL for effects on fertility is estimated to be 1000 ppm (the highest dose applied). In its turn, NOEC for developmental toxicity is estimated to be 250 ppm coinciding with the same value for NOEC for maternal toxicity. Reduced gravid uterus, placental and foetal body weights, and decreased ossification of thoracic vertebral centra at 600 ppm can be explained by maternal toxicity effects observed at 250 ppm as slight, but statistically significant reductions in body weight gain and feed consumption during the first 3 days of exposure.

In humans there is no clear evidence that exposure to tetrachloroethylene results in an increased risk to fertility (however, certain details are no given in the Chemical Safety Report (2010)) and developmental toxicity including spontaneous abortion.

According to CLP criteria, substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development. Besides, such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects. Hence, non classification of tetrachloroethylene for reproductive toxicity is justified taking into account also the lack of evidence from human data.

## 5.10 Endocrine disrupting properties

Not relevant for this evaluation.

## 5.11 Other effects

### 5.11.1 Non-human information

#### 5.11.1.1 Neurotoxicity

Not relevant for this evaluation.

#### 5.11.1.2 Immunotoxicity

Not relevant for this evaluation.

#### 5.11.1.3 Specific investigations: other studies

Not relevant for this evaluation.

### 5.11.2 Human information

Not relevant for this evaluation.

### 5.11.3 Summary and discussion of specific investigations

Not relevant for this evaluation.

## 5.12 Combined effects

Not relevant for this evaluation.

## 5.13 Derivation of DNEL(s) / DMEL(s)

### 5.13.1 Overview of typical dose descriptors for all endpoints

Not relevant for this evaluation.

### 5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

Not relevant for this evaluation.

## 5.14 Conclusions of the human health hazard assessment and related classification and labelling

The evaluating MSCA concludes that in addition to the harmonised classification in Annex VI of the CLP Regulation as Carc. Category 2, H351: suspected of causing cancer (Annex VI of Regulation (EC) No 1272/2008), tetrachloroethylene should be classified in accordance with CLP criteria also as:

- Skin Irrit. Category 2, H315: causes skin irritation;
- Eye Irrit. Category 2, H319: causes serious eye irritation;
- Skin. Sens. 1B, H317: may cause an allergic skin reaction.

With regard to labelling the following signal word codes and hazard statement codes shall be applied:

- GHS07; GHS08
- H315, H317, H319, H351.

According to 67/548/EEC the following classification is proposed in addition to harmonised classification as Carc. Cat. 3, R40: limited evidence of a carcinogenic effect:

- Xi, R38: irritating to skin,
- Xi, R36: irritating to eyes,
- R43: may cause sensitisation by skin contact.

# 6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not relevant for this evaluation.

# 7 ENVIRONMENTAL HAZARD ASSESSMENT

## 7.1 Aquatic compartment (including sediment)

### 7.1.1 Toxicity data

#### 7.1.1.1 Fish

##### 7.1.1.1.1 Short-term toxicity to fish

Two key studies with reliability "2" - one for freshwater fish another for marine fish - (Shubat PJ, Poirier SH, Knuth ML, Brooke LT, 1982 and Pearson CR, McConnell G, 1975) and 8 supporting studies with reliability "2" (Smith AD, Bharath A, Mallard C, Orr D, Smith K, Sutton JA, Vukmanich J, McCarty LS, Ozburn GW, 1991; Alexander HC, McCarty WM, Bartlett EA, 1978; Broderius S, Kahl M, 1985; Buccafusco RJ, Ells SJ, Leblanc GA, 1981; Knie J, Hälke A, Juhnke I, Schiller W, 1983; Walbridge CT, Fiandt JT, Phipps GL, Holcombe GW, 1983; Könemann H, 1981; Heitmuller PT, Hollister TA, Parrish PR, 1981) on assessment of tetrachloroethylene short-term toxicity to fish are provided. At the same time one supporting study with poorly reported data (assigned reliability "3") which cannot be used for assessment of short-term toxicity to fish is submitted (Yoshioka Y, Mizuno T, Ose Y, Sato T, 1986).

In the key study (Shubat PJ, et al. 1982) short-term toxicity to freshwater fish *Salmo gairdneri* (new name: *Oncorhynchus mykiss*) was determined. In this study, acute toxicity tests were conducted with tetrachloroethylene under flow-through conditions. Dimethylformamide (DMF) was used as an additive in one of the tests and was proportionally diluted with the toxicant. One fish died in tetrachloroethylene/DMF control chamber after 24 h of exposure. No cause of death was determined. In both tests, 81% of the deaths occured within the first three hours of exposure.

LC50 (96 h) for tetrachloroethylene tested alone was determined 4.99 mg/l. LC50 (96 h) for tetrachloroethylene tested with DMF was determined 5.84 mg/l.

A number of studies have been reported on the short-term toxicity to fish of tetrachloroethylene in freshwater:

- LC50 96 h 8.4 mg/l, flow-through tests were conducted on *Jordanella floridae* (age 2-4 days) (Smith AD, et al. 1991);
- LC50 96 h 18.4 mg/l, flow-through tests were conducted on *Pimephales promelas*. Methyl alcohol or ethyl alcohol was used as the carrier solvent. (Alexander HC, et al. 1978);
- LC50 96 h 23.8 mg/l, flow-through tests were conducted on *Pimephales promelas* (age 28-34 days) (Broderius S, et al. 1985);
- LC50 96 h 13 mg/l, static tests were conducted on *Lepomis macrochirus* (Buccafusco RJ, et al. 1981);
- LC50 96 h 130 mg/l, LC0 96 h 81 mg/l, LC100 96 h 201 mg/l tests were conducted on *Leuciscus idus* (Knie J, et al. 1983);
- LC50 96 h 13.4 mg/l, flow-through tests were conducted on *Pimephales promelas* (age 30-35 days) (Walbridge CT, et al. 1983);

- LC50 7 days 17.8 mg/l, static tests were conducted on *Poecilia reticulata* (age 2 – 3 month) (Könemann H, et al.1981).

In the key study (Pearson CR, et al. 1975) 96h LC50 for salt-water fish *Limanda limanda* was determined by the method of Doudoroff, et al. 1951. Tests were conducted under flow-through conditions. Due to the high volatility of tetrachloroethylene, it was impracticable to provide artificial aeration, so the only oxygen available was that in the influent sea water; a strong solution of the compound was metered into a mixing device at the inlet to the test tank, and concentrations were monitored regularly before, in and after the apparatus. LC50 (96 h) for tetrachloroethylene was determined 5 mg/l.

In supporting studies also the LC50 (96 h) 29-52 mg/l and NOEC (96 h) 29 mg/l were determined for salt-water fish *Cyprinodon variegatus* under semi-static conditions (Heitmuller PT, et al. 1981). (EU RAR, 2005)

The lowest valid LC50 (96 h) is 5 mg/l for the freshwater species *Salmo gairdneri* (new name: *Oncorhynchus mykiss*) and 5 mg/l for the salt water species *Limanda limanda.*

#### 7.1.1.1.2 Long-term toxicity to fish

1 key study with acceptable reliability "2" (Smith AD, Bharath A, Mallard C, Orr D, Smith K, Sutton JA, Vukmanich J, McCarty LS, Ozburn GW, 1991) on chronic toxicity to fish have been provided. 2 other studies are submitted (Lökle DM, Schecter AJ, Christian JJ, 1983; US EPA, 1980) however, those studies reliability assigned "3" and "4".

In long-term toxicity tests *Poecilia sphenops* (Lökle DM, et al. 1983) appears to be the most sensitive species with a 60-day LOEC of 1.6 mg/l. This study is not considered to be valid because no measures appear to have been taken to monitor concentrations or to minimise evaporation of tetrachloroethylene from the test solution; the resultant effect concentrations are based on nominal concentrations.

The next most sensitive species appears to be *Jordanella floridae* (key study - Smith AD, 1991). NOEC is determined based upon survivals: NOEC 10 days 1.99 mg/l and NOEC 28 days 2.34 mg/l. Tests were conducted under flow-through conditions in freshwaters. These results are considered as valid. (EU RAR, 2005).

### 7.1.1.2 Aquatic invertebrates

#### 7.1.1.2.1 Short-term toxicity to aquatic invertebrates

One key study with reliability "2" (Richter JE, Peterson SF, Kleiner CF, 1983) based on the ASTM: 1980 and 5 supporting studies with reliability "2" (Knie J, Hälke A, Juhnke I, Schiller W, 1983; Lay JP, Schauerte W, Klein W, Korte F, 1984; Bringmann G, Kühn R, 1982; LeBlanc GA, 1980; Call DJ, Brooke LT, Ahmad N, Richter JE, 1983) on assessment of tetrachloroethylene short-term toxicity to aquatic invertebrates are provided. At the same time 4 studies with poorly reported data (assigned reliability "3" and "4") are submitted (Yoshioka Y, Ose Y, Sato T, 1986; Bazin C, Chambon P, Bonnefille M, Larbaigt G, 1987; Pearson CR, McConnell G, 1975; US EPA, 1980). Those studies are considered not valid for assessment of acute toxicity for aquatic invertebrates.

In the key study (Richter, et al. 1983) short-term toxicity to freshwater aquatic invertebrates *Daphnia magna* was determined. Tests were conducted under static conditions in freshwater.

EC50 (48 h) 8.5 mg/l and LC50 (48 h) 9-18 mg/l for tetrachloroethylene were determined.

A number of studies have been reported on the short-term toxicity to aquatic invertebrates of tetrachloroethylene in freshwater:

- *Daphnia magna* 48 h EC0 7 mg/l, EC50 22 mg/l, EC100 988 mg/l tests were done according to EU Method C.2 (Acute Toxicity for Daphnia) (Knie J, et al. 1983);
- *Daphnia magna* 4 days LC100 25 mg/l static tests (Lay JP, et al. 1984);
- *Daphnia magna* 24 h EC0 65 mg/l, EC50 123-176 mg/l, EC100 250 mg/l static tests *(*Bringmann G, et al. 1982);
- *Daphnia magna* 48 h, LC50 18 mg/l static test carried according to DIN 38412 (L11) October 1982 standard (LeBlanc GA, 1980);
- *Tanytarsus dissimilis* (insect) 48 h EC50 28.7 – 33 mg/l static test (Call DJ, et al. 1983).

The lowest 48 h EC50 reported is for freshwater *Daphnia magna* is 8.5 mg/l (Richter JE, et al. 1983) tested under static conditions and is based on measured concentrations. The test conditions are fully described for this result and the test is therefore considered valid. (EU RAR, 2005).

#### 7.1.1.2.2 Long-term toxicity to aquatic invertebrates

One key study with reliability "2" (Richter JE, Peterson SF, Kleiner CF, 1983) and 1 supporting study with reliability "2" (Call DJ, Brooke LT, Ahmad N, Richter JE, 1983) on assessment of tetrachloroethylene short-term toxicity to aquatic invertebrates have been provided.

In the key study (Richter, et al. 1983) chronic toxicity to freshwater aquatic invertebrates *Daphnia magna* was determined. 28 days tests were conducted under semi-static conditions in freshwater.

28 days NOEC 510 μg/l for tetrachloroethylene was determined based upon reproduction.

In the supporting study (Call DJ, 1983) 28 days NOEC is 1.11 mg/l based upon reproduction effects. The test was carried out on *Daphnia magna* under static conditions in freshwater.

### 7.1.1.3 Algae and aquatic plants

One key study with reliability "2" (Brack W, Rottler H, 1994) as well as 5 supporting studies with reliability "2" (EPA, 1980; Knie J, Hälke A, Juhnke I, Schiller W, 1983; Erickson SJ, Freeman AE, 1978; Pearson CR, McConnell G, 1975) on assessment of tetrachloroethylene toxicity to algae are provided. One study with assigned reliability "3" is submitted (Erickson SJ, Hawkins CE, 1980), which is not considered as valid.

The key study has been conducted on *Chlamydomonas reinhardtii* freshwater algae (Brack W, et al. 1994). It was reported that a new, closed system is used, in which a $KHCO_3/K_2CO_3$ buffer to supply the algae with $CO_2$ is employed, but the buffer is separated from the test medium to avoid growth inhibition due to the ionic strength. The test was carried 72 hours. EC50 3.64 mg/l and EC10 1.77 mg/l were determined based on growth rate.

Various studies also were conducted and submitted:

- *Selenastrum capricornutum* (new name: *Pseudokirchnerella subcapitata*) freshwater algae NOEC is 816 mg/l (EPA, 1980);
- *Haematococcus pluvialis* freshwater algae 4 hours EC10 is > 36 mg/l based on inhibition of photosynthesis. (Knie J, et al. 1983) Test carried out in a Warburg apparatus;
- *Skeletonema costatum* salt water algae 96 hours EC50 is 500 mg/l under static condition. In this study EC50 was based on chlorophyll-a content and cell number. (US EPA, 1980);

- *Skeletonema costatum* salt water algae 7 days EC50 is > 16 mg/l under static condition. In this study EC50 was based on growth rate. (Erickson SJ and Freeman AE, 1978);
- *Phaeodactylum tricornutum* salt water algae EC50 10.5 mg/l, based on photosynthesis (Pearson CR, McConnell G, 1975).

In the key study 72-hour EC50 of 3.64 mg/l is reported for the algae *Chlamydomonas reinhardii* (Brack W, et al. 1994). The test is well described and can be considered as valid. In the same study a 72-hour EC10 1.77 mg/l is determined for the algae *Chlamydomonas Reinhardii* which may be considered as a 72 hours NOEC. A 48-hour NOEC of 1 mg/l is reported by Erickson and Hawkins (1980) for estuarine phytoplankton. No indication is given as to the species tested therefore the result is not considered valid. (EU RAR, 2005).

#### 7.1.1.4 Sediment organisms

Not relevant for this evaluation.

#### 7.1.1.5 Other aquatic organisms

Not relevant for this evaluation.

### 7.1.2 Calculation of Predicted No Effect Concentration (PNEC)

#### 7.1.2.1 PNEC water

Not relevant for this evaluation.

#### 7.1.2.2 PNEC sediment

Not relevant for this evaluation.

## 7.2 Terrestrial compartment

### 7.2.1 Toxicity test results

#### 7.2.1.1 Toxicity to soil macro organisms

Not relevant for this evaluation.

#### 7.2.1.2 Toxicity to terrestrial plants

Not relevant for this evaluation.

#### 7.2.1.3 Toxicity to soil micro-organisms

Not relevant for this evaluation.

#### 7.2.1.4 Toxicity to other terrestrial organisms

Not relevant for this evaluation.

### 7.2.2 Calculation of Predicted No Effect Concentration (PNEC soil)

Not relevant for this evaluation.

## 7.3 Atmospheric compartment

Not relevant for this evaluation.

## 7.4 Endocrine disrupting properties

Not relevant for this evaluation.

## 7.5 Microbiological activity in sewage treatment systems

### 7.5.1 Toxicity to aquatic micro-organisms

Not relevant for this evaluation.

### 7.5.2 PNEC for sewage treatment plant

Not relevant for this evaluation.

## 7.6 Non compartment specific effects relevant for the food chain (secondary poisoning)

### 7.6.1 Toxicity to birds

Not relevant for this evaluation.

### 7.6.2 Toxicity to mammals

Not relevant for this evaluation.

### 7.6.3 Calculation of PNECoral (secondary poisoning)

Not relevant for this evaluation.

## 7.7 Conclusion on the environmental hazard assessment and on classification and labelling

Taking into consideration ecotoxicological data for fish, invertebrates and algae the harmonised classification as Aquatic Chronic 2, according to CLP Regulation is confirmed. Short-term toxicity data:

- LC50 for freshwater and marine water fish is 5 mg/l (*Oncorhynchus mykiss;Limanda limanda)*;
- EC50/LC50 for freshwater invertebrates is 8.5 mg/l (*Daphnia magna*);
- EC50/LC50 for freshwater algae is 3.64 mg/l (*Chlamydomonas reinhardtii*).

Long-term toxicity data:

- 10 days NOEC for freshwater fish is 1.99 mg/l (*Jordanella floridae*);
- 28 days NOEC for freshwater invertebrates is 0.51 mg/l (*Daphnia magna*);

72 hours NOEC for freshwater algae is 1.77 mg/l.

# 8 PBT AND VPVB ASSESSMENT

## 8.1 Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

### 8.1.1 Persistence assessment

The degradation of tetrachloroethylene by various abiotic and biotic processes has been examined in the relevant environmental media.

*Hydrolysis*

Hydrolysis is not expected to be an important removal process for tetrachloroethylene as half-lives in the range from 8.8 months to several million years have been reported (Dilling et al., 1975; Jeffers et al 1989).

*Phototransformation in air*

In accordance with submitted data tetrachloroethylene degrades in atmosphere. Tetrachloroethylene undergoes reactions with hydroxyl radicals in the atmosphere. The half-life of tetrachloroethylene is calculated 50 days (US EPA, AOPWIN, 2000).

*Phototransformation in water*

Dilling LW et al., (1975) reported that tetrachloroethylene in water degraded by 75-76% in the direct sunlight and 59-65% after one year in the dark. Hence, photolysis is not likely to be a significant removal process for tetrachloroethylene.

*Biodegradation in water and soil*

Many studies have been reported on the biodegradation of tetrachloroethylene in aerobic and anaerobic test conditions. It was concluded that tetrachloroethylene is not readily biodegradable under the stringent conditions of a modified shake flask closed bottle biodegradation test (test performed in accordance OECD guideline 301 C) in aerobic test conditions.
At the same time tetrachloroethylene undergoes anaerobic biodegradation which is supported by simulation and screening tests.

According to REACH criteria summarized in Annex XIII, tetrachloroethylene meets the criteria of persistence (P and vP).

### 8.1.2 Bioaccumulation assessment

In a number of studies the BCF for fish is calculated, the values ranged from 49 to 77.1. Taking into account the data no significant bioaccumulation of tetrachloroethylene in fish is expected. The BCF of tetrachloroethylene in marine algae is 312 for *Heterosigma akashiwo* and 101 for *Skeletonema costatum*. The log $K_{ow}$ value for tetrachloroethylene is below 3, indicating a low potential for bioaccumulation.

According to REACH criteria summarized in Annex XIII, tetrachloroethylene does not meet the criteria of B or vB.

### 8.1.3 Toxicity assessment

Short-term toxicity data:

- LC50 for freshwater and marine water fish is 5 mg/l;
- EC50/LC50 for freshwater invertebrates is 8.5 mg/l;
- EC50/LC50 for freshwater algae is 3.64 mg/l.

Long-term toxicity data:

- NOEC for freshwater fish is 1.99 mg/l;
- NOEC for freshwater invertebrates is 0.51 mg/l;
- NOEC for freshwater algae is 1.77 mg/l.

All results are much higher than the criteria stated in REACH Annex XIII. In accordance to REACH a substance is considered to potentially meet the criteria for T when a NOEC or EC10 for marine or freshwater organisms is less than 0.01 mg/l.

Therefore, according to REACH criteria summarized in Annex XIII, tetrachloroethylene does not meet the criteria of T.

### 8.1.4 Summary and overall conclusions on PBT and vPvB Properties

According to REACH criteria summarized in Annex XIII it can be concluded that tetrachloroethylene:

- meets the criteria of persistence (P and vP);
- does not meet the criteria of B or vB;
- does not meet the criteria of T.

In accordance with Annex XIII of REACH the available data indicates that tetrachloroethylene meets criteria for persistence (P and vP), however does not meet the criteria for bioaccumulation nor toxicity.

It can be concluded that the tetrachloroethylene substance is not PBT/vPvB substance.

# 9 EXPOSURE ASSESSMENT

## 9.1 Human Health

### 9.1.1 Exposure assessment for worker

#### 9.1.1.1 Overview of uses and exposure scenarios

Manufacture of the substance itself as well as 7 types of possible uses involving a number of processes combined in a different groups of "contributing scenarios" (from 4 to 13 depending on the kind of use) are considered for exposure assessment of workers. The possible uses analysed include:

- IU1: use as intermediate
- IU2: industrial use in dry cleaning
- IU3: professional use in dry cleaning
- IU4: industrial use in surface cleaning
- IU5: industrial use in heat transfer media
- IU6: professional use in film cleaning and copying
- IU7: distribution and (re)packing

ECETOC TRA v2 model is used for exposure assessment in all cases.

#### 9.1.1.2 Scope and type of exposure

Inhalation route is considered as the most important exposure route. Besides, the dermal exposure route is considered, as well, however, Kezic et al. (2000) and Riihimäki & Pfäffli (1978) estimated a dermal uptake of only 0.3% and 1%, respectively, of the respiratory uptake. On the other hand, these figures do not consider the de-greasing properties of tetrachloroethylene, when brought as a liquid to the skin. After de-greasing, the skin is rendered much more permeable for tetrachloroethylene (Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene, 2009).

Oral route is considered as negligible as the bioaccumulation potential of this substance is very low. Therefore, secondary poisoning through food or generally through oral route can be regarded insignificant.

The following NOAEL (DNEL, OEL or other exposure limits) are taken into account:

- 20 ppm (138 mg/m$^3$) is regarded as the NOAEL (DNEL, OEL) for human repeated dose toxicity by inhalation route expressed as an 8 hours TWA value (SCOEL).
- Short term exposure limit (STEL) for 15 min. is 40 ppm (275 mg/m$^3$) (SCOEL). Nevertheless, the acute systemic and local effects are considered to be negligible and are not analysed.
- The DNEL for worker long-term systemic exposure via the dermal route is 39.4 mg/kg bw/day. Dermal DNEL is derived from inhalation DNEL (OEL) (extrapolation provided by Chemical Safety Report (2010).
- The long-term DNEL for systemic effects is considered to be sufficiently protective for local long-term effects, as well.

Taking into account that tetrachloroethylene is a skin irritant in humans, causing reddening and blistering and symptoms may persist for several months following severe skin contact, the appropriate gloves must be used at the same time providing protection against systemic and local dermal exposure. Following, the assessments resulting from exposure via the dermal route could be even omitted and the calculated combined Risk Characterization Ratio given below should be smaller.

The general risk management measures have been proposed regarding skin irritation and possible sensitisation not expressed as numerical threshold values: a) avoid direct skin contact with product; b) identify potential areas for indirect skin contact; c) wear gloves (tested to EN374) if direct hand contact with substance is likely; d) clean up contamination/spills as soon as they occur; e) wash off skin contamination immediately; f) provide basic employee training to prevent/minimise exposures and to report any skin effects that may develop.

#### 9.1.1.2.1 Monitoring data

No direct monitoring data provided in the Chemical Safety Report (2010). According to additional information provided by the Registrant with respect to air concentration in the occupational environment (8 hours TWA value):

- Manufacture of substance - according to Dow Deutschland Anlagengesellschaft GmbH: generally <1 ppm.
- Use as intermediate – as the same type of closed systems is used as for the manufacture, should be the same data.
- Industrial use in dry cleaning – no data available.
- Professional use in dry cleaning – median value of ~20 ppm in 1976, 3 ppm in 2000 (Nordic study on exposure to tetrachloroethylene in dry cleaning shops over the time period of 1947-2001, Annals of Occupational Hygiene, vol. 55, no. 4, 2011, p 387-396). Personal exposure up to 7.5 ppm. In addition, up to 12.5 ppm in 1997 as the worst case measurements according to Report 98.6.152 Forschungsinstitut Hohenstein. Besides, spot sampling ranged from 0.6-75 mg/m$^3$ (Aggazzotti et all, 1994).
- Industrial use in surface cleaning – according to Dow Europe GmbH: < 0.1 – 3.9 ppm.

- Industrial use in heat transfer media – no data available, but as closed systems used, should not be a concern for exposure. Very minor use.
- Professional use in film cleaning and copying – no data available, but very minor use.
- Distribution and (re)packing – data will be provides as they will become available.

#### 9.1.1.2.2 Modelled data

Manufacture of substance

13 groups of contributing scenarios are assessed yielding up to **96.7 mg/m$^3$** of long term inhalatory exposure for 8 hours in the mixing operations applying open systems. As the risk management measure, "Ensure that operation is undertaken outdoors" is proposed. In a number of groups of contributing scenarios the inhalatory exposure is estimated to be **69.1 mg/m$^3$** (general exposures in continuous process in closed systems with sample collection; equipment cleaning and maintenance, etc.).

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the equipment cleaning and maintenance process. The suggested risk management measure is to drain down system prior to equipment break-in or maintenance. In a number of processes it is up to **6.9 mg/kg/day** including mixing operations applying open systems.

Use as intermediate

12 groups of contributing scenarios are assessed yielding up to **69.1 mg/m$^3$** of long term inhalatory exposure for 8 hours in the number of groups of contributing scenarios (general exposures in continuous process in closed systems with sample collection; bulk product storage in closed systems with sample collection, etc.). Generally, no specific risk management measures are proposed.

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the equipment cleaning and maintenance process.

Industrial use in dry cleaning

8 groups of contributing scenarios are assessed yielding up to **96.7 mg/m$^3$** of long term inhalatory exposure for 8 hours in the material transfers by manual processes. As a risk management measure a necessity to provide a good standard of general ventilation (not less than 3-5 air changes per hour) is suggested. In a number of groups of contributing scenarios the long term inhalatory exposure for 8 hours reaches **69.1 mg/m$^3$** (general exposures by usage in contained systems in continuous process and application of cleaning products in closed systems, etc.).

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the equipment cleaning and maintenance process.

Professional use in dry cleaning

6 groups of contributing scenarios are assessed yielding up to **96.7 mg/m$^3$** of long term inhalatory exposure for 8 hours in a number of groups of contributing scenarios - general exposures by usage in contained batch processes and application of cleaning products in closed systems, equipment cleaning and maintenance process, etc.). As a risk management measures a necessity to provide a

good standard of general ventilation (not less than 3-5 air changes per hour) or to drain down system prior to equipment break-in or maintenance are proposed.

With respect to long term dermal exposure the highest value estimated is **6.9 mg/kg/day** in the number of groups of contributing scenarios - material transfers by manual processes, material transfers and drum/batch transfers, etc.

Industrial use in surface cleaning

.

8 groups of contributing scenarios are assessed yielding up to **120.9 mg/m$^3$** of long term inhalatory exposure for 8 hours in the general exposures, use in contained batch processes, application of cleaning products in closed systems and usage with local exhaust ventilation. As a risk management measure a necessity to provide good standard of general ventilation (not less than 3-5 air changes per hour) is proposed.

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the number of groups of contributing scenarios - material transfers by manual processes, equipment cleaning and maintenance process, etc.

Industrial use in heat transfer media

6 groups of contributing scenarios are assessed yielding up to **120.9 mg/m$^3$** of long term inhalatory exposure for 8 hours in the cleaning processes in closed systems and in the material transfers. As a risk management measures a necessity to provide good standard of general ventilation (not less than 3-5 air changes per hour) is proposed as well as to ensure that operation is undertaken outdoors.

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the equipment cleaning and maintenance process. The suggested risk management measure is to drain down system prior to equipment break-in or maintenance.

Professional use in film cleaning and copying

4 groups of contributing scenarios are assessed yielding up to **120.9 mg/m$^3$** of long term inhalatory exposure for 8 hours in the general exposures, usage in contained batch processes, usage with local exhaust ventilation. As a risk management measures a necessity to provide good standard of general ventilation (not less than 3-5 air changes per hour) is proposed. In one group of contributing scenarios the inhalatory exposure is estimated to be **96.7 mg/m$^3$** (material transfers, drum/batch transfers, usage in closed systems).

With respect to long term dermal exposure the highest value estimated is **13.7 mg/kg/day** in the equipment cleaning and maintenance process. The suggested risk management measure is to wear a respirator conforming to EN140 with Type A filter or better.

Distribution and (re)packing

7 groups of contributing scenarios are assessed yielding up to **120.9 mg/m$^3$** of long term inhalatory exposure for 8 hours in the process sampling and usage in closed systems. The suggested risk management measure is to provide good standard of general ventilation (not less than 3-5 air changes per hour)

With respect to long term dermal exposure the highest value estimated is **13.71 mg/kg/day** in the equipment cleaning and maintenance process. The suggested risk management measure is to drain down system prior to equipment break-in or maintenance.

#### 9.1.1.2.3 Comparison of monitoring and modelled data

No direct monitoring data provided in the Chemical Safety Report (2010). Additional direct monitoring data provided by the Registrant. Generally, all monitoring data are lower than the modelled data for all types of usage (when monitoring data are available).

## 9.1.2 Exposure assessment for consumer

#### 9.1.2.1 Overview of uses and exposure scenarios

Not relevant for this evaluation.

#### 9.1.2.2 Scope and type of exposure

#### 9.1.2.2.1 Monitoring data

Not relevant for this evaluation.

#### 9.1.2.2.2 Modelled data

Not relevant for this evaluation.

#### 9.1.2.2.3 Comparison of monitoring and modelled data

Not relevant for this evaluation.

## 9.2 Environmental exposure assessment

## 9.2.1 Aquatic compartment (incl. sediment)

#### 9.2.1.1 Overview of uses and exposure scenarios

Not relevant for this evaluation.

#### 9.2.1.2 Scope and type of exposure

##### 9.2.1.2.1 Monitoring data

Not relevant for this evaluation.

##### 9.2.1.2.2 Modelled data

Not relevant for this evaluation.

##### 9.2.1.2.3 Comparison of monitoring and modelled data

Not relevant for this evaluation.

### 9.2.2 Terrestrial compartment

#### 9.2.2.1 Overview of uses and exposure scenarios

Not relevant for this evaluation.

#### 9.2.2.2 Scope and type of exposure

##### 9.2.2.2.1 Monitoring data

Not relevant for this evaluation.

##### 9.2.2.2.2 Modelled data

Not relevant for this evaluation.

##### 9.2.2.2.3 Comparison of monitoring and modelled data

Not relevant for this evaluation.

### 9.2.3 Atmospheric compartment

#### 9.2.3.1 Overview of uses and exposure scenarios

Not relevant for this evaluation.

#### 9.2.3.2 Scope and type of exposure

##### 9.2.3.2.1 Monitoring data

Not relevant for this evaluation.

##### 9.2.3.2.2 Modelled data

Not relevant for this evaluation.

##### 9.2.3.2.3 Comparison of monitoring and modelled data

Not relevant for this evaluation.

## 9.3 Combined exposure assessment

Not relevant for this evaluation.

# 10 RISK CHARACTERISATION

## 10.1 Human Health

### 10.1.1 Workers

Manufacture of substance

13 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.87** for "mixing operations by usage in open systems by manual processes in small scale" as well as **0.85** for "equipment cleaning and maintenance".

The risk for workers is characterised as acceptable.

Use as intermediate

12 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.85** for "equipment cleaning and maintenance".

The risk for workers is characterised as acceptable.

Industrial use in dry cleaning

8 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.87** for "material transfers by manual processes" as well as **0.85** for "equipment cleaning and maintenance".

The risk for workers is characterised as acceptable.

Professional use in dry cleaning

6 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.77** for "equipment cleaning and maintenance" as well as **0.74** both for "general exposures, use in contained batch processes, application of cleaning products in closed systems" and for "material transfers, drum/batch transfers and usage in closed systems".

The risk for workers is characterised as acceptable.

Industrial use in surface cleaning

.

8 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.88** for "general exposures, use in contained batch processes, application of cleaning products in closed systems and usage with local exhaust ventilation" as well as **0.85** both for "material transfers by manual processes" and for "equipment cleaning and maintenance".

The risk for workers is characterised as acceptable.

Industrial use in heat transfer media

6 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.89** both for "cleaning in closed systems" and for "material transfers". Besides, the long term Risk Characterisation Ratio for "equipment cleaning and maintenance" is calculated to be **0.85**.

The risk for workers is characterised as acceptable.

Professional use in film cleaning and copying

4 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.89** for "general exposures, use in contained batch processes and usage with local exhaust ventilation". Additionally, the long term Risk Characterization Ratio for "equipment cleaning and maintenance" is estimated to be **0.85**.

The risk for workers is characterised as acceptable.

Distribution and (re)packing

7 groups of contributing scenarios are assessed.

The highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is estimated to be **0.89** for "process sampling in closed systems". Besides, the long term Risk Characterisation Ratio for "equipment cleaning and maintenance" is assessed to be **0.85.**

The risk for workers is characterised as acceptable.

### 10.1.2 Consumers

Not relevant for this evaluation.

### 10.1.3 Indirect exposure of humans via the environment

Not relevant for this evaluation.

## 10.2 Environment

### 10.2.1 Risk characterisation for PBT

Not relevant for this evaluation.

### 10.2.2 Aquatic compartment (incl. sediment)

Not relevant for this evaluation.

### 10.2.3 Terrestrial compartment

Not relevant for this evaluation.

### 10.2.4 Atmospheric compartment

Not relevant for this evaluation.

### 10.2.5 Microbiological activity in sewage treatment systems

Not relevant for this evaluation.

## 10.3 Overall risk characterisation

### 10.3.1 Human health (combined for all exposure routes)

There is no risk for consumers as the substance is not intended for consumers` usage. There is no indirect risk via environment due to negligible predicted exposure concentrations in different environmental compartments. Besides, the potential for bioaccumulation of the tetrachloroethylene is very low.

Taking into account that tetrachloroethylene is a skin irritant in humans and no numerical threshold values are given, the appropriate risk management measures are proposed, including usage of appropriate glows as the main.

For the manufacture of the substance as well as for 7 possible uses assessing 4-13 different groups of contributing scenarios in each type of use the highest long term Risk Characterisation Ratio for combined routes (inhalation + dermal) is up to **0.89**. As the worst case Risk Characterisation Ratio is less than “1”, the risk for workers is characterised as acceptable for all types of use of the tetrachloroethylene. Furthermore, the resulting Risk Characterisation Ratio could be even lower when appropriate protection glows are used avoiding any skin contacts.

### 10.3.2 Environment (combined for all exposure routes)

Not relevant for this evaluation.

## 11 OTHER INFORMATION

## 12 REFERENCES

Alexander HC, McCarty WM, Bartlett EA (1978). Toxicity of perchloroethylene, trichloroethylene, 1,1,1-trichloroethylene and methylene chloride to fathead minnows. Bull. Environ. Contamin. Toxicol., **20**, 344-352.

Banerjee S, Yalkowsky SH, Valvani SC (1980). Water Solubility and Octanol/Water Partition Coefficient of Organics. Limitations of the Solubility-Partition Coefficient Correlation. ACS Environ. Sci. Technol., **14**, 1227-1229.

Barrows ME, Petrocelli SR, Macek KJ, Carroll JJ (1980). Bioconcentration and elimination of selected water pollutants by the bluegill sunfish (*Lepomis macrochirus*). In: Haque R, ed. *Dynamics, exposure and hazard assessment of toxic chemicals.* Ann Arbor, MI, Ann Arbor Science, 379-392.

Bazin C, Chambon P, Bonnefille M, Larbaigt G (1987). Compared sensitivity of luminescent marine bacteria (*Photobacterium phosphoreum*) and *Daphnia* bioassays. Sciences de l'eau, **6**, 403-413.

Beliles RP, Brusick DJ, Mecler FJ (1980). Teratogenic–mutagenic risk of workplace contaminants: Trichloroethylene, perchloroethylene and carbon disulfide. Washington, DC, United States Department of Health, Education and Welfare (Contract No. 210-77-0074).

Brack W, Rottler H (1994). Toxicity testing of highly volatile chemicals with green algae. Environ. Sci. Pollut. Res. Int., **1**(4), 223-228.

Bringmann G, Kühn R (1982). Ergebnisse der Schadwirkung wassergefährdender Stoffe gegen *Daphnia magna* in einem weiterentwickelten stanardisierten Testverfahren. Zeitschrift für Wasser und Abwasser Forschung, **15**(1), 1-6.

Broderius S, Kahl M (1985). Acute toxicity of organic chemical mixtures to the fathead minnow. Aquat. Toxicol., **6**, 307-322.

Buccafusco RJ, Ells SJ, LeBlanc GA (1981). Acute toxicity of priority pollutants to bluegill (*Lepomis macrochirus*). Bull. Environ. Contamin. Toxicol., **26**(4), 446-452.

Call DJ, Brooke LT, Ahmad N, Richter JE (1983). Toxicity and metabolism studies with EPA priority pollutants and related chemicals in freshwater organisms. Washington, DC, United States Environmental Protection Agency (EPA 600/3-83-095; NTIS PB83-283665)

Carney EW, Thorsrud BA, Dugard PH, Zablotny CL (2006). Developmental toxicity studies in Crl:CD (SD) rats following inhalation exposure to trichloroethylene and perchloroethylene. Birth. Defects. Res., B77, 405-412.

Connor TH, Theiss JC, Hanna HA, Monteith DK, Matney TS (1985). Genotoxicity of organic chemical frequently found in the air of mobile homes. Toxicology Letters, **25**, 33-40.

CRC Handbook of Chemistry and Physics (1994-1995). 75$^{th}$ edition CRC PRess, Boca Raton, Florida, USA, Lider DR (ed.).

CSCL (1992). Data of existing chemicals based on the CSCL Japan: biodegradation and bioaccumulation. Edited by chemicals inspection and testing institute, Japan . CSCL= Chemical Substance Control Law

De Bruin WP, Kotterman MJJ, Posthumus MA, Schraa G, Zehnder AJB (1992). Complete biological reductive transformation of tetrachloroethylene to ethane. *Appl. Environ. Microbiol.*, **56**(6), 1996-2000.

Dilling WL, Tefertiller NB , Kallos GJ (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.

DiStefano TD, Gosset JM, Zinder SH (1992). Hydrogen as an electron donor for dechlorination of tetrachloroethylene by an anaerobic mixed culture. Appl. Environ. Microbiol, **58**(11), 3622-3629.

DiStefano TD, Gossett JM, Zinder SH (1991). Reductive dechlorination of high concentrations of tetrachloroethylene to ethene by an anaerobic enrichment culture in the absence of methanogenesis. *Appl. Environ. Microbiol.* **57**(8), 2287-2292.

Doyle P, Roman E, Beral V, Brookes M (1997). Spontaneous abortion in dry cleaning workers potentially exposed to perchloroethylene. Occup. Environ. Med., **54**, 848-853.

Duprat P, Delsant L, Gradiski D (1976). Irritant potency of the principal aliphatic chloride solvents on the skin and ocular mucous membranes of rabbits. Eur. J. Toxicol., **3**, 171-177.

ECETOC, 1999: Joint Assessment of Commodity Chemicals No.39 Tetrachloroethylene, European Centre for Ecotoxicology and Toxicology of Chemicals, Brussels.

Encyclopedia of Chemicals, Drugs and Biologicals (1989). 11th edition, Merck & Co., Inc., Rahway, N. J., USA, Budavari S (ed.).

Enzien MV, Picardal F, Hazen TC, Arnold RG, Fliermans CB (1994). Reductive dechlorination of trichloroethylene and tetrachloroethylene under aerobic conditions in a sediment column. Appl. Environ. Microbiol. **60**(6), 2200-2204.

Erickson SJ, Freeman AE (1978). Toxicity screening of fifteen chlorinated and brominated compounds using four species of marine plankton. In: Jolley RL, ed. Water chlorination: Environmental impact and health effects, **2**, 307–311.

Erickson SJ, Hawkins CE (1980). Effects of halogenated organic compounds on photosynthesis in estuarine phytoplankton. Bull. Environ. Contamin. Toxicol., **24**, 910-915.

EU (2008) European Union risk assessment report. Tetrachloroethylene. CAS No: 127-81-4, EINECS No: 204-825-9. Final draft human health report for publication. United Kingdom, on behalf of the European Union.

EU Risk Assessment Report. Tetrachloroethylene, 2005. Source: http://echa.europa.eu/documents/10162/130bc4f2-68a8-45d8-88d7-e6db88f76a98

Fathepure BZ, Boyd SA (1988). Dependence of tetrachloroethylene dechlorination on methanogenic substrate consumption by *Methanosarcina* sp. strain DCM. Appl. Environ. Microbiol., **54**(12), 2976-2980

Fathepure BZ, Nengu JP, Boyd SA (1987). Anaerobic bacteria that dechlorinate perchloroethene. Appl. Environ. Microbiol., **53**(11), 2671-2674.

Freedman DL, Gosset JM (1989). Biological reductive dechlorination of tetrachloroethylene and trichloroethylene to ethylene under methanogenic conditions. Appl. Environ. Microbiol., **55**(9), 2144-2151.

Hake CL, Stewart RD (1977). Human exposure to tetrachloroethylene: Inhalation and skin contact. Environ.Health Perspect., **21**, 231-238.

Heitmuller PT, Hollister TA, Parrish PR (1981). Acute toxicity of 54 industrial chemicals to sheepshead minnows (*Cyprinodon variegatus*). Bull. Environ. Contamin. Toxicol., **27**, 596-604.

Holliger C, Schraa G, Stams AJM, Zehnder AJB (1993). A highly purified enrichment culture couples the reductive dechlorination of tetrachloroethene to growth. Appl. Environ. Microbiol., **59**(9), 2991-2997.

Janssen, P.J.M. (1990). Preliminary Acute Inhalation Study to Investigate the Respiratory Irritating Properties of Proxitane 1507 in Male Rats. Report No. S.9003, Int. Doc. No. 56645/33/90. Duphar B.V., Weesp, The Netherlands, and Solvay, Brussels, Belgium.

Jeffers PM., Ward LM, Woytowitch LM, Wolfe NL (1989). Homogeneous Hydrolysis Rate Constants for Selected Chlorinated Methanes, Ethanes, Ethenes, and Propanes. Environ. Sci. Technol., **23**, 965-969.

Kästner M (1991). Reductive dechlorination of Tri- and tetrachloroethylenes depends on transition from aerobic to anaerobic conditions. Appl. Environ. Microbiol., **57**(7), 2039-2046.

Kezic S, Monster AC, Kruse J, Verberk MM (2000). Skin absorption of some vaporous solvents in volunteers. Int. Arch. Occup. Environ. Health., **73**, 415-422

Knie J, Hälke A, Juhnke I, Schiller W (1983). Ergbnisse der Untersuchungen von chemischen Stoffen mit vier Biotests. Deutsches Gewässerkundliche Mitteilungen, **3**, 77-79.

Könemann H (1981). Quantitative structure–activity relationships in fish toxicity studies. Part 1: Relationships for 50 industrial pollutants. Toxicol., **19**, 209-221.

Kringstad KP, Ljungquist PO, De Sousa F, Stromberg LM (1981). Identification and mutagenic properties of some chlorinated aliphatic hydrocarbons in spent liquor from kraft pulp chlorination. Environ. Sci. Technol., **15**, 562-566.

Kyyronen P, Taskinen H, Lindbohm ML, Hemminki K, Heinonen OP (1989). Spontaneous abortions and congenital malformations among women exposed to tetrachloroethylene in dry cleaning. J. Epidemiol. Commun. Health., **43**, 346-351.

Lay JP, Schauerte W, Klein W, Korte F (1984). Influence of tetrachloroethylene on the biota of aquatic systems: Toxicity to phyto- and zooplankton species in compartments of a natural pond. Arch. Environ. Contamin. Toxicol., **13**(2),135-142.

LeBlanc GA (1980). Acute toxicity of priority pollutants to water flea (*Daphnia magna*). Bull. Environ. Contamin. Toxicol., **24**(5), 684-691.

Liang LN, Grbi-Gali D (1993). Biotransformation of chlorinated aliphatic solvents in the presence of aromatic compounds under methanogenic conditions. Environ. Toxicol. Chem., **12**,1377-1393.

Ling S, Lindsay WA (1971). Perchloroethylene burns. British Med. J., **3**,115.

Lökle DM, Schecter AJ, Christian JJ (1983). Effects of chloroform, tetrachloroethylene and trichloroethylene on survival, growth and liver of *Poecilia sphenops*. Bull. Environ. Contamin. Toxicol., **30**, 199-205.

Lynge E, Andersen A, Rylander L, Tinnerberg H, Lindbohm ML, Pukkala E, Romundstad P, Jensen P, Clausen LB, Johansen K (2006). Cancer in persons working in dry cleaning in the Nordic countries. Environ. Health Perspect., **114**, 213-219.

Maibach HI, Wester RC (2002). PBPK modelling of the percutaneous absorption of perchloroethylene from a soil matrix in rats and humans. Toxicol. Sci., **67**, 17-31.

Maltoni C, Cotti G (1986). Results of long-term carcinogenicity bioassays of Sprague-Dawley rats administrated by ingestion. Acta Oncologica, **1**, 11-26.

Metz V, Graben N, Bock KD (1982). Symptoms and differential therapy of tetra-(=per)chloroethylene poisoning by ingestion or inhalation. Die Medizinische Welt, **33**, 892-894.

Meyer HJ (1973). Bronchopulmonary changes induced by trichloroethylene and other halogenated hydrocarbons. Bronches, **23**, 113-124.

Morgan B (1969). Dangers of perchloroethylene. British Medical Journal, **2**, 513.

Mudder TI, Musterman JL (1982). Development of empirical structure biodegradability relationships and biodegradability testing protocol for volatile and slightly soluble priority pollutants. Presented before the Div. Environ. Chem. Amer. Chem .Sot., Kansas City, 52-53.

Mumford SA, Phillips JWC (1950). The Physical Properties of Some Aliphatic Compounds. J. Chem. Soc., **19**, 75-84.

Murakami K, Horikawa K (1995). The induction of micronuclei in mice hepatocytes and reticulocytes by tetrachloroethylene. Chemosphere **31**(7), 3733-3739.

National Toxicology Programme (1986). Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Series no. 311. NIH Publication

Neely WB, Branson DR, Blau GE (1974). Partition coefficient to measure bioconcentration potential of organic chemicals in fish. *Environ. Sci. Technol.,* **8**(13), 1113-1115.

Ninomiya K, Saki M, Ohba E, Kashiwagi N (1994). Kinetic model for the biotransformation of tetrachloroethylene in groundwater. Water Sci. Technol., **30**(7), 3-18.

No. 86-2587. Research Triangle Park, NC: National Toxicology Program.,199.

OECD Guideline 301 C (1992): Ready Biodegradability: Modified MITI Test (I). ISBN: 9789264070349

OECD Guideline 305 C (2012): Bioaccumulation in Fish: Aqueous and Dietary Exposure. ISBN: 9789264185296

OECD Guideline No 414 (2001): Prenatal Developmental Toxicity Study. ISBN: 9789264070820

OECD Guideline No 451 (2009): Carcinogenicity Studies. ISBN: 9789264071186

OECD Guideline No 471 (1997): Bacterial Reverse Mutation Assay. ISBN: 9789264071247

OECD Guideline No 473 (1997): In vitro Mammalian Chromosome Aberration Test. ISBN: 9789264071261

OECD Guideline No 476 (1997): In vitro Mammalian Cell Gene Mutation Test. ISBN: 9789264071322

OECD Guideline No. 404 (2002): Acute Dermal Irritation/Corrosion. ISBN: 9789264070622

OECD Guideline No. 429 (2010): Skin Sensitisation. ISBN: 9789264071100

Parsons F, Lage GB (1985). Chlorinated organics in simulated groundwater environments. J. Am. Water Works Assoc., **77**(5), 52-59.

Pavlostathis SG, Zhuang P (1993). Reductive dechlorination of chloroalkenes in microcosms developed with a field contaminated soil. Chemosphere, **27**(4), 585-595.

Pearson CR, McConnell G (1975). Chlorinated $C_1$ and $C_2$ hydrocarbons in the marine environment. Proceedings of the Royal Society of London, Series B, **189**, 305-332.

Phelps TJ, Niedzielski JJ, Malachowsky KJ, Schram RM, Herbes SE, White DC (1991). Biodegradation of mixed-organic wastes by microbial consortia in continuous-recycle expanded bed reactors. Environ. Sci. Technol., **25**(8), 1461-1465.

Poet TS, Weitz KK, Gies RA, Edwards JA, Thrall KD, Corley RA, Tanojo H, Hui X,

Potter CL, Chang LW, DeAngelo AB, Daniel FB (1996). Effects of four trihalomethanes on DNA strand breaks, renal hyaline droplet formation and serum testosterone in male F-344 rats. Cancer Letters, **106**, 235-242.

Rampy LW, Quast JF, Balmer MF (1978). Results of long-term inhalation toxicity study on rats of perchloroethylene (tetrachloroethylene) formulation. In: Plaa GL, Duncan WAM, eds. Proceedings of the first international congress on toxicology. New York, NY, Academic Press.

Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene (2009). Source – http://ec.europa.eu/social/BlobServlet?docId=6409&langId=en

Redmond SF, Schappert KR (1987). Occupational dermatitis associated with garments. J. Occup. Med., 29, 243-244.

Richter JE, Peterson SF, Kleiner CF (1983). Acute and chronic toxicity of some chlorinated benzenes, chlorinated ethanes and tetrachloroethylene to *Daphnia magna*. Arch. Environ. Contamin. Toxicol., **12**(6), 679-684.

Riihimäki V, Pfäffli P (1978). Percutaneous absorption of solvent vapours in man. Scand. J.Work Environ. Health, **4**, 73-85.

Rowe VK, McCollister D, Spencer HC, Adams EM, Irish DD (1952). Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. AMA Arch. Ind. Hyg. Occup. Med., **5**, 566-579.

Scientific Committee on Occupational Exposure Limits (2008). Recommendation of the Scientific Committee on Occupational Exposure Limits for Tetrachloroethylene (Perchloroethylene).

Shubat PJ, Poirier SH, Knuth ML, Brooke LT (1982). Acute toxicity of tetrachlorethylene and trichlorethylene with dimethylformamide to rainbow trout (*Salmo gairdneri*). Bull. Environ. Contam. Toxicol., **28**(1), 7-10.

Smith AD, Bharath A, Mallard C, Orr D, Smith K, Sutton JA, Vukmanich J, McCarty LS, Ozburn GW (1991). The acute and chronic toxicity of ten chlorinated organic compounds to the American flagfish (*Jordanella floridae*). Arch. Environ. Contam. Toxicol., **20**, 94-102.

Stewart RD, Baretta ED, Dodd HC, Torkelson TR (1970). Experimental human exposure to tetrachloroethylene. Arch. Environ. Health, **20**, 225-229.

Stewart RD, Dodd HC (1964). Absorption of carbon tetrachloride, trichloroethylene, tetrachloroethylene, methylene chloride, and 1,1,1-trichloroethane through the human skin. Am. Ind. Hyg. Assoc. J., **25**, 439-446.

Tabak HH, Quave SA, Mashni CI, Barth EF (1981). Biodegradability studies with organic priority pollutant compounds. J. Water Pollution Control Federation, **53**(10), 1503-1518.

Tepe SJ, Dorfmueller MA, York RG, Manson JM (1980). Teratogenic evaluation of perchloroethylene in rats. Department of Environmental Health, University of Cincinnati, Cincinnati, OH, 45267.

Tinston DJ (1995). Perchloroethylene: multigeneration inhalation study in the rat. Report of Zeneca Central Toxicology Laboratory. Alderley Park, Macclesfield, Cheshire, Zeneca Central Toxicology Laboratory (Report No. CTL/P/4097).

Toraason M, Butler MA, Ruder A, Forrester C, Taylor L, Ashley DL, Mathias P, Marlow KL, Cheever KL, Kreig E, Wey H (2003). Effect of perchloroethylene, smoking and race on oxidative DNA damage in female dry cleaners. Mutation Research, 539, 9-18.

US EPA (1980). U.S. Environmental Protection Agency. Ambient water quality criteria for trichloroethylene. EPA Office of Water Regulations and Standards, US EPA Report No. EPA-44/5-80-077.

US EPA (2000). U.S. Environmental Protection Agency. AOPWIN™ 2000. Version 1.91. Source - http://www.epa.gov/oppt/exposure/pubs/episuite.htm

Vamvakas S, Herkenhoff M, Dekant W, Henschler D (1989). Mutagenicity of tetrachloroethene in the Ames test: Metabolic activation by conjugation with glutathione. J. Biochem. Toxicol., **4**, 21-27.

Van Duuren BL, Goldschmidt BM, Loewengart G, Smith AC, Melchionne S, Seldman I, Roth D (1979). Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. National Cancer Institute, **63**, 1433-1439.

Vogel TM, McCarty PL (1985). Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environ. Microbiol., **49**(5), 1080-1083.

Walbridge CT, Fiandt JT, Phipps GL, Holcombe GW (1983). Acute toxicity of ten chlorinated aliphatic hydrocarbons to the fathead minnow (*Pimephales promelas*). Arch. Environ. Contamin. Toxicol., **12**:661-666.

Wang X, Harada S, Watanabe M, Koshikawa H, Sato K, Kimura T (1996). Determination of bioconcentration potential of tetrachloroethylene in marine algae by $^{13}$C. Chemosphere, **33**(5), 865-877.

Weisburger EK (1977). Carcinogenicity studies on halogenated hydrocarbons. Environ. Health Perspect., **21**, 7-16.

Windham GC, Shusterman D, Swan SH, Fenster L, Eskenazi B (1991). Exposure to organic solvents and adverse pregnancy outcome. Am. J. Ind. Med., **20**, 241-259.

Yoshioka Y, Ose Y, Sato T (1986). Correlation of the five test methods to assess chemical toxicity and relation to physical properties. Ecotoxicol. Environ. Safety, **12**(1), 15-21.

Zhuang P, Pavlostathis SG (1995). Effect of temperature, pH and electron donor on the microbial reductive dechlorination of chloroalkenes. Chemosphere, **31**(6), 3537-3548.

# 13 ABBREVIATIONS

| | |
|---|---|
| ***AOPWIN*** | Programe that estimates the gas-phase reaction rate for the reaction between the most prevalent atmospheric oxidant, hydroxyl radicals, and a chemical. |
| ***ATP*** | Adaptation to Technical Progress |
| ***BCF*** | Bioconcentration Factor |
| ***B6C3F1*** | Strain Name of mice |
| ***CAS*** | Chemical Abstracts Service |
| ***CBA/J*** | Strain Name of mice |
| ***CLP*** | Regulation on classification, labelling and packaging |
| ***CMR*** | Carcinogenic, Mutagenic And Reprotoxic Chemicals |
| ***CNS*** | Central Nervous System |
| ***CSCL*** | Chemical Substance Control Law |
| ***CSR*** | Corporate Social Responsibility |
| ***DSD*** | Dangerous Substances Directive |
| ***DNA*** | Deoxyribonucleic Acid |
| ***DNEL*** | The Derived No-Effect Level |
| ***DMF*** | Dimethylformamide |
| ***DPM*** | Disintegrations Per Minute |
| ***ECHA*** | European Chemicals Agency |
| ***ECETOC*** | European Centre for Ecotoxicology and Toxicology of Chemicals |
| ***EC*** | Half Maximal Effective Concentration |
| ***EPA*** | Environmental Protection Agency |
| ***EUSES*** | European Union System for the Evaluation of Substances |
| ***IARC*** | International Agency for Research on Cancer |
| ***IUCLID*** | International Uniform Chemicals Information Database |
| ***IUPAC*** | International Union of Pure and Applied Chemistry |
| ***KP*** | Permeability Coefficient |
| ***LC*** | Lethal Concentration |
| ***LOAEL*** | Lowest Observed Adverse Effect Level |
| ***LOAEC*** | Lowest Observed Adverse Effect Concentration |
| ***MSCA*** | Member State Competent Authorities |

| | |
|---|---|
| ***NOAEL*** | No Observed Adverse Effect Level |
| ***NOEC*** | No Observed Effect Concentration |
| ***OECD*** | Organisation for Economic Co-operation and Development |
| ***OEL*** | Occupational Exposure Limits |
| ***PBTs*** | Persistent, Bioaccumulative and Toxic substances |
| ***RAR*** | Risk Assessment Report |
| ***REACH*** | Registration, Evaluation, Authorisation and restriction of Chemicals |
| ***SCOEL*** | Scientific Committee on Occupational Exposure Limits |
| ***SEV*** | Substance Evaluation |
| ***SI*** | Stimulation Index |
| ***STEL*** | Short Term Exposure Limit |
| ***TRA*** | Targeted Risk Assessment |
| ***TWA*** | Time-Weighted Average |