1,2-TRANSDICHLOROETHYLENE

(CAS #156-60-5)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: June 8, 2021

Expiration Date: June 8, 2026

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GreenScreen® Executive Summary for 1,2-Transdichloroethylene (CAS #156-60-5)

1,2-Transdichloroethylene is chloroethylene compound that is a volatile, water soluble colorless liquid at standard temperature and pressure, this is highly flammable. It is used as a solvent for waxes, resins, lacquers, and thermoplastics, for the extraction of rubber, as a refrigerant, an extractant of oil and fats from fish and meat, a degreasing agent, a surface cleaning agent, and a foam blowing additive. It can also be used in pharmaceutical manufacturing and silicone etching as a source of HCl. It is a byproduct of vinyl chloride, trichloroethylene (TCE), and tetrachloroethylene production, and can be withdrawn and purified from the waste streams of these processes. It can also be synthesized by thermal cracking of 1,1,2-trichloroethane or by chlorination of acetylene.

1,2-Transdichloroethylene was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C and developmental toxicity-D)
- Benchmark 2g
    - High Flammability-F

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,2-transdichloroethylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 1,2-transdichloroethylene were assigned a High score for the data gaps R or E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, aquatic toxicity, persistence and biodegradation, and bioaccumulation, and *in vitro* assays for mutagenicity and endocrine activity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

Type I (input data) uncertainties in 1,2-transdichloroethylene's NAMs dataset include no experimental or human data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and chronic aquatic toxicity. 1,2-Transdichloroethylene's Type II (extrapolation output) uncertainties include limited confidence in VEGA predictions due to low ADIs and concordance indices, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the lack of applicability domains for ToxCast models for endocrine activity, the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without defining the applicability domain, and not accounting for non-immunologic mechanisms of respiratory sensitization, and the questionable reliability of chronic aquatic toxicity predictions. Some of 1,2-Transdichloroethylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for 1,2-Transdichloroethylene

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	DG	*M*	DG	**M**	**L**	*M*	**M**	**L**	*M*	DG	**L**	*H*	**M**	*M*	**vL**	**vL**	*L*	**H**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Chemical Assessment for 1,2-Transdichloroethylene (CAS #156-60-5)

Method Version: GreenScreen® Version 1.4
Assessment Type[1]: Certified
Assessor Type: Licensed GreenScreen® Profiler

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: June 7, 2021

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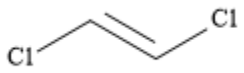
Organization: ToxServices LLC
Date: June 9, 2021

Expiration Date: June 9, 2026[2]

Chemical Name: 1,2-Transdichloroethylene

CAS Number: 156-60-5

Chemical Structure(s):



Also called:
Trans-1,2-dichloroethylene; (E)-1,2-Dichloroethene; (E)-1,2-Dichloroethylene; EINECS 205-860-2; Ethylene, 1,2-dichloro-, trans-; trans-1,2-Dichloroethene; trans-Acetylene dichloride; trans-Dichloroethylene; Ethene, 1,2-dichloro-, (1E)-; Ethylene, 1,2-dichloro-, (E)-; 1,2-Dichloroethene, trans-; 1,2-Dichloroethylene, all isomers; 1,2-trans-Dichloroethylene; Ethylene, 1,2-dichloro-, (E)- (ChemIDplus 2021)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A relatively complete dataset was identifed for 1,2-transdichloroethylene; therefore, no surrogates were used in this assessment.

Identify Applications/Functional Uses: (U.S. EPA 2020a)
1. Solvent for waxes resins, lacquers, and thermoplastics
2. Extractant of rubber
3. Refrigerant
4. Extractant of oil and fats from fish and meat
5. Degreasing agent
6. Surface cleaning agent
7. Foam blowing additive
8. HCl source in pharmaceutical manufacturing and silicone etching

[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for 1,2-Transdichloroethylene[4,5 6,7]: 1,2-Transdichloroethylene was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (carcinogenicity-C and developmental toxicity-D)
- Benchmark 2g
  - High Flammability-F

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), 1,2-transdichloroethylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if 1,2-transdichloroethylene were assigned a High score for the data gaps R or E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for 1,2-Transdichloroethylene

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
M	**L**	DG	*M*	DG	**M**	**L**	*M*	**M**	**L**	*M*	DG	**L**	*H*	**M**	*M*	**vL**	**vL**	*L*	**H**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As 1,2-transdichloroethylene is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

1,2-Transdichloroethylene is a chloroethylene compound that is an isomer of 1,2-dichloroethylene. It is used as a solvent for waxes, resins, lacquers, and thermoplastics, for the extraction of rubber, as a

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[5] See Appendix A for a glossary of hazard endpoint acronyms.
[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

refrigerant, an extractant of oil and fats from fish and meat, a degreasing agent, a surface cleaning agent, and a foam blowing additive. It can also be used in pharmaceutical manufacturing and silicone etching as a source of HCl. It is a byproduct of vinyl chloride, trichloroethylene (TCE), and tetrachloroethylene production, and can be withdrawn and purified from the waste streams of these processes. It can also be synthesized by thermal cracking of 1,1,2-trichloroethane or by chlorination of acetylene (U.S. EPA 2021a).

ToxServices assessed 1,2-transdichloroethylene against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020b). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

1,2-Transdichloroethylene is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for 1,2-transdichloroethylene can be found in Appendix C.

- 1,2-Transdichloroethylene is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- 1,2-Transdichloroethylene is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group II.
- 1,2-Transdichloroethylene is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - Australia GHS – H412 – Harmful to aquatic life with long last effects
    - German FEA – Substances Hazardous to Waters – Class 2 – Hazard to Waters.
    - Quebec CSST – WHMIS 1988 – Class D2B – Toxic material causing other toxic effects

Hazard Statement and Occupational Control

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements for 1,2-transdichloroethylene that is harmonized in the European Union (EU), as reported by the European Chemicals Agency and summarized in Table 1, below. General personal protective equipment (PPE) recommendations and occupational exposure limits (OEL) are presented in Table 2, below.

[8] DOT lists are not required lists for GreenScreen® List Translator v1.4. They are reference lists only.

Table 1: GHS H Statements for 1,2-Transdichloroethylene (CAS #156-60-5) (Pharos 2021)	
H Statement	**H Statement Details**
H332	Harmful if inhaled
H225	Highly flammable liquid and vapor
H412	Harmful to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for 1,2-Transdichloroethylene (CAS #156-60-5)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Half or full piece respirator; impervious gloves; safety goggles or face-shield; impervious protective clothing and protective boots	TCI America 2018	ACGIH TLV: TWA: 200 ppm	U.S. EPA 2020a
		OSHA PEL: 8-hr TWA: 200 ppm (790 mg/m^3)	
		NIOSH REL: 10-hr TWA: 200 ppm (790 mg/m^3)	
		NIOSH IDLH: 1,000 ppm	

ACGIH: American Conference of Governmental Industrial Hygienists
IDLH: Immediately Dangerous to Life or Health
NIOSH: National Institute for Occupational Safety and Health
OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limit
REL: Recommended Exposure Limits
TLV: Threshold Limit Value
TWA: Time Weighted Average

Physicochemical Properties of 1,2-Transdichloroethylene

1,2-Transdichloroethylene is a volatile, colorless liquid at standard temperature and pressure. It is highly soluble in water and its log K_{ow} of ~2.09 indicates it is not likely to bioaccumulate.

Table 3: Physical and Chemical Properties of 1,2-Transdichloroethylene (CAS #156-60-5)		
Property	**Value**	**Reference**
Molecular formula	$C_2H_2Cl_2$	ChemIDplus 2021
SMILES Notation	Cl\C=C\Cl	ChemIDplus 2021
Molecular weight	96.9438	ChemIDplus 2021
Physical state	Liquid	ECHA 2021
Appearance	Colorless	ECHA 2021
Melting point	-49.8°C	ChemIDplus 2021, ECHA 2021
Boiling point	48.7°C 47.64°C	ChemIDplus 2021; ECHA 2021
Vapor pressure	44.13 kPa at 25°C; 331 mm Hg at 25°C	ECHA 2021; U.S. EPA 2020a
Water solubility	4,520 mg/L at 25°C 6,300 mg/L at 25°C	ChemIDplus 2021; ECHA 2021
Dissociation constant	N/A	
Density/specific gravity	1.256 g/cm^3	ECHA 2021
Partition coefficient	Log K_{ow} = 2.09 Log K_{ow} = 2.06	ChemIDplus 2021;

Table 3: Physical and Chemical Properties of 1,2-Transdichloroethylene (CAS #156-60-5)		
Property	**Value**	**Reference**
		ECHA 2021, U.S. EPA 2020a

Toxicokinetics

Absorption

- Experimental data indicates 1,2-transdichloroethylene is well absorbed through the lungs following inhalation exposure, with approximately 72-75% of inhaled substance absorbed by the lungs (U.S. EPA 2020a).
- Blood-air partition coefficients of 6.08 and 9.58 have been reported for humans and rats, respectively, further suggesting 1.2-transdichloroethylene is well absorbed through the lungs (U.S. EPA 2020a, ECHA 2021).
- In closed-chamber gas uptake studies in rats, rapid absorption was demonstrated in the first 1.5-2 hours of exposure, with absorption leveling off as a steady state is approached. Approximately 50% of the gas remained in the chamber at the end of the first phase of absorption. A second phase of absorption followed which demonstrated proportional first-order decline in chamber levels of 1,2-transdichloroethylene at low concentrations (20-30 ppm) and slower, constant (zero-order) decline at higher concentrations (1,000-10,000 ppm). These data indicate saturation of 1,2-transdichloroethylene metabolism at higher concentrations (U.S. EPA 2020a).
- No dermal or oral absorption studies were identified.

Distribution

- No data on distribution of 1,2-transdichloroethylene were identified; however, tissue air partition coefficients of 8.96, 3.52 and 148, were reported for the liver, muscle, and fat, in an *in vitro* study in rats (ECHA 2021, U.S. EPA 2020a). These data suggest 1,2-transdichloroethylene will be distributed to the liver and will accumulate preferentially in fat (U.S. EPA 2020a).

Metabolism

- *In vitro* and *in vivo* studies suggest metabolism of 1,2-transdichloroethylene is initiated upon binding to the active site of hepatic microsomal cytochrome P450s, where it is then metabolized to an unstable epoxide intermediate that rearranges to form 2,2-dichloroacetaldehyde, which is eventually converted to dichloroacetic acid and 2,2-dichloroethanol acid by alcohol dehydrogenase (U.S. EPA 2020a).
- The primary metabolite is dichloroacetic acid, with only trace amounts of 2,2-dichloroethanol and 2,2-dichloroacetaldehyde (U.S. EPA 2020a).
- 1,2-Transdichloroethylene produces a lower amount of metabolites at a slower rate compared to its *cis* isomer (U.S. EPA 2020a).
- Turnover velocities (V_{max}) of 2.4 – 3.4 mg/hour-kg have been reported for 1,2-transdichlorowthylene (U.S. EPA 2020a).

Excretion

- The metabolite dichloroacetic acid is ultimately broken down into carbon dioxide or further metabolized (by oxidative dichlorination) to produce glyoxylate. Glyoxylate can further undergo oxidation to oxylate, which is either excreted in urine or reduced to glycolic acid, followed by transamination to glycine with subsequent formyl group transfer to form serine (U.S. EPA 2020a).

- It is predicted that trace amounts of 1,2-transdichloroethylene will be exhaled (U.S. EPA 2020a).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *M*
1,2-Transdichloroethylene was assigned a score of Moderate for carcinogenicity based on a marginal carcinogenicity concern from OncoLogic and positive predictions from Danish (QSAR). GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is marginal evidence for carcinogenicity (CPA 2018b). The confidence in the score is low as it is based on modeling and no experimental data were identified.

- Authoritative and Screening Lists
  - *Authoritative:* US EPA – IRIS Carcinogens (2005) – Inadequate information to assess carcinogenic potential.
  - *Screening:* Not present on any screening lists for this endpoint.
- VEGA 2021
  - CAESAR v2.1.9 model predicts 1,2-transdichloroethylene to be a carcinogen with low confidence. The global acceptability domain index (ADI) is 0.334, indicating that the prediction is not reliable (Appendix D).
  - ISS v1.0.2 model predicts 1,2-transdichloroethylene to be a non-carcinogen with moderate confidence. The ADI is 0.791, indicating that the prediction is reliable (Appendix D).
  - IRFMN/Antares v1.0.0 model predicts 1,2-transdichloroethylene to be a carcinogen with low confidence. The ADI is 0.538, indicating that the prediction is not reliable (Appendix D).
  - IRFMN/ISSCAN-CGX v1.0.0 model predicts 1,2-transdichloroethylene to be a possible non-carcinogen with low confidence. The ADI is 0.544, indicating that the prediction is not reliable (Appendix D).
  - IRFMN oral classification v1.0.0 predicts 1,2-transdichloroethylene is a non-carcinogen with moderate confidence. The ADI is 0.664, indicating that the prediction is not reliable (Appendix D).
  - IRFMN inhalation classification v1.0.0 predicts 1,2-transdichloroethylene is a carcinogen with moderate confidence. The ADI is 0.661, indicating that the prediction is not reliable (Appendix D).
- DTU 2021
  - Danish (Q)SAR Database for the CAS number 156-60-5 reports that 1,2-transdichloroethylene is in the domains of the E Ultra FDA RCA cancer model for the male mouse, and it is predicted to be negative. It is out of the domains of E Ultra FDA RCA cancer models for the male rat, female rat, rat, female mouse, mouse, and rodent. 1,2-Transdichloroethylene is in the domains of the Leadscope FDA RCA cancer models for the male rat, rat, mouse, and rodent models, which predict that it is positive. It is out of the domains of Leadscope FDA RCA cancer models for female rat, male mouse, and female mouse. Regarding the liver specific cancer in rat or mouse model, Case Ultra prediction is negative and the compound is in the applicability domain; 1,2-transdichloroethylene is outside the applicability domain of the overall battery, Leadscope and SciQSAR models (Appendix E).
- U.S. EPA 2021a

  - The carcinogenic potential of 1,2-transdichloroethylene was evaluated using OncoLogic™ (v9.0). ToxServices evaluated this chemical as a haloethylene compound. According to OncoLogic, haloalkenes can be direct-acting alkylating agents or carcinogenic through biotransformation to highly reactive electrophilic intermediates. The basis of the concern for haloalkenes carcinogenicity is the potential to alkylate cellular nucleophiles; however, many haloalkenes are non-genotoxic. Thus, the carcinogenic activity is believed to be related to cytotoxicity and various epigenetic mechanisms. Therefore, the concern level is determined based on structure-activity relationship analysis as well as mechanistic considerations. 1,2-Transdichloroethylene, a haloethylene with one chloro on one carbon and one chloro on the other carbon, and with the trans isomer predominating, has a level of concern of marginal (Appendix F).
- Based on a weight of evidence, a score of Moderate was assigned. VEGA models produced mixed results and most were reported with low reliability. Only one of the six models predicted 1,2-transdichloroethylene to be a non-carcinogen with moderate confidence and is a reliable result. Therefore, ToxServices included results of additional modeling programs in the weight of evidence. 1,2-Transdichloroethylene was not within the domain of several of the Danish (Q)SAR Database models and the results from this program were also mixed. It was in the domain for only one of the E Ultra FDA RCA cancer models, which predicted it to be negative, however, it was in the domain for four of the Leadscope FDA RCA cancer models, which all predicted it to be positive. Regarding the liver specific cancer in rat or mouse model, it was in the applicability domain for only one model, and the prediction was negative. Finally, OncoLogic predicted a marginal concern for carcinogenicity based on structure-activity relationship analysis as well as mechanistic considerations. Based on the marginal prediction from OncoLogic and positive predictions from Danish (Q)SAR, ToxServices conservatively assigned a score of Moderate.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L

1,2-Transdichloroethylene was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* and *in vivo* genotoxicity assays GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *In vitro:* 1,2-Transdichloroethylene was negative for mutagenicity in a GLP-compliant bacterial reverse mutation assay according to OECD Guideline 471. *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* WP_2 *uvr*A were exposed to the test substance (99.79% purity) in dimethyl sulfoxide (DMSO) at concentrations of 1.5, 5, 15, 50, 150, 500, 1,500 and 5,000 µg/plate with and without metabolic activation. Positive controls of 9-aminoacridine, 2-nitrofluorene, sodium azide, and methylmethanesulfonate were used. Cytotoxicity was reported at the high dose of 5,000 µg/plate. There were no increases in the frequency of revertants reported in any strain at any concentration with or without metabolic activation. Vehicle and positive controls were valid (Klimisch score 1 – reliable without restriction).
  - *In vitro:* 1,2-Transdichloroethylene was negative for mutagenicity in a bacterial reverse mutation assay similar to OECD Guideline 471 (GLP status not specified). *S. typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537 were exposed to the test substance (98%

purity) in DMSO at concentrations of 0, 100, 333, 1,000, 3,333, and 10,000 µg/plate with and without metabolic activation. Positive controls of 9-aminoacridine, sodium azide, 4-nitro-phenylenediamine, and 2-aminoanthracene were used. There were no increases in the frequency of revertants reported in any strain at any concentration with or without metabolic activation. Vehicle and positive controls were valid (Klimisch score 2 – reliable with restrictions).

- *In vitro:* 1,2-Transdichloroethylene was negative for mutagenicity in a GLP-compliant mammalian cell gene mutation assay according to OECD Guideline 476. Chinese hamster ovary (CHO) cells were exposed to the test substance (99.79% purity) in DMSO at concentrations of 1.89, 3.79, 7.58, 15.2, 30.3, 60.6, 121, 243, 485, 728, and 970 µg/mL with and without metabolic activation. Positive controls of benzo(a)pyrene and ethylmethanesulphonate were used. No cytotoxicity was reported. There were no increases in mutant frequency reported at any concentration with or without metabolic activation. Vehicle and positive controls were valid (Klimisch score 1 – reliable without restriction).
- *In vitro:* 1,2-Transdichloroethylene was negative for clastogenicity in a GLP-compliant chromosome aberration assay similar to OECD Guideline 473. CHO cells were exposed to the test substance (≥ 99% purity) in DMSO at concentrations of 1,600, 3,000 and 5,000 µg/mL with and without metabolic activation. Positive controls of cyclophosphamide and mitomycin C were used. The test substance did not induce chromosome aberrations at any dose with or without metabolic activation. Vehicle and positive controls were valid (Klimisch score 2 – reliable with restrictions).
- *In vitro:* 1,2-Transchloroethylene produced equivocal results in a sister chromatid exchange (SCE) assay similar to OECD Guideline 479 (GLP status not specified). CHO cells were exposed to the test substance (≥99% purity, solvent not reported) at concentrations of 160, 500, 1,600 and 5,000 µg/mL with and without metabolic activation. Positive controls of cyclophosphamide and mitomycin C were used. The test substance did not induce SCEs in the absence of metabolic activation; however, in the presence of metabolic activation, the test substance was judged to be equivocal based on the trend test ($P<0.005$) and the absence of significant increases (≥ 20%) at any of the individual dose points. Vehicle and positive controls were valid (Klimisch score 2 – reliable with restrictions).
    - *The significance of the SCE assay is controversial, and there is not in complete agreement in the toxicological community as to its ability to predict genotoxicity: "SCEs are not considered to be mutagenic effects because the exchange is assumed to be reciprocal with no gain, loss, or change of genetic material. However, they do indicate that the test material has interacted with the DNA in a way that may lead to chromosome damage. In in vitro studies, SCEs do not provide adequate evidence of mutagenicity, but do identify the need for definitive chromosomal aberration studies. When evidence of in vitro clastogenicity exists, the induction of SCEs is often used as evidence of likely in vivo clastogenic activity because the in vitro aberration data demonstrate the clastogenic activity of the compound and the in vivo SCE data demonstrate that the compound interacted with the DNA in the target tissue." (NSF 2018).*
- *In vivo:* 1,2-Transchloroethylene was negative for clastogenicity in a GLP-compliant micronucleus assay similar to OECD Guideline 474. Male and female B6C3F1 mice (10/sex/dose) were administered the test substance (≥99% purity) at doses of 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported average daily doses of 480, 920, 1,900, 3,850, and 8,065 mg/kg for males and 450, 915, 1,830, 3,760, and 7,925 mg/kg for females) continuously in the feed for 14 weeks. A positive control was not used in this study. There was no increase in the frequency of normochromatic erythrocytes (NCEs) in the peripheral

blood of male or female mice and no effect on the percentage of micronucleated polychromatic erythrocytes (PCEs) among total erythrocyte population, indicating no inhibition of stimulation of erythropoiesis in the bone marrow of exposed mice (Klimisch score 2 – reliable with restrictions).

- *In vivo:* 1,2-Transchloroethylene was negative for clastogenicity in a micronucleus assay similar to OECD Guideline 474 (GLP status not specified). Male B6C3F1 mice (10/dose) were administered the test substance (≥99% purity, vehicle not reported) at 500, 1,000, and 2,000 mg/kg via a single intraperitoneal injection and sacrificed at 17 hours after injection. The positive control was not identified; however, it was reported to be valid. There was no increase in the frequency of chromosome aberrations in the bone marrow of male mice (Klimisch score 2 – reliable with restrictions).
- *In vivo:* 1,2-Transchloroethylene was negative for SCE induction in a micronucleus assay similar to OECD Guideline 474 (non-GLP-compliant). Male B6C3F1 mice (5/dose) were administered the test substance (≥99% purity, vehicle not reported) at 500, 1,000, and 2,000 mg/kg via a single intraperitoneal injection and sacrificed at 23 hours after injection. The positive control was not identified; however, it was reported to be valid. The test item did not induce SCEs in the bone marrow of male mice (Klimisch score 2 – reliable with restrictions).

Reproductive Toxicity (R) Score (H, M, or L): DG

1,2-Transdichloroethylene was assigned a score of Data Gap for reproductive toxicity based on a lack of studies that examine reproductive functions of animals during exposure, although there were no effects to sperm parameters and estrous cyclicity in repeated dose toxicity studies in rats and mice.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In a GLP-compliant oral repeated dose toxicity study conducted similar to OECD Guideline 408, male and female F344/N rats (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 190, 380, 770, 1,540, and 3,210 mg/kg/day, respectively, in males, and 190, 395, 780, 1,580, and 3,245 mg/kg/day, respectively, in females) for 14 weeks. At the end of the study, sperm samples were collected from all male animals in dose groups ≥ 12,500 ppm and evaluated for sperm motility (spermatid heads per testis and per gram testis, spermatid counts, and epididymal spermatozoal motility and concentration). Additionally, the left cauda, left epididymis, and left testis were weighed. Vaginal samples were collected for 12 consecutive days before the end of the study from all females treated with ≥12,500, and evaluated for vaginal cytology. The percentage of time spent in the various estrous cycle stages and estrous cycle length were also evaluated. No adverse effects were reported on any of these parameters. Thus, a NOAEL of ≥50,000 ppm (3,210 and 3,245 mg/kg/day in males and females respectively) for reproductive parameters, the highest dose tested, can be established (Klimisch score 1 – reliable without restriction).
  - *Oral:* In a GLP-compliant oral repeated dose toxicity study conducted similar to OECD Guideline 408, male and female B6C3F1 mice (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 480, 920, 1,900, 3,850, and 8,065 mg/kg/day, respectively, in males, and 450, 915, 1,830, 3760, and 7,925 mg/kg/day, respectively, in females) for 14 weeks. There were no effects to sperm motility and vaginal cytology parameters. Thus, a NOAEL of

≥50,000 ppm (8,065 and 7,925 mg/kg/day in males and females respectively) for reproductive parameters, the highest dose tested, can be established (Klimisch score 1 – reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
1,2-Transdichloroethylene was assigned a score of Moderate for developmental toxicity based on reduced fetus weights in an inhalation prenatal developmental toxicity study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity (CPA 2018b). The confidence in the score is low as the decreased in female and combined fetus weights was reported in the presence of maternal toxicity and it is not stated if these effects were secondary to maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021, U.S. EPA 2020a
  - *Inhalation (vapor):* In a GLP-compliant prenatal developmental toxicity study conducted according to the U.S. EPA's Toxic Substances Control Act Test Guidelines: Final Rules. Federal Register 50: 39426-39428 and 39433-39434 (1985), pregnant female Crl:CD®BR rats (24/concentration) were exposed to 1,2-transcholoethylene (99.64% purity) vapor at concentrations of 0, 2,000, 6,000 and 12,000 ppm 6 hours/day on gestation days (GD) 7 to 16. Maternal animals were evaluated for clinical signs, body weight, and ovary and uterine content. Fetuses were examined for weight, sex, external alternations, visceral alterations, and skeletal alternations. A significant decrease in maternal body weight was reported at 12,000 ppm and decreased feed consumption was reported at all concentrations. A trend of increase in total and early resorptions at 6,000 and 12,000 ppm was not considered to be biologically significant by the authors as values were within historical control ranges. No differences were seen in pregnancy rate, fetuses per litter, number of stunted fetuses or in corpora lutea counts. Decreased mean female fetus weight and combined fetal weight were reported at 12,000 ppm. Additionally, a significant increase in developmental variations (increase in the number with visceral variations at the low and intermediate dose, as well as a significant increase in skeletal variations in the high concentration group) was reported at all three concentrations, however, results did not show a dose response relationship and thus were not considered to be compound related. Authors established a maternal toxicity NOAEC of 2,000 ppm (7.9 mg/L[9]) based on a slight suppression of weight gain and significantly reduced food consumption throughout dosing period, and a developmental NOAEC of 6,000 ppm (23.8 mg/L[10]) for this study based on reduced female and combined fetal weights (Klimisch Score 1 – reliable without restriction).

Endocrine Activity (E) Score (H, M, or L): DG
1,2-Transdichloroethylene was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.

[9] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (2,000 * 97) / 24,450 = 194,000 / 24,450 = 7.9 mg/L
[10] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (6,000 * 97) / 24,450 = 582,000 / 24,450 = 23.8 mg/L

- U.S. EPA 2021b
    - 1,2-Transdichloroethylene was active in 0/21 estrogen receptor (ER) assays, 0/14 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/9 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
    - 1,2-Transdichloroethylene was predicted to be inactive for androgen receptor agonism, antagonism, and binding using the COMPARA (consensus) model in ToxCast.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): M

1,2-Transdichloroethylene was assigned a score of Moderate for acute toxicity based on its association with H332 (harmful if inhaled) in the EU and an oral LD_{50} of 1,256 mg/kg in female rats. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when they are associated with H332 and have oral LD_{50} values >300-2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on an authoritative A listing and experimental data with support from screening lists.

- Authoritative and Screening Lists
    - *Authoritative:* EU GHS – H332: Harmful if inhaled.
    - *Screening:* Australia GHS – H332: Harmful if inhaled.
    - *Screening:* Japan GHS – Acute toxicity (oral) – Category 4 [H302].
    - *Screening:* New Zealand GHS – 6.1D (oral) – Acutely toxic.
- ECHA 2021
    - *Oral:* LD_{50} (male and female Sprague-Dawley rat) = 7,902 mg/kg (males) and 9,939 mg/kg (females) (GLP not specified, similar to OECD 420) (Klimisch score 2 – reliable with restrictions).
    - *Oral:* LD_{50} (male and female CD-1 mice) = 2,122 mg/kg (males) and 2,391 mg/kg (females) (GLP not specified, similar to OECD 420) (Klimisch score 2 – reliable with restrictions).
    - *Dermal:* LD_{50} (male and female New Zealand white rabbits) >5,000 mg/kg (GLP-compliant, similar to OECD 402) (Klimisch score 1 – reliable without restriction).
    - *Inhalation (vapor):* 4-hr LC_{50} (male and female Crl:CD®(SD)IGS BR rats) = 24,100 ppm (95.6 mg/L[11]) (GLP-compliant, OECD 403) (Klimisch score 1 – reliable without restriction).
- U.S. EPA 2020a
    - *Oral:* LD_{50} (female Wistar rat) = 1,256 mg/kg
    - *Inhalation (vapor):* 6-hr LC_{50} (OF1SPF mice, sex not reported) = 86,131 mg/m^3 (86.131 mg/L)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): L

1,2-Transdichloroethylene was assigned a score of Low for systemic toxicity (single dose) based on lack of adverse systemic effects below the guidance values following acute oral, dermal and inhalation exposures in animals. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA

[11] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (24,100 * 97) / 24,450 = 2,337,700 / 24,450 = 95.6 mg/L

2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan GHS – Specific target organs/systemic toxicity following single exposure – Category 1 [H370].
- ECHA 2021
  - *Oral:* In an acute oral toxicity study similar to OECD Guideline 420 (GLP status not specified), male and female Sprague-Dawley rats (10/sex/dose) were administered 1,2-transdichloroethylene (98% purity) in corn oil via gavage at unspecified doses. Clinical signs including central nervous system depression, ataxia, and depressed respiration were observed at all dose levels in a dose-dependent manner. No consistent compound-related gross pathological findings were reported at necropsy. LD_{50} values of 7,902 and 9,939 mg/kg were reported for males and females, respectively (Klimisch score 2 – reliable with restrictions).
  - *Oral:* In an acute oral toxicity study similar to OECD Guideline 420 (GLP status not specified), male and female CD-1 mice (92 males and 63 females in 9 dose levels) were administered 1,2-transdichloroethylene (98% purity) in emulphor at nine doses ranging from 800-3,500 mg/kg via gavage. No deaths were reported at ≤1,200 mg/kg; the 3,500 mg/kg dose was 100% lethal for males and 88% lethal for females. At doses of 1,600, 2,000 and 2,400 mg/kg clinical signs including decreased activity and ruffled fur, and at high dose levels, ataxia, loss of righting reflex, and ruffled fur were reported. Necropsy of dead animals reported evidence of hyperemia of the mucosal surface of the stomach and small intestines. LD_{50} values of 2,122, and 2,391 mg/kg were reported for males and females, respectively (Klimisch score 2 – reliable with restrictions).
  - *Dermal:* In a GLP-compliant acute dermal toxicity study similar to OECD Guideline 402, male and female New Zealand white rabbits (2 males and 3 females) were administered unchanged 1,2-transdichloroethylene (99.64% purity) at a dose of 5,000 mg/kg under occlusive conditions for 24 hours. There were no mortalities reported and clinical sings were limited to irritation at the test site. No significant changes to body weight were reported. Necropsy results were not specified. An LD_{50} of >5,000 mg/kg was reported (Klimisch score 1 – reliable without restriction).
  - *Inhalation (vapor):* In a GLP-compliant acute inhalation toxicity study according to OECD Guideline 403, male and female Crl:CD®(SD)IGS BR rats (5/sex/concentration) were exposed to 1,2-transchloroethylene vapor (99.89% purity) at concentrations of 0, 12,300, 22,500, 28,100, and 34,100 ppm for 4 hours via whole body inhalation. Mortality occurred at 22.500 ppm and above. Clinical signs included prostration and diminished response to alerting stimulus during exposure; rats recovered within 30 minutes upon cessation of exposure. Severe weight loss for one day was reported in rats exposed at 28,100 ppm. No gross abnormalities were reported at necropsy. A NOEC of 34,100 ppm (135.3 mg/L[12]) was identified by the authors (Klimisch score 1 – reliable without restriction).
- NITE 2006, 2014
  - 1,2-Transdichloroethylene in classified to Category 1 (H370) in Japan based on effects to the respiratory organs and the liver observed within the guidance value range corresponding to Category 1. There were reports of slight-severe fatty degeneration or fatty accumulation in hepatic lobules and Kupffer cells at inhalation concentrations 0.79 mg/L in rats, and severe

[12] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (34,100 * 97) / 24,450 = 3,307,700 / 24,450 = 135.3 mg/L.

pulmonary hyperemia, alveolar septal distention and pneumonic infiltration at inhalation concentrations of 3.97 mg/L and 11.90 mg/L (whether the trans-isomer or not was unknown. Furthermore, there were necropsy findings in rats of severe pulmonary capillary hyperemia, alveolar septal distention at oral doses of 1,000 mg/kg.

- Based on the weight of evidence, a score of Low was assigned. Although 1,2-transdichloroethylene is classified to Category 1 in Japan, which corresponds to a score of Very High, the effects reported in the justification appear to be the effects identified in the short-term repeated dose toxicity studies described below. Thus, ToxServices place more weight on the reliable studies reported in the ECHA REACH dossier for this endpoint. Acute oral, dermal, and inhalation studies identified no adverse systemic effects at doses below the guidance values for classification. Neurotoxicity reported in these studies are included in the single exposure neurotoxicity section below. Therefore, a score of Low was assigned for this endpoint.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score (H, M, or L): *M*

1,2-Transdichloroethylene was assigned a score of Moderate for systemic toxicity (repeated dose) based on a LOAEC of 0.79 mg/L (equivalent to 0.76 mg/L/6h/day) in an inhalation study in rats. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when inhalation (vapor) LOAEC values are >0.2 – 1 mg/L for 90-day studies (CPA 2018b). The confidence in the score is low as only one concentration was tested and no NOAEC could be established.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In a GLP-compliant oral repeated dose toxicity study similar to OECD Guideline 408, male and female F344/N rats (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 190, 380, 770, 1,540, and 3,210 mg/kg/day, respectively, in males, and 190, 395, 780, 1,580, and 3,245 mg/kg/day, respectively, in females) for 14 weeks. Animals were examined for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, neurobehavior, gross pathology, and histopathology. Body weight was significantly reduced at the high dose. Mild decreases in hematocrit values, hemoglobin concentrations and erythrocyte counts were reported at ≥25,000 ppm in females and ≥6,250 ppm males. No toxicologically relevant changes to clinical chemistry were reported by the authors. Absolute kidney weight was significantly decreased in males exposed to ≥25,000 ppm and liver weights of females was significantly increased in ≥6,250 ppm females; however, no gross macroscopic lesions were observed. No histopathological changes were reported. The authors identified a NOAEL of ≥50,000 ppm (3,210 and 3,245 mg/kg/day in males and females respectively), the highest dose tested, for this study (Klimisch score 1 – reliable without restriction). *ToxServices identified a NOAEL of 12,500 ppm (1,540 and 1,580 mg/kg/day for males and females, respectively) based on reduced body weight.*
  - *Oral:* In an oral repeated dose toxicity study similar to OECD Guideline 408 (GLP status not specified), male and female Sprague-Dawley rats (20/sex/dose) were administered 1,2-transdichloroethylene (98% purity) in 1% emulphor in deionized water in the drinking water at doses of 500, 1,500 and 3,000 mg/kg/day (actual ingested reported as 402, 1,314, and 3,114 mg/kg/day, respectively, in males and 353, 1,257, and 2,809 mg/kg/day, respectively, in females) for 90 days. There were no adverse changes to body weight or effects to

hematology, clinical chemistry, or urinalysis parameters. Female kidney weight were increased; however, there were no gross or histopathological lesions reported. The authors identified a NOAEL of ≥3,000 mg/kg/day (3,144 and 2,890 mg/kg/day in males and females respectively), the highest dose tested (Klimisch score 2 – reliable with restrictions).

- *Oral:* In a GLP-compliant oral repeated dose toxicity study similar to OECD Guideline 408, male and female B6C3F1 mice (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 480, 920, 1,900, 3,850, and 8,065 mg/kg/day, respectively, in males, and 450, 915, 1,830, 3760, and 7,925 mg/kg/day, respectively, in females) for 14 weeks. Animals were examined for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, neurobehavior, gross pathology, and histopathology. Body weight was significantly reduced in high dose males and females exposed to ≥12,500 ppm. No remarkable changes to hematological or clinical chemistry parameters were reported. Relative liver weight was increased in males exposed to ≥12,500 ppm and females exposed to ≥25,000 ppm. No gross macroscopic lesions or histopathological changes were reported. The authors identified a NOAEL of ≥50,000 ppm (8,065 and 7,925 mg/kg/day in males and females respectively), the highest dose tested, for this study (Klimisch score 1 – reliable without restriction). *ToxServices identified a NOAEL of 6.250 ppm, equivalent to 915 mg/kg/day based on reduced body weight.*
- *Oral:* In an oral repeated dose toxicity study similar to OECD Guideline 408 (GLP status not specified), male and female CD-1 mice (140/sex/treated group, 260/sex/control) were administered 1,2-transdichloroethylene (98% purity) in 10% emulphor in deionized water in the drinking water at doses of 0.1, 1, and 2 mg/mL (reported as 17, 175, and 387 mg/kg/day, respectively, in males and 23, 224, and 452 mg/kg/day, respectively, in females) for 90 days. There were no adverse changes to body weight or effects noted at gross and histopathological examinations. Liver weights were increased in mid dose males, lung weights were decreased in high dose females, and thyroid weight was decreased in mid and high dose females. No remarkable, dose-related, changes were noted in hematology or clinical chemistry parameters. The authors identified a NOAEL of ≥2 mg/mL (387 and 452 mg/kg/day in males and females respectively), the highest dose tested (Klimisch score 2 – reliable with restrictions).
- *Oral:* In a 14-day repeated dose toxicity study (GLP status and guideline not specified), male CD-1 mice (9-10/dose) were administered 1,2-transdichloroethylene (98% purity) in 10% emulphor in deionized water at doses of 21 and 210 mg/kg/day via gavage for 14 days. There were no adverse effects to weight gain, and the weights of the brain, liver, spleen, lungs. thymus, kidney, and testes were not affected by exposure. There were no changes to hematological parameters; however, fibrinogen levels were decreased (12%) at the high dose and prothrombin activity increased slightly (as manifested by a 7% decrease in prothrombin time). There was a significant decrease (29%) in lactate dehydrogenase (LDH) levels of the high dose group. The authors identified a NOAEL of ≥210 mg/kg/day, the highest dose tested (Klimisch score 2 – reliable with restrictions).
- *Inhalation (vapor):* In a GLP-compliant OECD Guideline 413 inhalation repeated dose toxicity study, male and female Crl:CD®(SD) BR rats (15/sex/concentration) were exposed to 1,2-transdichloroethylene (99.69% purity) vapor at concentrations of 0, 200, 1,000 and 4,000 ppm via whole body inhalation 6 hours/day, 5 days/week for 90 days. Animals were examined for mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. Additionally, ophthalmoscopic examinations were performed. No adverse treatment-related effects were reported on any of the parameters measured. The author identified a NOAEC of 4,000 ppm (approximately

15.9 mg/L[13]), the highest concentration tested, for this study (Klimisch score 1 – reliable without restriction). However, U.S. EPA (2020b) reported a NOAEC and LOAEC of 1,000 and 4,000 ppm (4.0 and 15.9 mg/L, respectively) based on a statistically significant decrease in white blood cell and lymphocyte counts in male rats.

- U.S. EPA 2020a
  - *Inhalation (vapor):* In short-term and subchronic exposure study, female SPF Wistar rats (6/concentration/duration) were exposed to 1,2-transdichloroethylene (purity not reported) at concentrations of 0 or 200 ppm (reported as equivalent to 0 or 793 mg/m^3 8 hours/day, 5 days/week for 1, 2, 8, or 16 weeks. Gross necropsies were performed at sacrifice, and histopathological findings included capillary hyperemia and distension of the alveolar septum in the lungs of exposed rats. Fatty accumulation in the liver lobules and Kupffer cells was also reported in treated rats, however, the incidence was not significantly different from controls. Study authors considered the lung lesions to be systemic and the LOAEC was established at 793 mg/m^3 (0.793 mg/L) for this study. *This is equivalent to 0.755 mg/L/6h/day after adjustment for exposure duration and frequency (i.e., 0.793 mg/L x 8 hours/6 hours x 5 days/7 days).*

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): M

1,2-Transdichloroethylene was assigned a score of Moderate for neurotoxicity (single dose) based on evidence of transient narcotic effects in acute toxicity studies in animals. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when a Category 3 classification for transient narcotic effects is warranted (CPA 2018b). The confidence in the score is high it is based on consistent clinical observations across multiple studies and exposure routes.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2020a
  - Effects indicative of central nervous system (CNS) depression, including prostration and decreased responsiveness during exposure and lethargy, irregular respiration, and weakness in survivors after exposure were reported in rats exposed to 12,300 – 34,100 ppm for 4 hours.
  - Mice and cats displayed disequilibrium and lethargy at vapor concentrations of 43,000 mg/m^3, with narcosis and death occurring at 72,000 mg/m^3.
- ECHA 2021
  - *Oral:* In an acute oral toxicity study similar to OECD Guideline 420 (GLP status not specified), male and female Sprague-Dawley rats (10/sex/dose) were administered 1,2-transdichloroethylene (98% purity) in corn oil via gavage at unspecified doses. Clinical signs including central nervous system depression, ataxia, and depressed respiration were observed at all dose levels in a dose-dependent manner. No consistent compound-related gross pathological findings were reported at necropsy (Klimisch score 2 – reliable with restrictions).
  - *Oral:* In an acute oral toxicity study similar to OECD Guideline 420 (GLP status not specified), male and female CD-1 mice (92 males and 63 females in 9 dose levels) were administered 1,2-transdichloroethylene (98% purity) in emulphor at nine doses ranging from 800-3,500 mg/kg via gavage. At doses of 1,600, 2,000 and 2,400 mg/kg clinical signs including decreased activity and ruffled fur, at high dose levels, ataxia, loss of righting reflex, and ruffled fur were reported (Klimisch score 2 – reliable with restrictions).

[13] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (4,000 * 97) / 24,450 = 388,000 / 24,450 = 15.9 mg/L

- *Inhalation (vapor):* In a GLP-compliant acute inhalation toxicity study according to OECD Guideline 403, male and female Crl:CD®(SD)IGS BR rats (5/sex/concentration) were exposed to 1,2-transchloroethylene vapor (99.89% purity) at concentrations of 0, 12,300, 22,500, 28,100, and 34,100 ppm for 4 hours via whole body inhalation. Mortality occurred at 22.500 ppm and above. Clinical signs included prostration and diminished response to alerting stimulus during exposure; rats recovered within 30 minutes upon cessation of exposure. No gross abnormalities were reported at necropsy (Klimisch score 1 – reliable without restriction).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L

1,2-Transdichloroethylene was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurotoxic effects in oral and inhalation toxicity studies in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In a GLP-compliant oral repeated dose toxicity study similar to OECD Guideline 408, male and female F344/N rats (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 190, 380, 770, 1,540, and 3,210 mg/kg/day, respectively, in males, and 190, 395, 780, 1,580, and 3,245 mg/kg/day, respectively, in females) for 14 weeks. A neurobehavioral examination was conducted at weeks 4 and 13. Animals were tested for body position, activity level, coordination of movement, gait, general behavior, head flick, head searching, compulsive biting or licking, backward walking, self-mutilation, circling, convulsions, tremors, lacrimation or chromodacryorrhea, salivation, piloerection, pupillary dilation or constriction, unusual respiration, diarrhea, excessive or diminished urination, and vocalization. No adverse effects were observed on any of these parameters. Therefore, a neurotoxicity NOAEL of ≥50,000 ppm (3,210 and 3,245 mg/kg/day in males and females respectively), the highest dose tested, can be established (Klimisch score 1 – reliable without restriction).
  - *Oral:* In a GLP-compliant oral repeated dose toxicity study similar to OECD Guideline 408, male and female B6C3F1 mice (10/sex/dose) were administered 1,2-transdichloroethylene (≥99% purity) in the feed at 3,125, 6,250, 12,500, 25,000 and 50,000 ppm (reported as 480, 920, 1,900, 3,850, and 8,065 mg/kg/day, respectively, in males, and 450, 915, 1,830, 3760, and 7,925 mg/kg/day, respectively, in females) for 14 weeks. Results of the functional observation battery indicated no exposure-related findings of neurotoxicity (no further details). Therefore, a neurotoxicity NOAEL of ≥50,000 ppm (8,065 and 7,925 mg/kg/day in males and females respectively), the highest dose tested, can be established (Klimisch score 1 – reliable without restriction).
  - *Inhalation (vapor):* In a GLP-compliant OECD Guideline 413 inhalation repeated dose toxicity study, male and female Crl:CD®(SD) BR rats (15/sex/concentration) were exposed to 1,2-transdichloroethylene (99.69% purity) vapor at concentrations of 0, 200, 1,000 and 4,000 ppm via whole body inhalation 6 hours/day, 5 days/week for 90 days. A neurobehavioral examination was not conducted however, the alerting response to an auditory stimulus was checked 3 times during each exposure and immediately after exposure prior to being removed from the chambers. No effects were reported on this parameter.

Therefore, a NOAEC of 4,000 ppm (approximately 15.9 mg/L[14]), the highest concentration tested, can be established (Klimisch score 1 – reliable without restriction).

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *M*

1,2-Transdichloroethylene was assigned a score of Moderate for skin sensitization based on the presence of a structural alert as identified by Toxtree and the positive predictions from OECD Toolbox and LabMol. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when there is limited evidence of skin sensitization and a Category 1B classification is warranted (CPA 2018b). The confidence in the score is low as it is based on modeling and no experimental data were identified for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Payne and Walsh 1994
  - 1,2-Transdichloroethylene is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh. See Appendix G for complete list of structural alerts.
- OECD 2020a
  - 1,2-Transdichloroethylene is predicted to be a skin sensitizer using the OECD Toolbox model using the read-across methodology (see Appendix H).
- Toxtree 2018
  - 1,2-Transdichloroethylene is predicted to be a skin sensitizer using the Toxtree model using decision tree methodology. This chemical is identified as a substrate for the following electrophilic mechanisms known to produce a skin sensitization reaction: SN2-nucleophilic aliphatic substitution (see Appendix I).
- VEGA 2021
  - The CAESAR model predicted 1,2-transdichloroethylene as a non-sensitizer with low confidence. The ADI is 0.424 indicating the prediction is not reliable (Appendix J).
  - The IRFMN/JRC model predicted 1,2-transdichloroethylene as a non-sensitizer with low confidence. The ADI is 0.427 indicating the prediction is not reliable (Appendix J).
- LabMol 2020
  - The LabMol Pred-Skin platform predicts 1,2-transdichloroethylene is a skin sensitizer based on the Bayesian outcome prediction with high confiability. Pred-Skin estimates confiability (or degree of confidence in the prediction) by calculating the ratio of predictions made by internal models (trees in the random forest statistical model), the applicability domain (AD), and maps for the predicted fragment contribution of the structure (Borba et al. 2021). The Bayesian outcome is based on positive predictions from DPRA, KeratinoSens, h-CLAT, LLNA and HRIPT/HMT models, with confiability scores of 89.9%, 56.2%, 63%, 83.7% and 74%, respectively. However, It may be noted 1,2-transdichloroethylene was outside the domain for all models (Appendix K).
- Based on the weight of evidence, a score of Moderate was assigned. 1,2-Transdichloroethylene does not contain any structural alerts for skin sensitization as identified by Payne and Walsh (1994), however, it has not been identified as a substrate for SNS2-nucleophilic aliphatic substitution by Toxtree. Additionally, read-across using the OECD Toolbox program predicts 1,2-transdichloroethylene to be a sensitizer. Modeling predictions by VEGA were negative, however,

[14] The concentration in ppm was converted to mg/L using the following equation: mg/L = (ppm * MW) / 24,450. Therefore, mg/L = (4,000 * 97) / 24,450 = 388,000 / 24,450 = 15.9 mg/L

both models were of low reliability. Finally, the LabMol Pred-Skin platform predicts 1,2-transdichloroethylene is a skin sensitizer based on the Bayesian outcome prediction with high confiability. Based on the presence of a structural alert as identified by Toxtree and the positive predictions from OECD Toolbox and LabMol, this chemical is a potential skin sensitizer, and a score of Moderate was assigned.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): DG
1,2-Transdichloroethylene was assigned a score of Data Gap for respiratory sensitization based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020a
  - 1,2-Transdichloroethylene does not contain any structural alerts for respiratory sensitization (Appendix L)
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of 1,2-transdichloroethylene according to ECHA's guideline (ECHA 2017), which states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). 1,2-Transdichloroethylene does not contain any structural alerts, but is expected to be a skin sensitizer based on positive prediction data. According to the ECHA guidance, the positive skin sensitization results and lack of structural alerts and evidence of respiratory sensitization indicate that there is insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Due to the positive predictions for skin sensitization and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Data Gap was assigned.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
1,2-Transdichloroethylene was assigned a score of Low for skin irritation/corrosivity based on ToxServices not classifying it as a dermal irritant under GHS. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan GHS – Skin corrosion/irritation – Category 2 [H315].
  - *Screening:* New Zealand GHS – 6.3A – Irritating to the skin (Cat. 2).
- ECHA 2021
  - 1,2-Transchloroethylene was not classified as a dermal irritant in a GLP-compliant acute dermal irritation assay similar to OECD Guideline 404. New Zealand white rabbits (1 female and 5 males) were administered 0.5 mL unchanged test substance (99.64% purity) to clipped skin for 24 hours under semi-occlusive conditions. The mean (24, 48 and 72 hour) individual erythema scores were 1.3, 0.67, 0.67, 0, 1.67, and 2.3, and the mean individual

edema scores were all 0. The authors did not classify 1,2-transdichloroethylene as a dermal irritant under the conditions of this assay (Klimisch score 2 – reliable with restrictions).
    - *Based on GHS guidance (UN 2019), as at least 4 of 6 animals did not have a mean score of ≥1.5 and <2.3 for erythema or edema, a Category 3 classification is not warranted.*
- NITE 2014
    - 1,2-Transdichloroethylene is classified to GHS Category 2 in Japan based on reports of mild to moderate erythema in a skin irritation test following a 24-hour occlusive application of a 0.5 mL undiluted test substance to rabbits (assumed to be study described above). In addition, application of 5,000 mg/kg of the test substance to the skin of rabbits resulted in severe skin irritation (assumed to be acute dermal toxicity study reported in Acute Mammalian Toxicity endpoint above). Finally, 1,2-transdichloroethylene has been described to be irritating to the skin of humans.
- Based on a weight of evidence, a score of Low was assigned. Although 1,2-transdichloroethylene is classified to Category 2 in Japan, which corresponds to a score of High, the study which reported mild to moderate erythema in rabbits is assumed to be the same study descried in the ECHA REACH Dossier. Based on GHS guidance (UN 2019) a GHS classification is not warranted for this study, as described above. Furthermore, application of 5,000 mg/kg (~13 mL) test substance to the skin of rabbits that resulted in severe skin irritation is a much larger dose than that recommended in OECD Guideline dermal irritation studies. Therefore, ToxServices used the results from the GLP-compliant acute dermal irritation assay similar to OECD Guideline 404 reported in the REACH dossier to classify this endpoint. As a classification is not warranted based on the results of this study, a score of Low was assigned.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*

1,2-Transdichloroethylene was assigned a score of High for eye irritation/corrosivity based on severe irritation reported in an acute ocular irritation study in rabbits and its classification as a Category 2A irritant in Japan and New Zealand. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A for ocular irritation (CPA 2018b). The confidence in the score is low as the study did not report scores that allow for quantitative GHS classification and it is based on screening lists.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Japan GHS – Serious eye damage/eye irritation – Category 2A [H319].
    - *Screening:* New Zealand GHS – 6.4A – Irritating to the eye (Cat. 2a).
- ECHA 2021
    - 1,2-Transdichloroethylene was irritating to the eye in a GLP-compliant acute ocular irritation assay similar to OECD Guideline 405. One eye of New Zealand white rabbits (n=2) was instilled with unchanged test substance (99.64% purity) and observed for 3 days following exposure. The eye of one rabbit was washed 20 seconds after instillation; the remaining rabbits eye was left unwashed. Severe corneal opacity was noted in the washed eye. Moderate iritis and conjunctival redness and blood tinged discharge was noted in both treated eyes; moderate and mild chemosis was noted in washed and unwashed eyes, respectively. Corneal injury was also noted. Both treated eyes were normal by day 3. The mean (24, 48 and 72 hour) corneal opacity, iris, redness, and chemosis scores were 0, 0, 3, and 0, respectively in the unwashed eye and 1.67, 0.33, 1, and 0.67, respectively, in the washed eye. Authors concluded 1,2-transdichloroethylene to be irritating to the eye under the conditions of this assay (Klimisch score 2 – reliable with restrictions).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M

1,2-Transdichloroethylene was assigned a score of Moderate for acute aquatic toxicity based on the EC_{50} of 36.36 mg/L in green algae. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity values are >10 to 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - 96-hr LC_{50} (*Lepomis macrochirus*, bluegill sunfish) = 135 mg/L (GLP status and method not specified) (Klimisch score 2 – reliable with restrictions)
  - 48-hr EC_{50} (*Daphnia magna*, daphnia) = 220 mg/L (non-GLP, U.S. EPA-600/3-75-009) (Klimisch score 2 – reliable with restrictions)
  - 48-hour biomass EC_{50} (*Pseudokirchneriella subcapitata*, green algae) = 36.36 mg/L (GLP status not specified, similar to OECD 202) (Klimisch score 2 – reliable with restrictions)
- U.S. EPA 2017a
  - 1,2-Transdichloroethylene belongs to the vinyl/allyl/propargyl halides ECOSAR chemical class. The most conservative predicted acute E/LC_{50} values are 15.9 mg/L in fish (96h), 12.9 mg/L in daphnia (48h), and 19.2 mg/L in green algae (96h) (Appendix M).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*

1,2-Transdichloroethylene was assigned a score of Moderate for chronic aquatic toxicity based on an estimated ChV of 9.09 mg/L in algae. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are >1.0 to 10 mg/L (CPA 2018b). The confidence in the score is low as no experimental data were identified, and modeling and estimations were performed to predict toxicity in all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017a
  - 1,2-Transdichloroethylene belongs to the vinyl/allyl/propargyl halides ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 6.47 mg/L in fish, 0.088 mg/L in daphnia, and 4.35 mg/L in green algae (Appendix M).
- U.S. EPA 2013
  - Applying neutral organics/classes with excess toxicity acute to chronic ratios (ACR) of 10, 10, and 4 to the lowest acute toxicity values of 135, 220, and 36.36 mg/L for fish, daphnia, and algae, respectively predicts ChVs of 13.5, 22, and 9.09 mg/L, respectively.
- Based on the weight of evidence, a score of Moderate was assigned. No chronic aquatic experimental data were identified; therefore, modeling was performed using ECOSAR. ECOSAR predictions report a ChV of 0.088 mg/L for daphnia, which corresponds to a score of Very High. However acute aquatic toxicity data indicate that algae may be more sensitive than daphnia. In addition, modeled acute aquatic toxicity data are more conservative than measured data, indicating that modeled chronic data may be conservative as well. Therefore, ToxServices applied the ACR of 4 to the experimental EC_{50} to estimate a ChV of 9.09 mg/L which corresponds to a classification of Moderate.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): vL

1,2-Transdichloroethylene was assigned a score of Very Low for persistence based on it being readily biodegradable and meeting the 10-day window in an OECD Guideline 301D assay. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they are readily biodegradable and meet the 10-day window (CPA 2018b). The confidence in the score is high as it is based on a reliable experimental data for the target substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Environment Canada (EC) – CEPA Domestic Substances List (DSL) - Persistent.
- ECHA 2021
  - In a ready biodegradability test similar to OECD Guideline 301D (GLP status not specified), aerobic, domestic, activated sludge (adaption not specified) was exposed to 5 and 10 mg/L 1,2-transdichloroethylene (purity not reported) for 28 days. For the 5 mg/L sample, 67% was degraded in 7 days and 95% was degraded in 28 days with 33% lost in 10 days due to volatility. For the 10 mg/L sample, 40% was degraded in 7 days, and 93% was degraded by 28 days, with 26% loss due to volatilization. The authors concluded the test substance exhibits slow biodegradative activity concomitant with relatively moderate rate of volatilization; however, the relatively significant volatilization in the non-biological volatility control series did not preclude the biodegradative activity of microbiota in culture media (Klimisch score 2 – reliable with restrictions).
- HSDB 2018
  - Vapor-phase 1,2-transdichloroethylene will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals, ozone and nitrate radicals; the half-lives for these reactions in air are estimated to be 6.9, 57 and 310 days, respectively.
  - It does not contain chromophores that absorb at wavelengths >290 nm and, therefore, is not expected to be susceptible to direct photolysis by sunlight.
  - Based on a Henry's Law constant of 9.38×10^{-3} atm-m^3/mole volatilization from water surfaces is expected. Volatilization half-lives for a model river and model lake are 3 hours and 4 days, respectively.
  - 1,2-Transdichloroethylene is not expected to undergo hydrolysis in the environment due to the lack of functional groups that hydrolyze under environmental conditions.
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that 1,2-transdichloroethylene is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 51.5% will partition to water with a half-life of 37.5 days, 32.9% will partition to air with a half-life of 4.75 days, 15.4% will partition to soil with a half-life of 75 days, and 0.195% will partition to sediment with a half-life of 337.5 days (Appendix N).
- Based on the weight of evidence, a score of Very Low was assigned. Although 1,2-transdichloroethylene is listed on the EC DSL as Persistent, which corresponds to a score of High to Very High, this listing is based on a predicted large half-life in air. It is ToxServices' internal policy to assign the hazard score for persistence based on the dominant environmental compartment(s) (ToxServices 2020). EPI Suite™ modeling indicates water is the dominant compartment. Therefore, ToxServices used the experimental data reported in the ECHA REACH dossier to assign the score for this endpoint.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
1,2-Transdichloroethylene was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 2.06 and estimated BCF values of ≤12.14. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when measured log K_{ow} values are ≤ 4 and the BCF is ≤100 (CPA 2018b). The confidence in the score is high as it is based on a measured value with support from modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - 1,2-Transdichloroethylene has a log K_{ow} of 2.06.
- U.S. EPA 2017b
  - BCFBAF predicts a BCF of 10.62 using the regression based model based on a measured log K_{ow} of 2.06, and a BCF of 12.14 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix N).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
1,2-Transdichloroethylene was assigned a score of Low for reactivity based on it not being explosive or oxidizing and its NFPA and HMIS reactivity ratings of 0. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low due to the lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - 1,2-Transdichloroethylene does not contain chemical groups associated with explosive properties and is incapable of reacting exothermically with combustible materials.
- TCI America 2018
  - A safety data sheet for 1,2-transdichloro reports an instability rating of 0 from NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and a physical hazard rating of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").

Flammability (F) Score (vH, H, M, or L): H
1,2-Transdichloroethylene was assigned a score of High for flammability based on its association with H225, its listing by the U.S. DOT as Class 3 Group II and ToxServices classifying it as a GHS Category 2 flammable liquid under GHS. GreenScreen® criteria classify chemicals as a High hazard for flammability when they are classified as a GHS Category 2 with H225 and listed on the U.S. DOT as Class 3 Packing Group II (CPA 2018b). The confidence in the score is high as it is based on authoritative A lists and experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* EU GHS – H225: Highly flammable liquid and vapor.
  - *Authoritative:* U.S. DOT – Class 3 Group II.
  - *Screening:* Australia GHS – Highly flammable liquid and vapor.
  - *Screening:* Japan GHS – Flammable liquids – Category 2 [H225].

    - *Screening:* New Zealand GHS – 3.1B – Flammable Liquids: high hazard.
    - *Screening:* Quebec CSST – WHMIS 1988 – Class B2 – Flammable liquids.
- ECHA 2021
    - 1,2-Transdichloroethylene has a flash point of 2.22°C.
- U.S. EPA 2020a
    - 1,2-Transdichloroethylene has a flash point of 6°C in a closed cup assay.
- Based on a flash point of 2.22°C and a boiling point of 47.64-48.7°C, 1,2-transdichloroethylene is classified as a GHS Category 2 flammable liquid (UN 2019).

Use of New Approach Methodologies (NAMs)[15] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, aquatic toxicity, persistence and biodegradation, and bioaccumulation, and *in vitro* assays for mutagenicity and endocrine activity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020c, OECD 2020b). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020b):

- Type I: Uncertainties related to the input data used
- Type II: Uncertainties related to extrapolations made

As shown in Table 4, Type I (input data) uncertainties in 1,2-transdichloroethylene's NAMs dataset include no experimental or human data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and chronic aquatic toxicity. 1,2-Transdichloroethylene's Type II (extrapolation output) uncertainties include limited confidence in VEGA predictions due to low ADIs and concordance indices, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the lack of applicability domains for ToxCast models for endocrine activity, the limitation of OECD Toolbox in identifying structural alerts for respiratory sensitization without defining the applicability domain, and not accounting for non-immunologic mechanisms of respiratory sensitization, and the questionable reliability of chronic aquatic toxicity predictions. Some of 1,2-Transdichloroethylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** No *in vivo* experimental data are available. **Skin sensitization**: No experimental data are available. **Respiratory sensitization**: No experimental data are available. There are no validated test methods for this endpoint. **Chronic aquatic toxicity**: No experimental data are available.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Danish (Q)SAR database contain predictions for a limited number of chemicals and the target chemical is not in the applicability domain for multiple models (DTU 2021). Of the one model in VEGA that produced a reliable (i.e., Global AD index >0.7) prediction, the concordance index of the ISS model is 0.504,

[15] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

	which is below the desirable score of 0.7, limiting the confidence of the prediction from this model. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[16]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[17] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[18]. **Endocrine activity:** ToxCast models do not define applicability domain; the *in vivo* relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Skin sensitization:** Payne and Walsh (1994) and Toxtree only identify structural alerts, and no applicability domain can be defined (Toxtree 2018). No reliable models were produced in VEGA (VEGA 2021). Although the Bayesian outcome prediction in LabMol had high confiability, the target substance was out of the domain for individual models. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. **Chronic aquatic toxicity**: The reliability of predicted chronic aquatic toxicity is questionable as the predicted acute values are more conservative than the measured acute values.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA /OncoLogic/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay

[16] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[17] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[18] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays/ToxCast models
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	Y	*In silico* modeling: VEGA/Payne and Walsh (1994) structural alerts/ Toxtree/OECD Toolbox/LabMol
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301D Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for 1,2-Transdichloroethylene (CAS #156-60-5)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / 1,2-Transdichloroethylene / 156-60-5	*M*	L	DG	*M*	DG	M	L	*M*	M	L	*M*	DG	L	*H*	M	*M*	vL	vL	*L*	H

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	No		
2	No	No	No	No	Yes	No	Yes
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
1,2-Transdichloroethylene	2

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

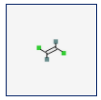
Chemical Name	Final GreenScreen® Benchmark Score
1,2-Transdichloroethylene	2

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for 1,2-Transdichloroethylene (CAS #156-60-5)



156-60-5
trans-1,2-Dichloroethylene
ALSO CALLED (E)-1,2-Dichloroethene, (E)-1,2-Dichloroethylene, 1,2-dichloroethene, 1,2-dichloroethylene , 43695-7...
View all synonyms (10)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GS Score	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
All Hazards	LT-P1	H-L	-	-	-	-	M	-	-	pC	-	-	-	H	H	-	-	M	vH-H	pC	-	H	vH	-	-	-	R

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Carcinogenicity	H-L	NoGS	US EPA - IRIS Carcinogens	(2005) Inadequate information to assess carcinogenic potential	
Acute Mammalian Toxicity	M	LT-UNK	EU - GHS (H-Statements)	H332 - Harmful if inhaled	+5
	H-M	LT-UNK	GHS - Australia	H332 - Harmful if inhaled	
	M	LT-UNK	GHS - Japan	Acute Toxicity (oral) - Category 4 [H302]	
	M	LT-UNK	GHS - New Zealand	6.1D (oral) - Acutely toxic	
	H	NoGS	US EPA - PPT Chemical Action Plans	Chronic mammalian toxicity - TSCA criteria met	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H332 - Harmful if inhaled (unverified)	
Neurotoxicity-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H336 - May cause drowsiness or dizziness (unverified)	
Skin Irritation/Corrosivity	H	LT-UNK	GHS - Japan	Skin corrosion / irritation - Category 2 [H315]	+1
	H	LT-UNK	GHS - New Zealand	6.3A - Irritating to the skin (Cat. 2)	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - Japan	Serious eye damage / eye irritation - Category 2A [H319]	+2

	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Terrestrial Ecotoxicity	M	NoGS	GHS - New Zealand	9.3C - Harmful to terrestrial vertebrates	
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	+1
	pC	NoGS	US EPA - PPT Chemical Action Plans	Medium environmental persistence - TSCA Criteria met	
Bioaccumulation	pC	NoGS	US EPA - PPT Chemical Action Plans	Moderate bioaccumulation potential - TSCA Criteria met	
Flammability	H	LT-UNK	EU - GHS (H-Statements)	H225 - Highly flammable liquid and vapour	+5
	H	LT-UNK	GHS - Australia	H225 - Highly flammable liquid and vapour	
	H	LT-UNK	GHS - Japan	Flammable liquids - Category 2 [H225]	
	H	LT-UNK	GHS - New Zealand	3.1B - Flammable Liquids: high hazard	
	vH-M	LT-UNK	Québec CSST - WHMIS 1988	Class B2 - Flammable liquids	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H225 - Highly flammable liquid and vapour (unverified)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	M	LT-UNK	GHS - Australia	H412 - Harmful to aquatic life with long lasting effects	+2
	U	LT-UNK	EU - GHS (H-Statements)	H412 - Harmful to aquatic life with long lasting effects	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified)	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	Québec CSST - WHMIS 1988	Class D2B - Toxic material causing other toxic effects	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	vH	LT-UNK	GHS - Japan	Specific target organs/systemic toxicity following single exposure - Category 1 [H370]	

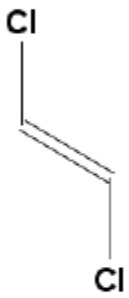
Restricted Substance Lists (8)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- China's limit standard for volatile organic compounds: Limit standard for volatile organic compounds content in adhesives (GB 33372-2020) ✱
- China's limit standard for volatile organic compounds: Limit standard for volatile organic compounds content in printing inks (GB 38507-2020) ✱
- Cradle to Cradle Certified Products Standard Version 4.0 Restricted Substances List (RSL) - Effective July 1, 2021: Core Restrictions ✱
- GSPI - Six Classes of Problematic Chemicals: Organic Solvents (Currently halogenated organic solvents) ✱
- Health Canada - Cosmetic Ingredient Hotlist: Ingredients that are Prohibited for Use in Cosmetic Products
- MA Toxics Use Reduction Act (TURA) listed substances: Reportable Chemicals
- MDH - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern

APPENDIX D: VEGA Carcinogenicity Results for 1,2-Transdichloroethylene (CAS #156-60-5)

1. Prediction Summary

Prediction for compound Molecule 0

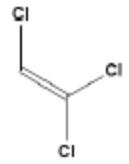


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found)
- predicted substance falls into a neuron that is populated by no compounds of the training set

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.676
P(NON-Carcinogen): 0.324
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

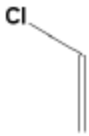
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 79-01-6
Dataset id: 765 (Training set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

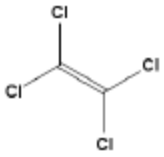
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 75-01-4
Dataset id: 796 (Test set)
SMILES: C=CCl
Similarity: 0.871

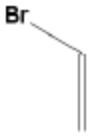
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 127-18-4
Dataset id: 727 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.764

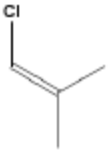
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 593-60-2
Dataset id: 795 (Training set)
SMILES: C=CBr
Similarity: 0.732

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 513-37-1
Dataset id: 278 (Training set)
SMILES: C(=C(C)C)Cl
Similarity: 0.715

Experimental value: Carcinogen
Predicted value: Carcinogen

Compound #6

CAS: 75-38-7
Dataset id: 798 (Test set)
SMILES: FC(F)=C
Similarity: 0.713

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.334 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.873 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✖	**Concordance for similar molecules** Concordance index = 0.499 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
⚠	**Atom Centered Fragments similarity check** ACF index = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found).
✔	**Model class assignment reliability** Pos/Non-Pos difference = 0.352 Explanation: model class assignment is well defined.
✖	**Neural map neurons concordance** Neurons concordance = 0.5 Explanation: predicted substance falls into a neuron that is populated by no compounds of the training set.

Symbols explanation:

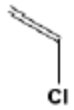
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

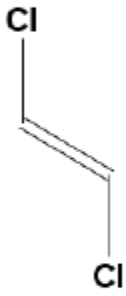
(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:



Fragment defined by the SMILES: C=CCl
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0

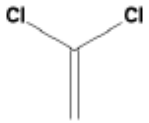


Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- some similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

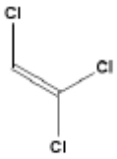
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 75-35-4
Dataset id: 91 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 79-01-6
Dataset id: 68 (Training set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

Experimental value: Carcinogen
Predicted value: Carcinogen

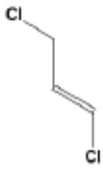
Alerts (not found in the target): SA44 Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene

Compound #3

CAS: 75-01-4
Dataset id: 253 (Training set)
SMILES: C=CCl
Similarity: 0.871

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA4 Monohaloalkene

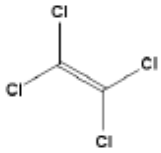


Compound #4

CAS: 542-75-6
Dataset id: 64 (Training set)
SMILES: C(=CCl)CCl
Similarity: 0.77

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA4 Monohaloalkene; SA8 Aliphatic halogens

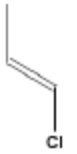


Compound #5

CAS: 127-18-4
Dataset id: 229 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.764

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA44 Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene



Compound #6

CAS: 590-21-6
Dataset id: 442 (Training set)
SMILES: C(=CCl)C
Similarity: 0.754

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA4 Monohaloalkene

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.791
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.881
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 1
Explanation: accuracy of prediction for similar molecules found in the training set is good.

Concordance for similar molecules
Concordance index = 0.504
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

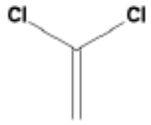
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value
The following relevant fragments have been found: Carcinogenity alert no. 57

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural alerts: Carcinogenity alert no. 57
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

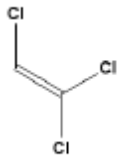


Compound #1

CAS: N.A.
Dataset id: 977 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57



Compound #2

CAS: N.A.
Dataset id: 541 (Training set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

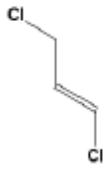
Alerts (found also in the target): Carcinogenity alert no. 57

Compound #3

CAS: N.A.
Dataset id: 794 (Training set)
SMILES: C=CCl
Similarity: 0.871

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57

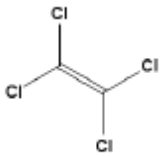


Compound #4

CAS: N.A.
Dataset id: 1259 (Training set)
SMILES: C(=CCl)CCl
Similarity: 0.77

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57

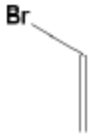


Compound #5

CAS: N.A.
Dataset id: 731 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.764

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57



Compound #6

CAS: N.A.
Dataset id: 793 (Training set)
SMILES: C=CBr
Similarity: 0.732

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 59

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.538
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.877
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.33
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.33
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

The feature has a good assessment, model is reliable regarding this aspect.
The feature has a non optimal assessment, this aspect should be reviewed by an expert.
The feature has a bad assessment, model is not reliable regarding this aspect.

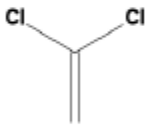
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: Carcinogenity alert no. 57

Structural alert for carcinogenity defined by the SMARTS: CCl

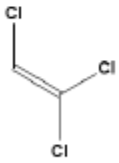
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 977 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57



CAS: N.A.
Dataset id: 541 (Training set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57

CAS: N.A.
Dataset id: 794 (Training set)
SMILES: C=CCl
Similarity: 0.871

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 57

1. Prediction Summary

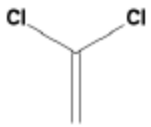
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

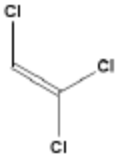
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 75-35-4
Dataset id: 651 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

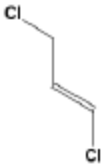
CAS: 79-01-6
Dataset id: 58 (Training set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #3

CAS: 75-01-4
Dataset id: 207 (Training set)
SMILES: C=CCl
Similarity: 0.871

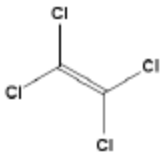
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: 542-75-6
Dataset id: 54 (Training set)
SMILES: C(=CCl)CCl
Similarity: 0.77

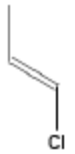
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 127-18-4
Dataset id: 187 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.764

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: 590-21-6
Dataset id: 366 (Training set)
SMILES: C(=CCl)C
Similarity: 0.754

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.544 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.877 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.337 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0.337 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

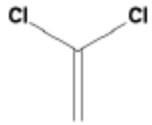
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

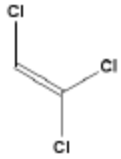
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 75-35-4
Dataset id: 442 (Test set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #2

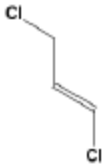
CAS: 79-01-6
Dataset id: 304 (Test set)
SMILES: C(=C(Cl)Cl)Cl
Similarity: 0.875

Experimental value: Carcinogen
Predicted value: Carcinogen

Compound #3

CAS: 75-01-4
Dataset id: 317 (Training set)
SMILES: C=CCl
Similarity: 0.871

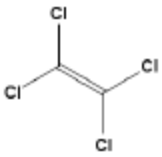
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 542-75-6
Dataset id: 115 (Training set)
SMILES: C(=CCl)CCl
Similarity: 0.77

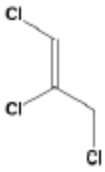
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 127-18-4
Dataset id: 288 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.764

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 96-19-5
Dataset id: 722 (Training set)
SMILES: C(=C(CCl)Cl)Cl
Similarity: 0.762

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.664 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.881 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.496 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0.504 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

1. Prediction Summary

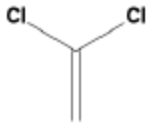
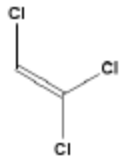
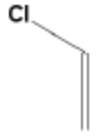
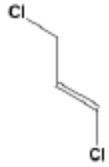
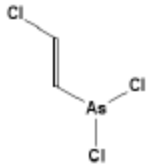
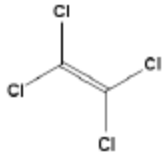
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted Inhalation Carcinogenic class: Carcinogen
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

	Compound #1 CAS: 75-35-4 Dataset id: 409 (Training set) SMILES: C=C(Cl)Cl Similarity: 0.887 Experimental value: NON-Carcinogen Predicted value: Carcinogen
	Compound #2 CAS: 79-01-6 Dataset id: 255 (Training set) SMILES: C(=C(Cl)Cl)Cl Similarity: 0.875 Experimental value: Carcinogen Predicted value: Carcinogen
	Compound #3 CAS: 75-01-4 Dataset id: 263 (Test set) SMILES: C=CCl Similarity: 0.871 Experimental value: Carcinogen Predicted value: Carcinogen
	Compound #4 CAS: 542-75-6 Dataset id: 94 (Training set) SMILES: C(=CCl)CCl Similarity: 0.77 Experimental value: Carcinogen Predicted value: Carcinogen
	Compound #5 CAS: 541-25-3 Dataset id: 535 (Test set) SMILES: C(=C[As](Cl)Cl)Cl Similarity: 0.767 Experimental value: NON-Carcinogen Predicted value: NON-Carcinogen
	Compound #6 CAS: 127-18-4 Dataset id: 244 (Training set) SMILES: C(=C(Cl)Cl)(Cl)Cl Similarity: 0.764 Experimental value: Carcinogen Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.661 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.881 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.496 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0.496 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

APPENDIX E: Danish (Q)SAR Carcinogenicity Results for 1,2-Transdichloroethylene (CAS #156-60-5)

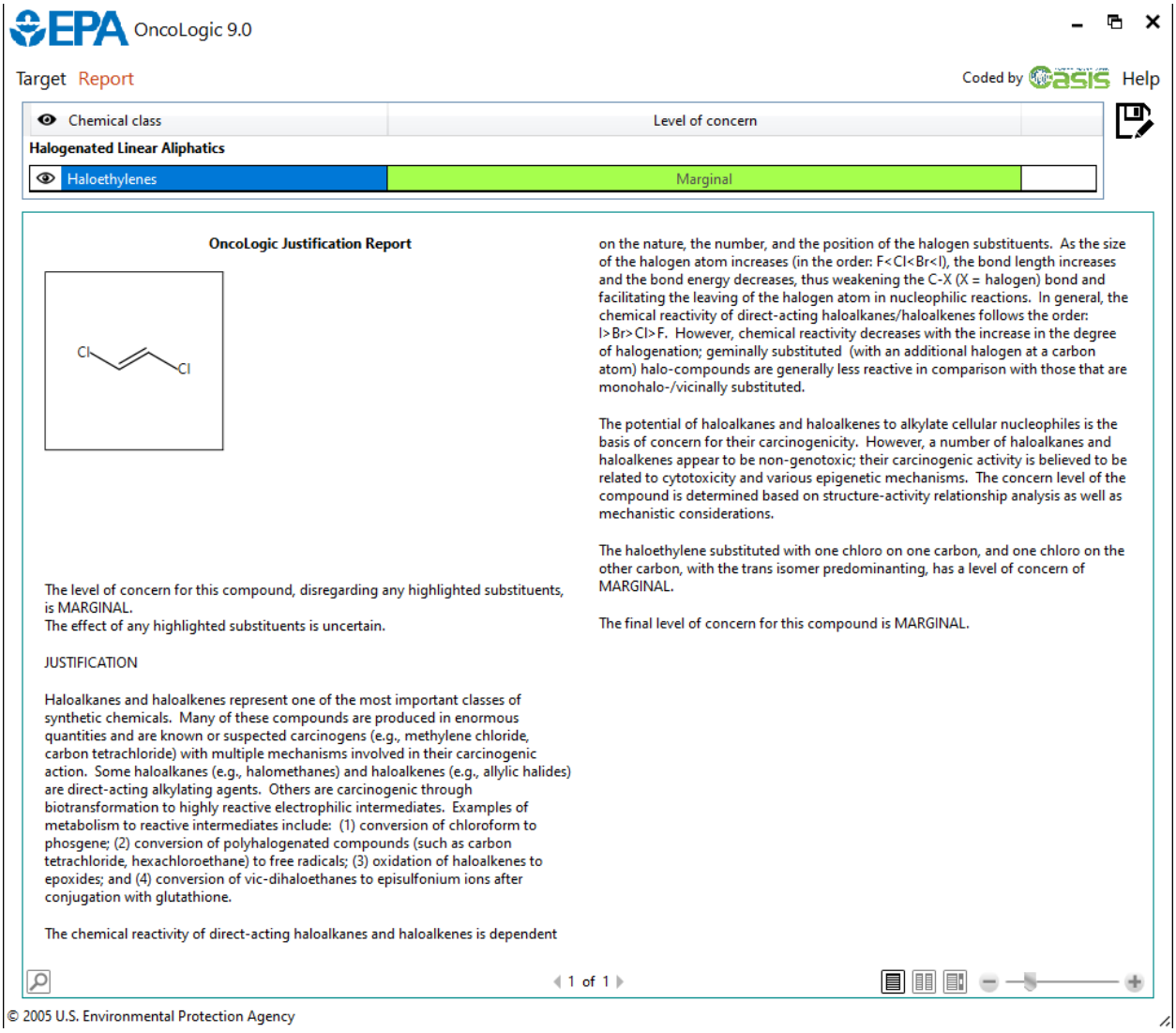
Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	POS_OUT	POS_IN
FDA RCA Cancer Female Rat	POS_OUT	POS_OUT
FDA RCA Cancer Rat	POS_OUT	POS_IN
FDA RCA Cancer Male Mouse	NEG_IN	INC_OUT
FDA RCA Cancer Female Mouse	POS_OUT	INC_OUT
FDA RCA Cancer Mouse	POS_OUT	POS_IN
FDA RCA Cancer Rodent	POS_OUT	POS_IN
Commercial models from CASE Ultra and Leadscope		
FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement		

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Halogenated Linear Aliphatic Hydrocarbone Type Compounds
OECD QSAR Toolbox v.4.2 profilers	
Profiler predictions are supporting information to be used together with the relevant QSAR predictions	

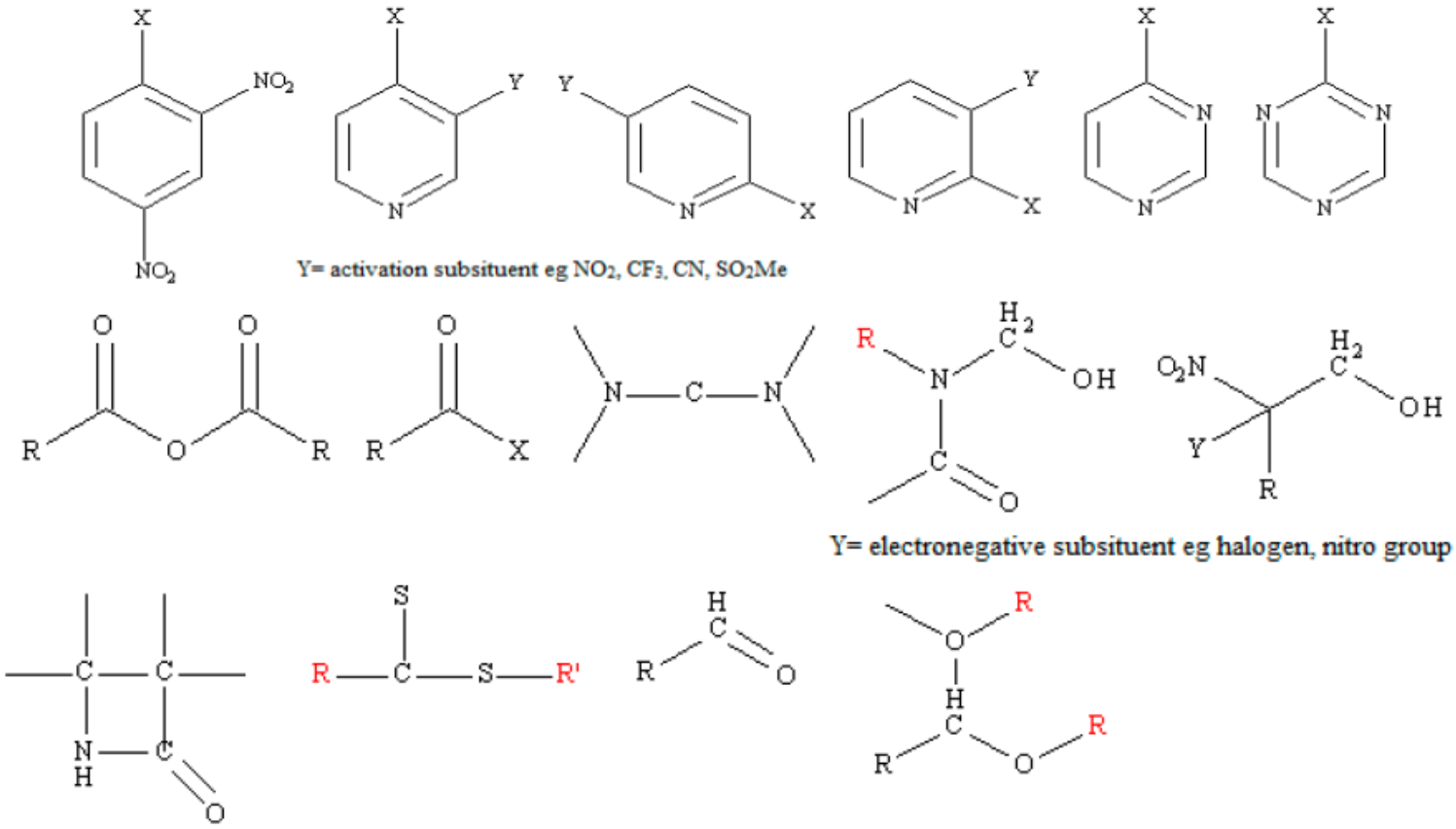
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_OUT	NEG_IN	POS_OUT	INC_OUT
DTU-developed models					

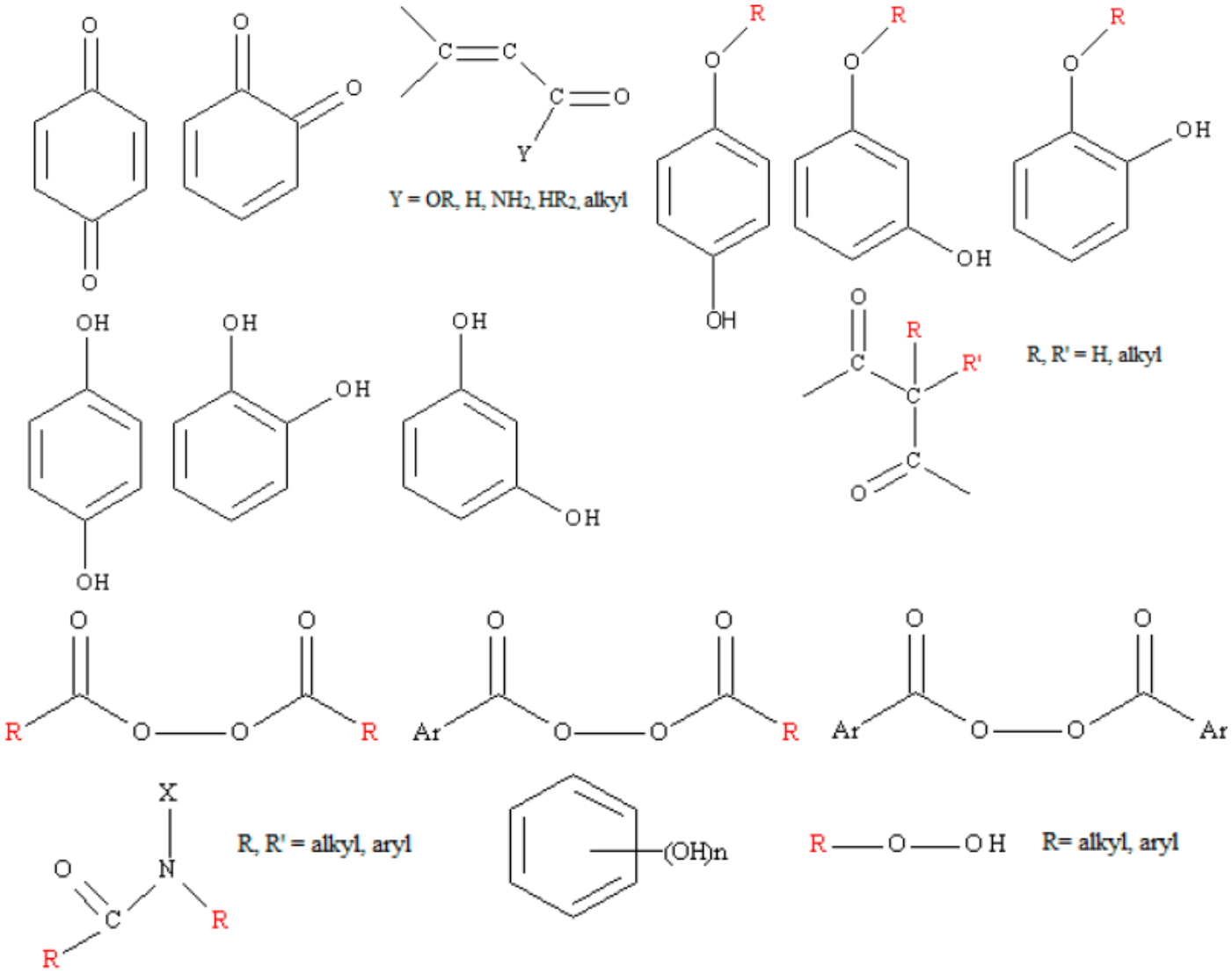
APPENDIX F: OncoLogic Carcinogenicity Results for 1,2-Transdichloroethylene (CAS #156-60-5)

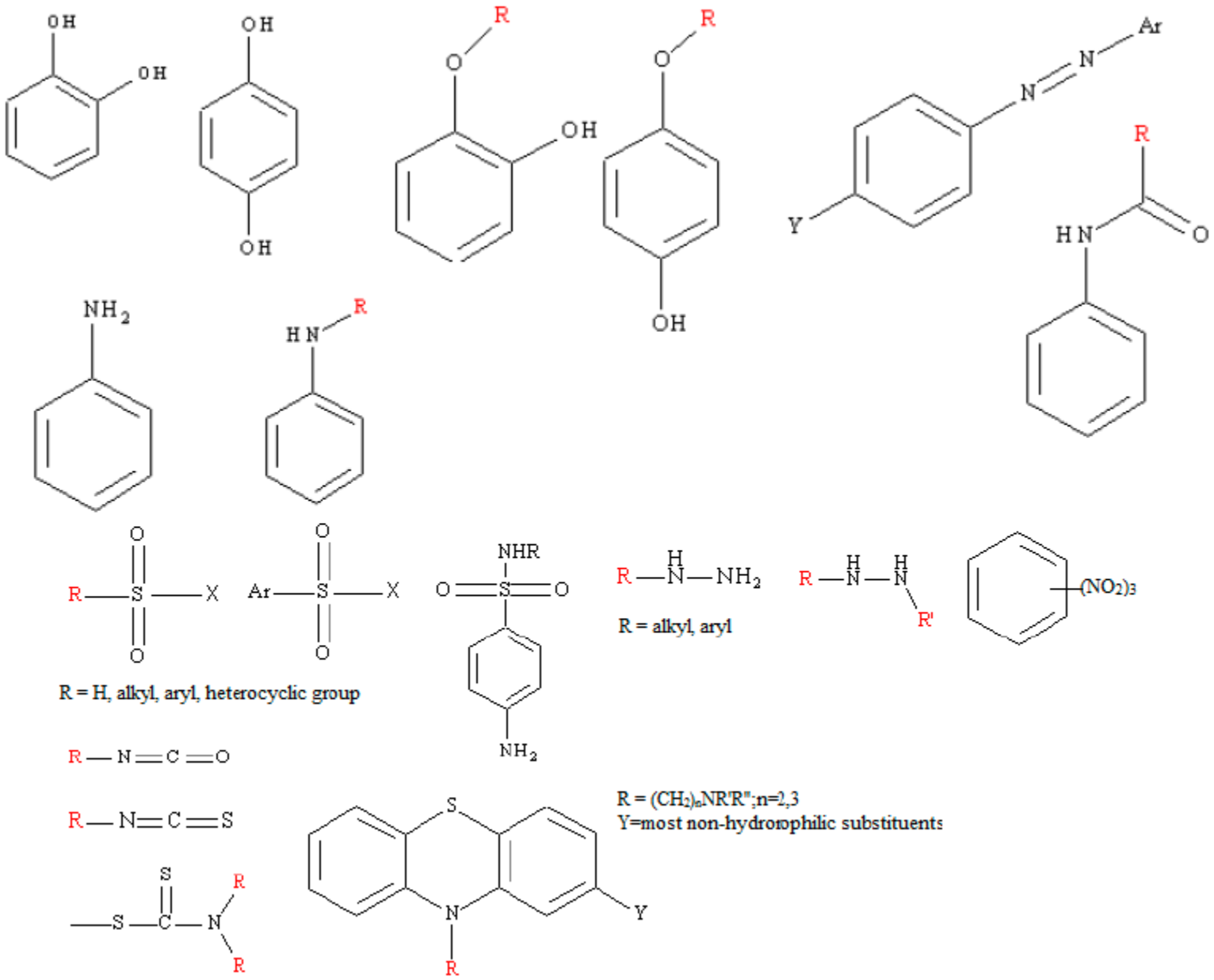


APPENDIX G: Known Structural Alerts for Skin Sensitization

Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). 1,2-Transdichloroethylene does not possess any of known structural alerts identified below.

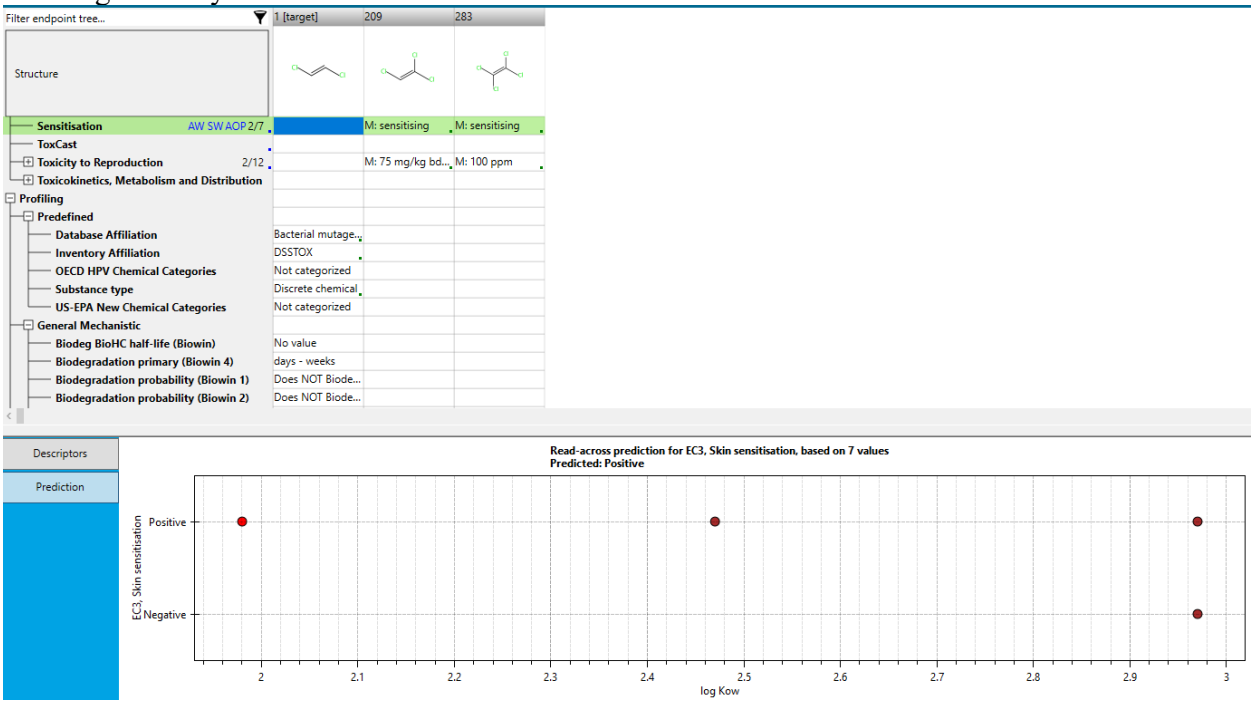




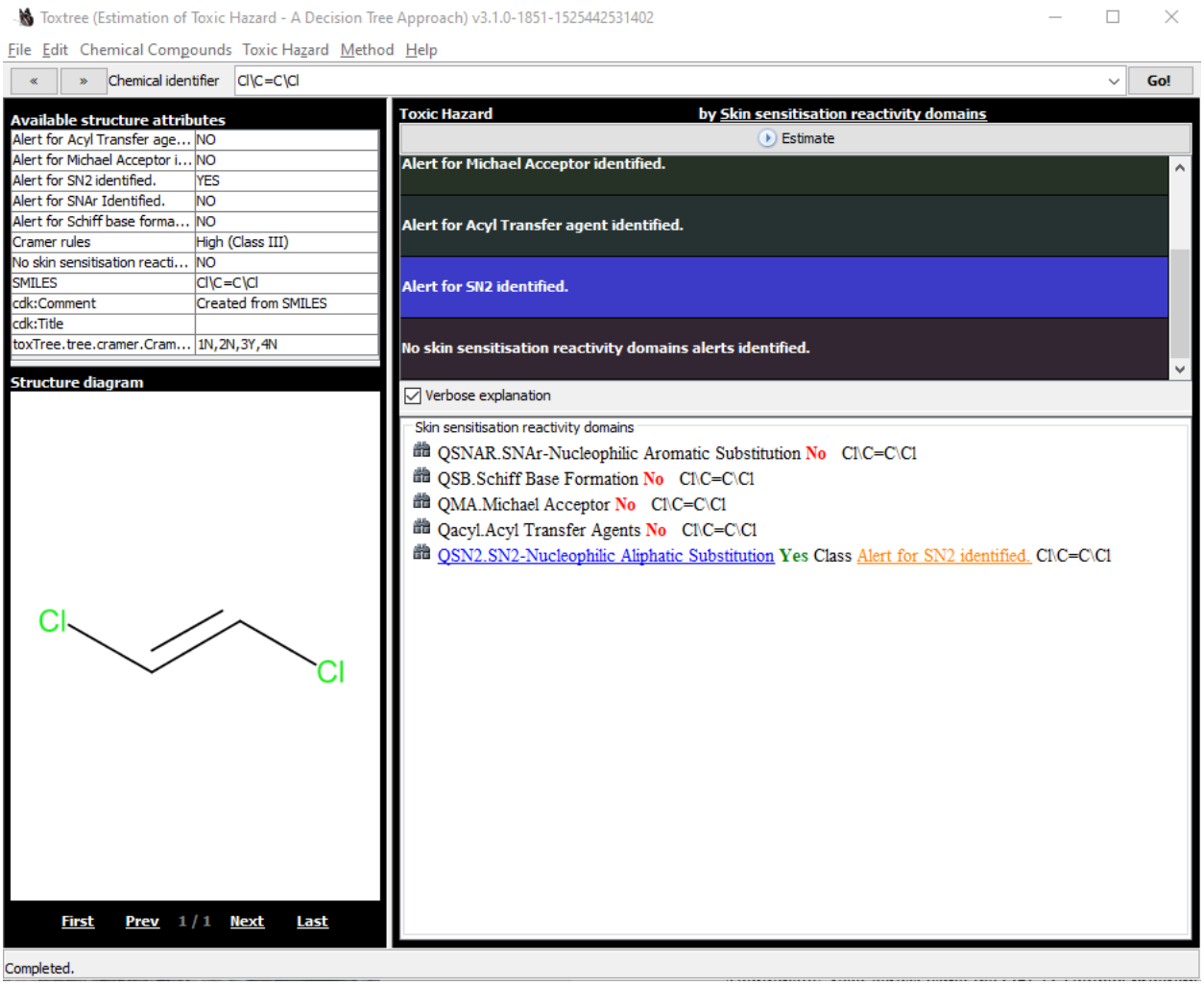


APPENDIX H: OECD Toolbox Skin Sensitization Results for 1,2-Transdichloroethylene (CAS #156-60-5)

Read across chemicals were defined by “Protein binding alerts for skin sensitization by OASIS” and subcategorized by “Chemical Elements”.



APPENDIX I: Toxtree Skin Sensitization Results for 1,2-Transdichloroethylene (CAS #156-60-5)



APPENDIX J: VEGA Skin Sensitization Results for 1,2-Transdichloroethylene (CAS #156-60-5)

1. Prediction Summary

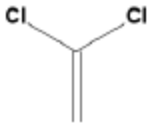
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is NON-Sensitizer, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- no similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted skin sensitization activity: NON-Sensitizer
O(Active): 0.43
O(Inactive): 0.57
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

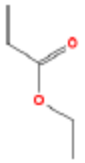
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 75-35-4
Dataset id: 209 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

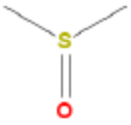
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #2

CAS: 140-88-5
Dataset id: 88 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.477

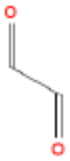
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #3

CAS: 67-68-5
Dataset id: 84 (Training set)
SMILES: O=S(C)C
Similarity: 0.473

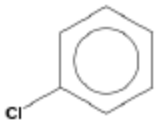
Experimental value: Sensitizer
Predicted value: NON-Sensitizer



Compound #4

CAS: 107-22-2
Dataset id: 103 (Training set)
SMILES: O=CC=O
Similarity: 0.461

Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 108-90-7
Dataset id: 54 (Training set)
SMILES: c1ccc(cc1)Cl
Similarity: 0.459

Experimental value: NON-Sensitizer
Predicted value: Sensitizer

Compound #6

CAS: 50-00-0
Dataset id: 98 (Test set)
SMILES: O=C
Similarity: 0.459

Experimental value: Sensitizer
Predicted value: NON-Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.424 Explanation: the predicted compound is outside the Applicability Domain of the model.
✖	**Similar molecules with known experimental value** Similarity index = 0.567 Explanation: no similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
⚠	**Concordance for similar molecules** Concordance index = 0.772 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✖	**Atom Centered Fragments similarity check** ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

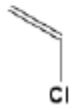
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:



Fragment defined by the SMILES: C=CCl
The fragment has never been found in the model's training set

1. Prediction Summary

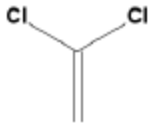
Prediction for compound Molecule 0

Prediction: Reliability:

Prediction is NON-Sensitizer, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- no similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: C(=CCl)Cl
Experimental value: -
Predicted skin sensitization activity: NON-Sensitizer
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

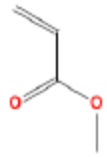
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 75-35-4
Dataset id: 207 (Training set)
SMILES: C=C(Cl)Cl
Similarity: 0.887

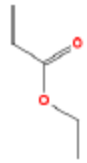
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #2

CAS: 96-33-3
Dataset id: 164 (Training set)
SMILES: O=C(OC)C=C
Similarity: 0.494

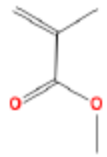
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #3

CAS: 140-88-5
Dataset id: 33 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.477

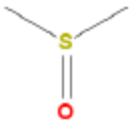
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #4

CAS: 80-62-6
Dataset id: 305 (Test set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.476

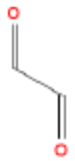
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 67-68-5
Dataset id: 30 (Training set)
SMILES: O=S(C)C
Similarity: 0.473

Experimental value: Sensitizer
Predicted value: NON-Sensitizer



Compound #6

CAS: 107-22-2
Dataset id: 40 (Training set)
SMILES: O=CC=O
Similarity: 0.461

Experimental value: Sensitizer
Predicted value: Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.427 Explanation: the predicted compound is outside the Applicability Domain of the model.
✖	**Similar molecules with known experimental value** Similarity index = 0.584 Explanation: no similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
⚠	**Concordance for similar molecules** Concordance index = 0.749 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✖	**Atom Centered Fragments similarity check** ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

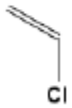
✔ The feature has a good assessment, model is reliable regarding this aspect.

⚠ The feature has a non optimal assessment, this aspect should be reviewed by an expert.

✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:



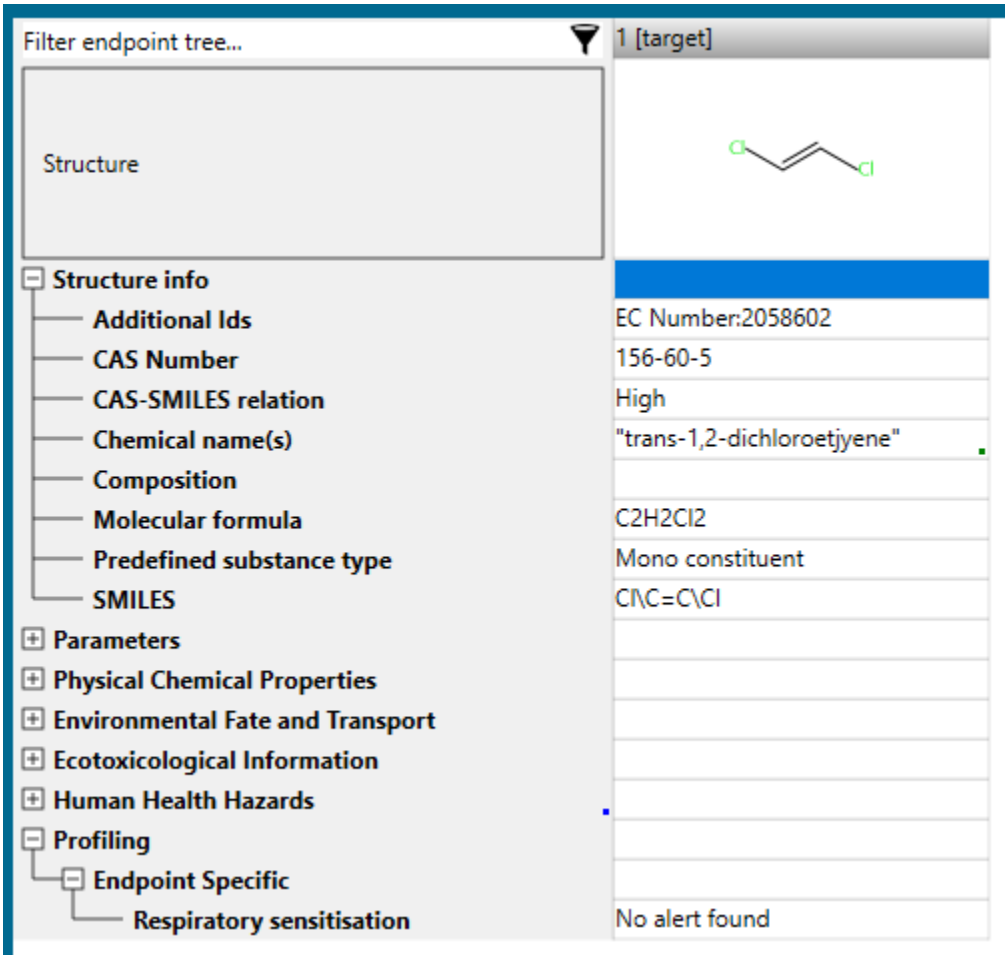
Fragment defined by the SMILES: C=CCl
The fragment has never been found in the model's training set

APPENDIX K: LabMol Skin Sensitization Results for 1,2-Transdichloroethylene (CAS #156-60-5)

Chemical Exposure	Molecular initiating event *in chemico*	Cellular response *in vitro*		Tissue / Organ response *in vivo*	Organism response *in vivo*	Pred-Skin 3.0 Outcome *in silico*
•Skin Penetration •Electrophilic substance: directly or via auto-oxidation or metabolism	Covalent interaction with proteins in the skin (OECD442C) Haptenation: covalent modification of epidermal proteins	Keratinocyte responses (OECD442D) • Activation of inflammatory cytokines •Induce cytoprotective genes	Dendritic cells (DCs) (OECD442E) • Induction of inflammatory cytokines •Mobilization of DCs	Proliferation of antigen-specific T cells (OECD429) •Histocompatibility complex representation by DCs •Activation of T cells •Proliferation of activated T cells	Inflammation upon challenge allergen To maximise the use of existing knowledge, we also incorporate historical HRIPT (human repeated insult patch test) and HMT (human maximization test)	The Bayesian model is a consensus model integrating predictions from all the other assays for an integrative qualitative risk assessment (QRA) of skin sensitization based on the weight of evidence (WoE).
•Exposure consideration ? •Physicochemical and Biopharmaceutical properties ? •Skin Penetration ? •Skin Metabolism ? 	**Prediction DPRA** Sensitizer (+) (AD, Confiability) (Outside , 89.8%) Probability map 	**Prediction KeratinoSens** Sensitizer (+) (AD, Confiability) (Outside, 56.2%) Probability map 	**Prediction h-CLAT** Sensitizer (+) (AD, Confiability) (Outside, 63.0%) Probability map 	**Prediction LLNA** Sensitizer (+) (AD, Confiability) (Outside, 83.7%) Probability map 	**Prediction HRIPT/HMT** Sensitizer (+) (AD, Confiability) (Outside, 74.0%) Probability map 	**Bayesian Outcome** Sensitizer (+) (Confiability) (High)

Low (-) confidence prediction for the Bayesian model means two or more individual predictions are in disagreement with Bayesian Outcome.

APPENDIX L: OECD Toolbox Respiratory Sensitization Results for 1,2-Transdichloroethylene (CAS #156-60-5)



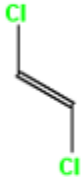
APPENDIX M: ECOSAR Modeling Results for 1,2-Transdichloroethylene (CAS #156-60-5)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
156605	Ethene, 1,2-dichloro-, (E)-	C(=CCl)Cl

Structure



Details	
Mol Wt	96.94
Selected LogKow	2.08
Selected Water Solubility (mg/L)	3500
Selected Melting Point (°C)	-49.8
Estimated LogKow	1.98
Estimated Water Solubility (mg/L)	2389.56
Measured LogKow	2
Measured Water Solubility (mg/L)	3500
Measured Melting Point (°C)	-80

Class Results:	

Vinyl/Allyl/Propargyl Halides

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	15.94	6	
Daphnid	48h	LC50	12.95	6	
Green Algae	96h	EC50	19.21	6.4	
Fish		ChV	6.47	8	
Daphnid		ChV	0.09	8	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Green Algae		ChV	4.35	8	• The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document
Fish (SW)	96h	LC50	10.98	5	
Mysid (SW)	96h	LC50	5.55	6	
Earthworm	14d	LC50	121.91	6	

APPENDIX N: EPI Suite™ Modeling Results for 1,2-Transdichloroethylene (CAS #156-60-5)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 000156-59-2
SMILES : C(=CCL)CL
CHEM : 1,2-DICHLOROETHENE (CIS)
MOL FOR: C2 H2 CL2
MOL WT : 96.94
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.06
Boiling Point (deg C) : 60.10
Melting Point (deg C) : -80.00
Vapor Pressure (mm Hg) : 200
Water Solubility (mg/L): 4520
Henry LC (atm-m3/mole) : 0.00408

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.98
Log Kow (Exper. database match) = 1.86
Exper. Ref: HANSCH,C ET AL. (1995)
Log Kow (Exper. database match) = 2.09
Exper. Ref: HANSCH,C ET AL. (1995)
Log Kow (Exper. database match) = 2.00
Exper. Ref: HANSCH,C ET AL. (1995); isomer avg.

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 53.95 (Adapted Stein & Brown method)
Melting Pt (deg C): -94.13 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 209 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 2.79E+004 (Mean VP of Antoine & Grain methods)
MP (exp database): -57 deg C
BP (exp database): 55 deg C
VP (exp database): 2.01E+02 mm Hg (2.68E+004 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 2498
log Kow used: 2.06 (user entered)
melt pt used: -80.00 deg C
Water Sol (Exper. database match) = 6410 mg/L (25 deg C)
Exper. Ref: HORVATH,AL ET AL. (1999)
Water Sol (Exper. database match) = 4520 mg/L (25 deg C)
Exper. Ref: HORVATH,AL ET AL. (1999)
Water Sol (Exper. database match) = 3500 mg/L (25 deg C)
Exper. Ref: YALKOWSKY,SH & DANNENFELSER,RM (1992)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 2153.5 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Vinyl/Allyl Halides

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.19E-002 atm-m3/mole (3.24E+003 Pa-m3/mole)
Group Method: 1.94E-002 atm-m3/mole (1.97E+003 Pa-m3/mole)
Exper Database: 4.08E-03 atm-m3/mole (4.13E+002 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: 4.080E-003 atm-m3/mole (4.134E+002 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 5.644E-003 atm-m3/mole (5.719E+002 Pa-m3/mole)
VP: 200 mm Hg (source: User-Entered)
WS: 4.52E+003 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.06 (user entered)
Log Kaw used: -0.778 (user entered)
Log Koa (KOAWIN v1.10 estimate): 2.838
Log Koa (experimental database): 2.560

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.4786
Biowin2 (Non-Linear Model) : 0.1117
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.6386 (weeks-months)
Biowin4 (Primary Survey Model) : 3.5067 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4247
Biowin6 (MITI Non-Linear Model): 0.1858
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6597
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 2.67E+004 Pa (200 mm Hg)
Log Koa (Exp database): 2.560
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.12E-010
Octanol/air (Koa) model: 8.91E-011
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 4.06E-009
Mackay model : 9E-009
Octanol/air (Koa) model: 7.13E-009

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 2.4872 E-12 cm3/molecule-sec [Cis-isomer]
OVERALL OH Rate Constant = 2.8224 E-12 cm3/molecule-sec [Trans-isomer]
Half-Life = 4.300 Days (12-hr day; 1.5E6 OH/cm3) [Cis-isomer]
Half-Life = 3.790 Days (12-hr day; 1.5E6 OH/cm3) [Trans-isomer]
Ozone Reaction:
OVERALL Ozone Rate Constant = 0.001789 E-17 cm3/molecule-sec [Cis-]
OVERALL Ozone Rate Constant = 0.003579 E-17 cm3/molecule-sec [Trans-]
Half-Life = 640.478 Days (at 7E11 mol/cm3) [Cis-isomer]
Half-Life = 320.239 Days (at 7E11 mol/cm3) [Trans-isomer]
Fraction sorbed to airborne particulates (phi):
6.53E-009 (Junge-Pankow, Mackay avg)
7.13E-009 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 39.6 L/kg (MCI method)
Log Koc: 1.598 (MCI method)
Koc : 61.3 L/kg (Kow method)
Log Koc: 1.787 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.026 (BCF = 10.62 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.2333 days (HL = 0.5844 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.084 (BCF = 12.14)
Log BAF Arnot-Gobas method (upper trophic) = 1.084 (BAF = 12.14)
log Kow used: 2.06 (user entered)

Volatilization from Water:
Henry LC: 0.00408 atm-m3/mole (entered by user)
Half-Life from Model River: 1.146 hours
Half-Life from Model Lake : 95.06 hours (3.961 days)

Removal In Wastewater Treatment:
Total removal: 62.24 percent
Total biodegradation: 0.05 percent
Total sludge adsorption: 1.17 percent
Total to Air: 61.02 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**32.9**	**114**	**1000**
Water	**51.5**	**900**	**1000**

Soil 15.4 1.8e+003 1000
Sediment 0.195 8.1e+003 0
Persistence Time: 160 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	32.9	114	1000
Water	51.5	900	1000
water	(51.5)		
biota	(0.000296)		
suspended sediment	(0.00306)		
Soil	15.4	1.8e+003	1000
Sediment	0.195	8.1e+003	0

Persistence Time: 160 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	32.2	114	1000
Water	50.5	900	1000
water	(50.5)		
biota	(0.00029)		
suspended sediment	(0.00356)		
Soil	17.2	1.8e+003	1000
Sediment	0.209	8.1e+003	0

Persistence Time: 163 hr

Licensed GreenScreen® Profilers

1,2-Transdichloroethylene GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Rachel Doerer, M.P.H.
Toxicologist
ToxServices LLC

1,2-Transdichloroethylene GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC