# ETHYLENE

**(CAS #74-85-1)**

**GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT**

**Prepared by:**

**ToxServices LLC**

**Assessment Date: November 12, 2021**

**Expiration Date: November 12, 2026**

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## GreenScreen® Executive Summary for Ethylene (CAS #74-85-1)

Ethylene is colorless gas under standard temperature and pressure. It a volatile organic compound (VOC) that flammable but is not reactive. It serves as a building block for chemical synthesis, especially polyethylene synthesis, and functions as a refrigerant, anesthetic, solvent, and fruit ripening promoter. The United States Food and Drug Administration (U.S. FDA) recognizes ethylene as an acceptable indirect food additive in adhesives and coatings, paper and paperboard components, and polymers.

Ethylene 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)
- Benchmark 2g
  - Very High Physical Hazards (flammability-F)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), ethylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if ethylene were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* genotoxicity assays, *in silico* endocrine activity and skin sensitization assessments, use of structural alerts to evaluate skin and respiratory sensitization, and ECOSAR modeling for acute and chronic aquatic toxicity. 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 ethylene's NAMs dataset include no *in vivo* and/or *in vitro* experimental data for endocrine activity, skin and respiratory sensitization, and acute and chronic aquatic toxicity, and lack of a testing method for skin sensitization for a gas. Ethylene's Type II (extrapolation output) uncertainties include limitations in the applicability domains of the (Quantitative) Structure Activity Relationship ((Q)SAR) models applied in this assessment and exogenous metabolic systems used in *in vitro* genotoxicity tests that do not entirely mirror *in vivo* metabolism. Some of ethylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data in the case of mutagenicity and the use of surrogate *in vivo* data for skin sensitization.

### GreenScreen® Hazard Summary Table for Ethylene

| 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** | *L* | *L* | DG | **L** | | **L** | *M* | **L** | *L* | *L* | *L* | *L* | *M* | *M* | *L* | **vL** | *L* | **vH** |

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 Ethylene (CAS #74-85-1)

**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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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 10, 2021, November 8, 2021

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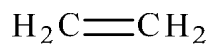
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 10, 2021; November 12, 2021

Expiration Date: November 12, 2026[2]

**Chemical Name:** Ethylene

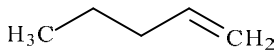
**CAS Number:** 74-85-1

**Chemical Structure(s):**



**Also called:**
Acetene; Bicarburretted hydrogen; EC 200-815-3; Ethene; Olefiant gas; UN1038; UN1962; 74-85-1; 9002-88-4; 1,2-ethylene; ethan-1,2-diyl; MFCD00084423; UN 1038; UN 1962; Plastipore; Ethyleneradical; Methylidenecarbene; 68037-39-8 (ChemIDplus 2021, PubChem 2021).

**Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):**
As ethylene is a gas, testing for skin sensitization and irritation and eye irritation is not technically feasible. ToxServices evaluated the potential for the alpha olefins propene (CAS #115-07-1) and but-1-ene (CAS #106-98-9) to serve as surrogates for these endpoints but they are also gases. Pent-1-ene (CAS #109-67-1) is the smallest alpha olefin that is a liquid under standard temperature and pressure. Therefore, ToxServices used sensitization and irritation data for pent-1-ene in addition to modeling of ethylene to address those data gaps. Since pent-1-ene is a liquid while ethylene is a gas, ToxServices considered pent-1-ene to be a weak surrogate.



Surrogate: Pent-1-ene (CAS #109-67-1)

**Identify Applications/Functional Uses** (HSDB 2018)**:**
1. Refrigerant.
2. Anesthetic.
3. Solvent.
4. Initiating gas to promote ripening of fruits.

[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).

5. Starting material for synthesis of polyethylene, ethylene oxide, ethylene dichloride, ethylbenzene, ethanol, and acetaldehyde.

**Known Impurities[3]:**
The specific purities present in ethylene depends on the specific catalyst system used during production and may include acetylene, ethane, methane, carbon monoxide, carbon dioxide, oxygen, sulfur, and hydrogen gases (HSDB 2018). The screen is performed on the theoretical pure substance.

**GreenScreen® Summary Rating for Ethylene[4,5 6,7]:** Ethylene 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)
- Benchmark 2g
  - Very High Physical Hazards (flammability-F)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), ethylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if ethylene were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

**Figure 1: GreenScreen® Hazard Summary Table for Ethylene**

| 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** | *L* | *L* | DG | **L** | | **L** | *M* | **L** | *L* | *L* | *L* | *L* | *M* | *M* | *L* | **vL** | *L* | **vH** |

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**
Ethylene exists as a gas under standard temperature and pressure with only moderate water solubility; therefore, it is expected to volatilize from soils and water (HSDB 2018). Hydrolysis is not expected for ethylene as it lacks functional groups that hydrolyze under environmental conditions. Additionally, it is not expected to undergo direct photolysis via sunlight as it absorbs ultraviolet (UV) light at 175.2 nm. It is expected to degrade in the atmosphere following reaction with photochemically-produced hydroxyl

[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.

radicals with a half-life of two days (transformation products not identified). Biodegradability data in soil or water are not available for ethylene; however, it is predicted to biodegrade to ethylene oxide (CAS #75-21-8) when exposed to acclimated cell free extracts. Although ethylene oxide is an LT-1 compound (Pharos 2021), it is readily biodegradable in OECD Guideline 301 ready biodegradability tests (ECHA 2021a). Therefore, it is not a relevant transformation product as defined under Section 11.4.3 of the GreenScreen® Guidance (CPA 2018b). Formaldehyde (CAS #50-00-0) has also been identified as a common degradation product for ethylene in air (Government of Canada 2016). Although formaldehyde is an LT-1 compound (Pharos 2021), it is also readily biodegradable in an OECD Guideline 301 D ready biodegradability test (UNEP 2003). Therefore, it also is not a relevant transformation product as defined under Section 11.4.3 of the GreenScreen® Guidance (CPA 2018b). Based on the absence of relevant transformation products, ToxServices did not adjust the Benchmark Score for ethylene based on transformation products.

**Table 1: Environmental Transformation Product Summary**

| Life Cycle Stage | Transformation Pathway | Environmental Transformation Product | CAS # | Feasible (Yes or No) | Relevant (Yes or No) | GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[8,9] |
|---|---|---|---|---|---|---|
| End | Biodegradation | Ethylene oxide | 75-21-8 | Yes | No | LT-1 (IARC Group 1 Carcinogen, EU GHS Category 1 carcinogen and mutagen) |
| End | Unspecified | Formaldehyde | 50-00-0 | Yes | No | LT-1 (IARC Group 1 Carcinogen, EU GHS Category 1 carcinogen) |

## Introduction

Ethylene is an alpha olefin that has a variety of uses, including use as a refrigerant, anesthetic, solvent, initiating gas to promote ripening of fruits (such as bananas, citrus fruits, honeydew melons, and pears), and "building block" for the manufacture of other chemicals, such as polyethylene, ethylene oxide, ethylene dichloride, ethylbenzene, ethanol, and acetaldehyde (HSDB 2018). It is produced via pyrolysis/steam cracking of petroleum hydrocarbons or dehydration of ethanol. The United States Food and Drug Administration (U.S. FDA) recognizes ethylene as an acceptable indirect food additive in adhesives and coatings (21 CFR §175.105), paper and paperboard components (21 CFR §176.180), and in polymers (21 CFR §177.1210, §177.1310, §177.1312, §177.1320, §177.1330, §177.1340, §177.1350, §177.1360, §177.1380, §177.1390, §177.1520, §177.1570, §177.1630, §177.1950, §177.2600, and §177.2800) (U.S. FDA 2021).

ToxServices assessed ethylene against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

**U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)**

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020). 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).

Ethylene is not listed on the U.S. EPA's 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),[10] 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 ethylene can be found in Appendix C.

- Ethylene is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Ethylene (UN1038, UN1962) is listed on the U.S. DOT list as a Hazard Class 2.1 flammable gas (no packing group).
- Ethylene is on the following list for multiple endpoints:
  - Québec CSST - WHMIS 1988 - Class D2B - Toxic material causing other toxic effects.
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

**Hazard Statement and Occupational Control**

A harmonized EU Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification is available for ethylene (ECHA 2021b); it is classified as a GHS Category 1 flammable gas (H220) and a GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (H336), as identified in Table 2, in addition to being classified as a pressurized gas. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) are identified in Table 3.

**Table 2: GHS H Statements for Ethylene (CAS #74-85-1) (ECHA 2021b)**

| H Statement | H Statement Details |
|---|---|
| H220 | Extremely flammable gas. |
| H336 | May cause drowsiness or dizziness. |

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

| Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Ethylene (CAS #74-85-1) | | | |
|---|---|---|---|
| **Personal Protective Equipment (PPE)** | **Reference** | **Occupational Exposure Limits (OEL)** | **Reference** |
| Gloves, face shield/safety glasses, protective clothing, full-face respirator | HSDB 2018 | ACGIH TLV: 8h TWA: 200 ppm | HSDB 2018 |
| ACGIH: American Conference of Governmental Industrial Hygienists<br>TLV: Threshold Limit Value<br>TWA: Time Weighted Average | | | |

**Physicochemical Properties of Ethylene**

Ethylene is a colorless gas under standard temperature and pressure. It is highly volatile (vapor pressure = 60,755 mm Hg) and is moderately soluble in water (131 mg/L) but is slightly more soluble in octanol (log $K_{ow}$ = 1.13).

| Table 4: Physical and Chemical Properties of Ethylene (CAS #74-85-1) | | |
|---|---|---|
| **Property** | **Value** | **Reference** |
| Molecular formula | C2-H4 | ChemIDplus 2021 |
| SMILES Notation | C=C | ChemIDplus 2021 |
| Molecular weight | 28.0536 g/mol | ChemIDplus 2021 |
| Physical state | Gas | HSDB 2018, ECHA 2021c |
| Appearance | Colorless | HSDB 2018, ECHA 2021c |
| Melting point | -169.2°C | HSDB 2018, ECHA 2021c |
| Boiling point | -103.77°C | HSDB 2018, ECHA 2021c |
| Vapor pressure | 8,100 kPa (60,755 mm Hg) at 15°C<br>52,100 mm Hg at 25°C | ECHA 2021<br>HSDB 2018 |
| Water solubility | 131 mg/L at 25°C | HSDB 2018, ECHA 2021c |
| Dissociation constant | Not applicable, no ionic structure | ECHA 2021 |
| Density/specific gravity | 50.5678 g/mL at -104°C<br>Relative density = 0.98 at 20°C | HSDB 2018<br>ECHA 2021 |
| Partition coefficient | Log $K_{ow}$ = 1.13 at 25°C<br>log $K_{ow}$ = 1.85 | HSDB 2018, ECHA 2021c<br>Government of Canada 2016 |

**Toxicokinetics**

*Absorption*:

Ethylene gas is rapidly absorbed in rats, with steady state concentrations in blood and tissues reached within 12 hours. Approximately 15% of inhaled ethylene was absorbed, but a significant fraction of the absorbed ethylene is eliminated via exhaled air, resulting in approximately 3% retained dose at steady state (ECHA 2021c)

*Distribution*:

Studies using radioactive markers indicate that ethylene and its metabolites distribute into most tissues. With the exception of blood, tissue:air partition coefficients are similar in human and rat tissues. The rat

blood partition coefficient is approximately twice that for humans owing to differences in protein binding. The metabolite ethylene oxide form adducts with hemoglobin and other proteins or DNA (ECHA 2021c).

*Metabolism*:

A portion of the absorbed ethylene is metabolized via the activity of cytochrome P-450s (CYP450s) to ethylene oxide (CAS #75-21-8) which may be further metabolized to ethylene glycol (CAS #107-21-1) via the activity of epoxide hydrolase or enzymatic or non-enzymatic conjugation with glutathione (ECHA 2021c).

*Excretion*:

Unmetabolized ethylene is eliminated via exhaled air, while polar metabolites are removed from the body via urinary excretion with smaller amounts eliminated in feces (ECHA 2021c).

**Hazard Classification Summary**

**Group I Human Health Effects (Group I Human)**

**Carcinogenicity (C) Score (H, M, or L): M**
Ethylene was assigned a score of Moderate for carcinogenicity based on an authoritative listing. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when they are classified to MAK Carcinogen Group 3B (CPA 2018b). The confidence in the score is high as it is based on an authoritative A listing.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK Carcinogen Group 3B - Evidence of carcinogenic effects but not sufficient for classification.
      - The basis for the MAK carcinogenicity classification for ethylene oxide is its metabolism to ethylene oxide, a known human carcinogen (MAK 1998).
    - IARC Group 3 - Agent is not classifiable as to its carcinogenicity to humans.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021c
  - *Inhalation*: In a non-GLP-compliant Combined Chronic Toxicity / Carcinogenicity Study conducted in a manner similar to OECD Guideline 453, Fischer 344 rats (120/sex/group) were administered whole body inhalation exposures to ethylene gas (purity not specified, contained 5.76 ppm nitrogen, 2.81 ppm ethane, 1.86 ppm methane, 1.02 ppm oxygen, < 5 ppm carbon dioxide, and < 5 ppm carbon monoxide) at 0, 300, 1,000, or 3,000 ppm for 6 hours/day, 5 days/week for 106 weeks. Treatment did not increase the tumor incidence or type of tumors identified at necropsy (Klimisch Score 2, reliable with restrictions).

**Mutagenicity/Genotoxicity (M) Score (H, M, or L): L**
Ethylene was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in a battery of *in vitro* assays and *in vivo* tests. 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 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 2021c
  - *In vitro*: Ethylene (99.5% analytical purity) was negative for mutagenicity in a modified Ames test conducted in a manner similar to OECD Guideline 471 (only one strain tested) in *Salmonella typhimurium* test strain TA100 using a gaseous exposure system at concentrations of 0.5-20% (≤ 200,000 ppm) with and without exogenous metabolic activation (S9 from livers of rats induced with Aroclor). The positive controls (benzo(a)pyrene and 2-nitrofluorene) were reported as valid (Klimisch Score 2, reliable with restrictions).
  - *In vitro*: Ethylene (purity not specified) was negative for mutagenicity in an Ames reverse mutation assay in *S. typhimurium* test strains TA98, TA100, TA1535, and TA1537 using a gaseous exposure system at concentrations of 20,000 or 100,000 ppm with and without exogenous metabolic activation (S9 from livers of rats induced with Aroclor 1254). No details were provided regarding vehicle, untreated negative, or positive controls (Klimisch Score 2, reliable with restrictions).
  - *In vitro*: Ethylene (99.4% purity) in nitrogen carrier gas was negative for clastogenicity in a GLP compliant, OECD Guideline 473 *in vitro* mammalian chromosome aberration test in Chinese hamster ovary (CHO) cells at concentrations from 92-275 μg/mL with and without exogenous metabolic activation (S9 from livers of rats induced with Aroclor 1254). The vehicle, untreated negative, and positive (4-nitroquinoline 1-oxide, cyclophosphamide) controls were reported as valid (Klimisch Score 1, reliable without restriction).
  - *In vivo*: Ethylene (99.4% analytical purity) was negative for clastogenicity in a GLP-compliant. EPA OTS 798.5395 assay (*in vivo* mammalian cytogenics tests: erythrocyte micronucleus assay) in F344/DuCrl rats (10/sex/group) after exposure to 0, 300, 1,000, 3,000, or 10,000 ppm gas via whole body inhalation 6 hours/day, 5 days/week for 13 weeks. Treatment did not increase the frequency of micronuclei in peripheral blood reticulocytes or femoral bone marrow. The vehicle, negative, and positive (cyclophosphamide) controls were reported as valid (Klimisch Score 1, reliable without restriction).
  - *In vivo*: Ethylene (99.99% purity) was negative for clastogenicity in a GLP-compliant, OECD Guideline 474 mammalian erythrocyte micronucleus test in male Fischer 344 rats (10/group) after exposure to 0, 40, 1,000, or 3,000 ppm via whole body inhalation exposures 6 hours/day, 5 days/week, for 4 weeks. Treatment did not increase the frequency of femoral micronucleated erythrocytes. The vehicle, negative, and positive (ethylene oxide) controls were reported as valid (Klimisch Score 1, reliable without restriction).
  - *In vivo*: Ethylene (99.99% analytical purity) was negative for mutagenicity in an *in vivo* Hrpt Locus Mutation test in male Fischer 344 rats (7/group) after whole body inhalation exposure to 0, 40, 1,000, or 3,000 ppm gas 6 hour/day, 5 days/week, for 4 weeks. Treatment did not increase the Hrpt mutant frequencies in splenic T cells. The vehicle, negative, and positive (ethylene oxide) controls were reported as valid (Klimisch Score 2, reliable with restrictions).
  - *In vivo*: Ethylene (99.99% analytical purity) was negative for mutagenicity in an *in vivo* Hrpt Locus Mutation test in male B6C3F1 mice (7/group) after whole body inhalation exposure to 0, 40, 1,000, or 3,000 ppm gas 6 hour/day, 5 days/week, for 4 weeks. Treatment did not increase Hrpt mutant frequencies in splenic T cells. The vehicle, negative, and positive (ethylene oxide) controls were reported as valid (Klimisch Score 2, reliable with restrictions).

- *In vivo*: Ethylene was negative for clastogenicity in a GLP-compliant, OECD Guideline 474 mammalian erythrocyte micronucleus test in male B6C3F1 mice (10/group) after whole body inhalation exposure to 0, 40, 1,000, or 3,000 ppm 6 hours/day, 5 days/week, for 4 weeks. Treatment did not increase the incidence of micronucleated femoral erythrocytes. The vehicle, negative, and positive (ethylene oxide) controls were reported as valid (Klimisch Score 1, reliable without restriction).

**Reproductive Toxicity (R) Score (H, M, or L):** *L*
Ethylene was assigned a score of Low for reproductive toxicity based on the absence of adverse effects on reproductive parameters in an OECD Guideline 421 reproduction/developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on results of a screening test that evaluates fewer endpoints that a full multi-generation reproductive toxicity test.

- 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 2021c
  - In a GLP-compliant, OECD Guideline 421 reproduction/developmental toxicity screening test, Crl: CD BR rats (10/sex/dose) were administered head-only inhalation exposures to ethylene gas (99.94% purity) at 0, 200, 1,000, or 5,000 ppm (equivalent to 230, 1,147, and 5,737 mg/m$^3$, respectively) 6 hours/day for a minimum of 28 days consisting of two weeks prior to mating, during mating, and until day 28 for males or day 20 of gestation for females. Treatment did not produce adverse effects on estrus cyclicity, fertility or fecundity, litter size, or histopathology of the testis, epididymis, or ovaries. The authors established a reproductive NOAEC of 5,000 ppm (equivalent to 5,737 mg/m$^3$ or 5.737 mg/L[11]) based on the lack of effects on reproduction at up to the highest concentration tested (Klimisch Score 1, reliable without restriction).

**Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L):** *L*
Ethylene was assigned a score of Low for developmental toxicity based on the absence of adverse effects on developmental parameters in an OECD Guideline 421 reproduction/developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on results of a screening test that evaluates fewer endpoints that a full prenatal developmental toxicity test.

- 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 2021c
  - In the GLP-compliant, OECD Guideline 421 reproduction/developmental toxicity screening test described above for reproductive toxicity, Crl: CD BR rats (10/sex/dose) were administered head-only inhalation exposures to ethylene gas (99.94% purity) at 0, 200, 1,000, or 5,000 ppm (equivalent to 230, 1,147, and 5,737 mg/m$^3$, respectively) 6 hours/day for a minimum of 28 days (two weeks prior to mating, during mating, and until day 28 for males or day 20 of gestation for females). Offspring were sacrificed on postnatal day 4.

[11] 5737 mg/m$^3$ * 1 m$^3$/1000 L = 5.737 mg/L.

Treatment did not adversely affect litter size, sex ratio, mean pup weight, pup growth and clinical condition, or external examinations. The authors identified a developmental NOAEC of 5,000 ppm (equivalent to 5,737 mg/m$^3$ or 5.737 mg/L[12]) based on the lack of effects on offspring at up to the highest concentration tested (Klimisch Score 1, reliable without restriction).

**Endocrine Activity (E) Score (H, M, or L):** DG

Ethylene was assigned a score of Data Gap for endocrine activity based on insufficient data identified.

- 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 2021
  - Ethylene was predicted to be inactive for estrogen receptor agonism, antagonism, and binding using the CERAPP Potency Level (Consensus) model. It was also predicted to be inactive for androgen receptor agonism, antagonism and binding using the COMPARA (Consensus) model in ToxCast (Appendix D).
- DTU 2021
  - Ethylene, its predicted metabolites from *in vivo* rat metabolism simulator, and predicted metabolites from the rat liver S9 metabolism simulator, contain no structural alerts for estrogen receptor binding (Appendix E).
  - Ethylene was predicted to be negative and in domain by the SciQSAR model for estrogen receptor α binding (full training set and balanced training set) and activation (Appendix E).
  - Ethylene was predicted to be negative and in domain by the SciQSAR model for androgen receptor inhibition (Appendix E).
  - Ethylene was out of the domain for the Leadscope model for thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*) and QSAR2 (Rat *in vitro*) models (Appendix E).
- VEGA 2021
  - Ethylene was predicted to be inactive in the Estrogen Receptor Relative Binding Affinity model (IRFMN) with low reliability [Global applicability domain (AD) Index = 0] (Appendix F).
  - Ethylene was predicted to be non-active in the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with low reliability (Global AD Index = 0) (Appendix F).
  - Ethylene was predicted to be non-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with moderate reliability (Global AD Index = 0.777, similarity index = 0.604, accuracy index = 1, concordance index = 1) (Appendix F).
  - Ethylene was predicted to be inactive in the Thyroid Receptor Alpha effect (NRMEA) 1.0.0 model with strong reliability (Global AD Index = 0.832, similarity index = 0.692, accuracy index = 1, concordance index = 1) (Appendix F).
  - Ethylene was predicted to be inactive in the Thyroid Receptor Beta effect (NRMEA) 1.0.0 model with strong reliability (Global AD Index = 0.832, similarity index = 0.692, accuracy index = 1, concordance index = 1) (Appendix F).
  - Ethylene was predicted to be inactive in the Aromatase activity (IRFMN) 1.0.0 model with moderate reliability (Global AD Index = 0.715, similarity index = 0.511, accuracy index = 1, concordance index = 1) (Appendix F).
- Based on the weight of evidence, ToxServices assigned a Data Gap for endocrine activity. While it lacks structural alerts for estrogenic, androgenic, and thyroid hormone activity, no *in vivo* data are

[12] 5737 mg/m3 * 1 m$^3$/1000 L = 5.737 mg/L.

available to determine ethylene's effects on circulating estrogen, androgen, and thyroid hormone levels. Therefore, ToxServices assigned a Data Gap for this endpoint.

**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): L**

Ethylene was assigned a score of Low for acute toxicity based on a 4-hour $LC_{50}$ > 65.4 mg/L in rats and an estimated $LC_{50}$ of 826.5 mg/L in mice. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when inhalation $LC_{50}$s are > 20 mg/L for gases or vapors (CPA 2018b). The confidence in the score is high as it is based on measured data from a rat study.

- 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 2021c
  - *Inhalation*: 4-hour $LC_{50}$ (male Holtzman rats) > 57,000 ppm (> 65.4 mg/L) (non-GLP-compliant) (Klimisch Score 2, reliable with restrictions).
    - Note: the rats in this study were administered three daily doses of Aroclor 1254 via gavage immediately preceding the ethylene exposure. The REACH dossier authors concluded that the lack of mortality in all dose groups was sufficient to conclude that the $LC_{50}$ for ethylene is greater than the highest concentration administered.
  - *Inhalation*: 5-hour whole body $LC_{50}$ (male Fischer 344 rats) > 10,000 ppm (> 11.473 mg/L) (non-GLP-compliant) (Klimisch Score 2, reliable with restrictions).
    - Note: the rats in this study were administered three daily doses of Aroclor 1254 via gavage immediately preceding the ethylene exposure. The REACH dossier authors concluded that the lack of mortality in at the administered concentration was sufficient to conclude that the $LC_{50}$ for ethylene is greater than this concentration.
- UNEP 2002
  - The $LC_{50}$ in mice is estimated to be 950,000 ppm.
    - Based on a conversion factor of 1 ppm / 0.87 mg/m$^3$ (Government of Canada 2016), this value is equivalent to 826,500 mg/m$^3$ or 826.5 mg/L.

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

Ethylene was assigned a score of Data Gap for systemic toxicity (single dose) based on insufficient data identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified. As the acute $LC_{50}$ values reported in ECHA (2021c) were determined from studies that involved pretreatment with Aroclor 1254, these studies were not considered for single exposure organ toxicity since there is no way to differentiate between effects of Aroclor 1254 and ethylene.

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

Ethylene was assigned a score of Low for systemic toxicity (repeated dose) based on systemic toxicity NOAECs ≥ 2.45 mg/L following subchronic or chronic exposures. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when inhalation NOAECs are greater than 1.0 mg/L for 6 hours/day exposures (CPA 2018b). The confidence in the score is high as it is based on measured data from high quality studies (GLP-compliant and internationally or nationally-accepted guidelines).

- 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 2021c
  - *Inhalation*: In a GLP-compliant, OECD Guideline 413/EU Method B.29/EPA OPPTS 870.3465 subchronic repeated inhalation exposure toxicity test, F344/DuCrl rats (10/sex/group) were administered whole body inhalation exposures to ethylene gas (99.4% purity) at 0, 300, 1,000, 3,000, or 10,000 ppm (equivalent to 0, 344.2, 1,147.3, 3,442, and 11,473 mg/m$^3$, respectively) 6 hours/day, 5 days/week for 13 weeks (65 days of exposure). The animals were evaluated for clinical signs of toxicity, body weight, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, hemoglobin adducts, gross pathology, organ weights, and histopathology. Treatment-related effects were limited to eosinophilic rhinitis in the nasal passages of rats in all concentration groups. No evidence of systemic toxicity was identified at up to the highest concentration tested. Therefore, the authors identified a local effects LOAEC of 300 ppm (344.2 mg/m$^3$ or 0.246 mg/L for a seven-day/week exposure frequency[13]) and a systemic toxicity NOAEC of 10,000 ppm (equivalent to 11,473 mg/m$^3$ or 8.2 mg/L for a seven-day/week exposure frequency[14]) (Klimisch Score 1, reliable without restrictions).
  - *Inhalation*: In a GLP compliant subchronic repeated inhalation exposure toxicity study, male Fischer 344 rats (6/group) were administered whole body inhalation exposures to ethylene gas (99.999% purity) at 10,000 ppm (equivalent to 11,473 mg/m$^3$) for 4 or 13 weeks, and male Wistar rats were administered whole body inhalation exposures at 10,000 ppm for 13 weeks. The exposures occurred for 6 hours/day, 5 days/week. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, gross pathology, organ weights (lymph nodes only), and histopathology. Treatment produced subacute rhinitis with accompanying airway epithelial remodeling in Fischer rats after 4 and 13 weeks and Wistar rats after 13 weeks. The lesions in F344 rats were less severe after 4 weeks relative to those identified after 13 weeks. The incidence and severity of lesions were higher in F344 rats than in Wistar rats. The authors identified a local effects LOAEC of 10,000 ppm (equivalent to 11,473 mg/m$^3$ or 8.2 mg/L for a seven-day/week exposure frequency as calculated previously), the only concentration tested, based on the nasal lesions (Klimisch Score 1, reliable without restrictions).
  - *Inhalation*: In the non-GLP-compliant combined chronic toxicity/carcinogenicity study described above for carcinogenicity, Fischer 344 rats (120/group) were administered whole body inhalation exposures to ethylene gas (purity not specified, 5.76 ppm nitrogen, 2.81 ppm ethane, 1.86 ppm methane, 1.02 ppm oxygen, < 5 ppm carbon dioxide, < 5 ppm carbon monoxide) at 0, 300, 1,000, or 3,000 ppm (equivalent to 0, 344.2, 1,147, and 3,442 mg/m$^3$) 6 hours/day, 5 days/week for 106 weeks. No effects on clinical signs, body weight,

[13] 344.2 mg/m$^3$ * 5 days/7 days * 1 m$^3$/1,000 L = 0.246 mg/L.
[14] 11,473 mg/m$^3$ * 5 days/7 days * 1 m$^3$/1,000 L = 8.2 mg/L.

ophthalmoscopic examination, clinical chemistry, urinalysis, organ weights, gross pathology, or histopathology were observed. The authors identified a NOAEC of 3,000 ppm (3,442 mg/m$^3$ or 2.45 mg/L based on a seven-day/week exposure frequency[15]) based on the lack of effects (Klimisch Score 2, reliable with restrictions).

- UNEP 2002, ECHA 2021c
  - In a 90-day inhalation study, male and female albino rats (15/sex/dose, strain not specified) were administered 0, 300, 1,000, 3,000, or 10,000 ppm (equivalent to 0, 345, 1,150, 3,450, and 11,500 mg/m$^3$, respectively) for 6 hours/day, 5 days/week. No treatment-related effects on body weight, food consumption, hematology, clinical chemistry, gross pathology, or histopathology were observed. The authors identified 10,000 ppm (equivalent to 11,500 mg/m$^3$) or approximately 8.2 mg/L for a seven-day/week exposure frequency) as the NOEC for this study (Klimisch Score 4, not assignable).

**Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L):** *M*
Ethylene was assigned a score of Moderate for neurotoxicity (single dose) based on an authoritative listing. GreenScreen® criteria classify chemicals as a Low to Moderate hazard for neurotoxicity (single dose) when classified as GHS Category 3 specific target organ toxicants following single exposures for narcotic effects by the EU (CPA 2018b). ToxServices conservatively assigned a Moderate score for this endpoint in order to be protective of human health. The confidence in the score is low as it is based on an authoritative B list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU GHS (H-Statements) - H336 - May cause drowsiness or dizziness [Specific target organ toxicity - single exposure; Narcotic effects - Category 3].
  - *Screening:*
    - GHS - Australia H336 - May cause drowsiness or dizziness [Specific target organ toxicity - single exposure; Narcotic effects - Category 3].
    - GHS – Japan - H336 - May cause drowsiness or dizziness [Specific target organs/systemic toxicity following single exposure - Category 3].
      - Based on ethylene's use as an anesthetic in humans (NITE 2006, 2013).
    - Grandjean and Landrigan - Neurotoxic Chemicals – Neurotoxic
- ECHA 2021a
  - Ethylene was commonly used as an anesthetic as an 80% ethylene 20% oxygen mixture.

**Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L**
Ethylene was assigned a score of Low for neurotoxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated exposures for neurotoxicity under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study (GLP-compliant and internationally accepted guideline).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Grandjean and Landrigan - Neurotoxic Chemicals - Neurotoxic

[15] 3,442 mg/m$^3$ * 5 days/7days * 1m$^3$/1,000 L = 2.45 mg/L

- ECHA 2021c
    - *Inhalation*: In a GLP-compliant, OECD Guideline 413/EU Method B.29/EPA OPPTS 870.3465 subchronic repeated inhalation exposure toxicity test, F344/DuCrl rats (10/sex/group) were administered whole body inhalation exposures to ethylene gas (99.4% purity) at 0, 300, 1,000, 3,000, or 10,000 ppm (equivalent to 0, 344.2, 1,147.3, 3,442, and 11,473 mg/m$^3$, respectively) 6 hours/day, 5 days/week for 13 weeks (65 days of exposure). The animals were evaluated for neurobehavior via assessments of grip strength, sensory and motor activity, and rectal temperature. No treatment-related effects were identified for these endpoints. Therefore, ToxServices identified a neurotoxicity NOAEC of 10,000 ppm (equivalent to 11,473 mg/m$^3$ or 8.2 mg/L for a seven-day/week exposure frequency as calculated above), the highest concentration tested (Klimisch Score 1, reliable without restrictions).
- Based on the lack of neurobehavioral effects in a test battery conducted as part of a subchronic inhalation exposure test in rats, ToxServices did not classify ethylene as a specific target organ toxicant following repeated exposures for neurotoxicity under GHS criteria (UN 2019).

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

Ethylene was assigned a score of Low for skin sensitization based on negative modeling and negative data for the surrogate pent-1-ene in an LLNA. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as it is based on modeling and data for a weak surrogate.

- 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
    - Ethylene is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh (1994). See Appendix G for complete list of structural alerts.
- OECD 2020a
    - Ethylene is predicted to not be a skin sensitizer using the OECD Toolbox model using the read-across methodology. See Appendix H for justification.
- Toxtree 2018
    - Ethylene is predicted to not be a skin sensitizer using the Toxtree model using decision tree methodology. This chemical has not been identified as a substrate for any of the five electrophilic mechanisms known to produce a skin sensitization reaction. See Appendix I for justification.
- VEGA 2021
    - Ethylene is predicted to not be a skin sensitizer with low reliability using the VEGA models. See Appendix J for justification.
- ECHA 2021d
    - *Surrogate: Pent-1-ene (CAS #109-67-1)*: A GLP-compliant, OECD Guideline 429/EU Method B.42 local lymph node assay (LLNA) was performed with female CBA/CaOlaHsd mice (4/group) administered topical applications of pent-1-ene (purity not specified) in acetone/olive oil (4:1 v/v) at 0%, 25%, 50%, or 100% on three consecutive days. The animals were sacrificed five days after the first dose and the draining auricular lymph nodes were isolated for the proliferation assessment. The stimulation indices (SIs) were 0.83, 0.82, and 0.58 for the 25%, 50%, and 100% treatments, respectively. As none of the SIs exceeded

a value of 3, the authors concluded that pent-1-ene was not sensitizing under the tested conditions (Klimisch Score 1, reliable without restriction).

**Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L):** *L*

Ethylene was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- 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
  - Ethylene does not contain any structural alerts for respiratory sensitization (Appendix K)
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA 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). As ethylene was not predicted to be sensitizing to the skin and the surrogate pent-1-ene was not sensitizing in an LLNA (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by ethylene, and as ethylene does not contain any structural alerts for respiratory sensitization (OECD 2020a), ethylene is not expected to be a respiratory sensitizer.

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

Ethylene was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation produced by the surrogate pent-1-ene in a rabbit test. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as it is based on data for a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2002
  - There is no evidence to suggest that ethylene is an irritant, but the liquid may cause frost injuries.
- ECHA 2021d
  - *Surrogate: Pent-1-ene (CAS #109-67-1)*: A non-GLP-compliant dermal irritation test conducted in a manner similar to EU Method B.4 was performed with Russian (albino) rabbits (3 females) administered topical applications of 0.5 mL undiluted pent-1-ene (purity not specified) to shaved intact or scarified skin under occlusive dressing for 4 hours. The dermal reactions were evaluated at 1, 24, 48, and 72 hours. Treatment did not produce erythema or edema at any of these time points; the mean erythema and edema scores at 24, 48, and 72 hours were both 0/4. The authors concluded that pent-1-ene was not irritating under the tested conditions (Klimisch Score 2, reliable with restrictions).

**Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L):** *L*
Ethylene was assigned a score of Low for eye irritation/corrosivity based on ToxServices not classifying it as an ocular irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as it is based on data for a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2002
  - There is no evidence to suggest that ethylene is an irritant but the liquid may cause frost injuries.
- ECHA 2021d
  - *Surrogate: Pent-1-ene (CAS #109-67-1)*: A non-GLP-compliant ocular irritation test conducted in a manner similar to EU Method B.5 was performed with Russian albino rabbits (3 females) administered ocular instillations of 0.1 mL undiluted pent-1-ene (purity not specified). The ocular reactions were evaluated 1, 24, 48, and 72 hours after instillation. At 24, 48, and 72 hours, the mean corneal opacity score was 0/4, the mean iris score was 0/2, and the mean conjunctival score was 1/3 (individual animal scores of 1, 1, and 1), and the mean chemosis score was 0.1 (individual animal scores of 0, 0.3, and 0). The conjunctival redness persisted to the end of the 72-hour observation period and consisted of grade 1 slight hyperemia. The conjunctival swelling was identified in one animal and completely resolved within 48 hours of instillation. Conjunctival secretion was also detected in two animals but resolved completely within 24 hours. The authors concluded that pent-1-ene was not irritating under the tested conditions.
- Under GHS criteria (UN 2019), a chemical is classified as irritating to the eyes if it produces mean scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following readings at 24, 48, and 72 hours, with reversibility of the irritation effects occurring within 21 days (Category 2A) or 7 days (Category 2B). Based on the mean conjunctival redness score of 1 and chemosis score of 0.1, ToxServices did not classify pent-1-ene, and by extrapolation ethylene, as an ocular irritant under GHS criteria.

## Ecotoxicity (Ecotox)

**Acute Aquatic Toxicity (AA) Score (vH, H, M, or L):** *M*
Ethylene was assigned a score of Moderate for acute aquatic toxicity based on estimated acute aquatic toxicity values as low as 55.81 mg/L for aquatic invertebrates and 30.327 mg/L for 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). This score is supported by Japan's classification of ethylene as a GHS Category 3 acute aquatic toxicant. The confidence in the score is low as it is based on modeling and a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS Japan H402 - Harmful to aquatic life [Hazardous to the aquatic environment (acute) - Category 3].
- ECHA 2021c
  - 96-hour $LL_{50}$ (*Oncorhynchus mykiss*, rainbow trout) = 115 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).

  - 96-hour $LC_{50}$ (fish) = 126.012 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 48-hour $LL_{50}$ (*Daphnia magna*) = 215 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 48-hour $LC_{50}$ (daphnia sp.) = 62.482 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 72-hour $EL_{50}$ (*Pseudokirchneriella subcapitata*, algae) = 119.325 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 96-hour $EC_{50}$ (green algae) = 30.327 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
- U.S. EPA 2017a
  - Ethylene belongs to the Neutral Organics ECOSAR chemical class. The most conservative predicted acute E/$LC_{50}$ values are 105.19 mg/L in fish (96h), 55.81 mg/L in daphnia (48h), and 31.41 mg/L in green algae (96h) (Appendix L).

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

Ethylene was assigned a score of Moderate for chronic aquatic toxicity based on the lowest estimated chronic aquatic toxicity values of 4.51-9.14 mg/L for all three trophic levels. 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 it is based on 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.
  - *Other:*
    - GHS – Japan - H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3].
- ECHA 2021c
  - 30-day chronic toxicity value (fish) = 12.385 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 32-day NOELR (*Oncorhynchus mykiss*, rainbow trout) = 22.083 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 21-day NOELR (*D. magna*) = 41.311 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - Chronic aquatic toxicity value (daphnia species) = 6.311 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - 72-hour NOELR (*P. subcapitata*, algae) = 22.859 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
  - Chronic aquatic toxicity value (green algae) = 7.07 mg/L (estimated) (Klimisch Score 2, reliable with restrictions).
- U.S. EPA 2017a
  - Ethylene belongs to the Neutral Organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 9.14 mg/L in fish, 4.51 mg/L in daphnia, and 7.07 mg/L in green algae (Appendix L).

## Environmental Fate (Fate)

**Persistence (P) Score (vH, H, M, L, or vL):** *L*
Ethylene was assigned a score of Low for persistence based on an estimated half-life of 15 days in water and 1.125 days in air, its predicted dominant environmental compartments. GreenScreen® criteria classify chemicals as a Low hazard for persistence when water or air are the dominant environmental compartments and the half-lives in water and air are < 16 days and < 2 days, respectively (CPA 2018b). The confidence in the score is low as it based on 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.
- UNEP 2002
  - Ethylene has a predicted half-life of 1.45 days in the atmosphere (all relevant pathways). It has a half-life of 1-28 days in water under aerobic conditions.
- Government of Canada 2016
  - Ethylene has environmental half-lives of 1-28 days in soil and water, 4-112 days in sediment, and 1.01 days in air.
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that ethylene is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 71.9% will partition to water with a half-life of 360 hour (15 days), 26.9% will partition to air with a half-life of 27 hours (1.125 days), and 1.04% will partition to soil with a half-life of 720 hours (30 days) (Appendix M).

**Bioaccumulation (B) Score (vH, H, M, L, or vL): vL**
Ethylene was assigned a score of Very Low for bioaccumulation based on estimated BCFs ≤ 4 and a measured log $K_{ow}$ of 1.13. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCFs are no greater than 100 and log $K_{ow}$ values are no greater than 4 (CPA 2018b). The confidence in the score is high as it is based on measured log $K_{ow}$ values supported by modeled BCFs.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2002
  - Ethylene is not expected to bioaccumulate because it has an estimated log $K_{ow}$ of 1.13 and the vapor pressure is high. The calculated (QSAR) BCF is 4.
- Government of Canada 2016
  - Based on a log $K_{ow}$ of 1.85, a BCF of 1.774 was calculated for ethylene.
- U.S. EPA 2017b
  - BCFBAF predicts a BCF/BAF of 0.413using the regression-based model based on a measured log $K_{ow}$ of 1.13, and a BCF of 2.087 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix M).

## Physical Hazards (Physical)

**Reactivity (Rx) Score (vH, H, M, or L):** *L*
Ethylene was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity

when no GHS classification is available (CPA 2018b). The confidence in the score was low as it is not based on measured data or authoritative lists.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of ethylene. These procedures are listed in the GHS (UN 2019).
  - Based on the structure of its components or moieties, ethylene is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (see Appendix N).
  - Based on the structure of its components or moieties, ethylene is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.
- ECHA 2021c
  - Ethylene does not contain structural alerts for explosive or oxidizing properties.
- Based on the above information, ToxServices did not classify ethylene as a reactive chemical under GHS criteria (UN 2019).

**Flammability (F) Score (vH, H, M, or L): vH**

Ethylene was assigned a score of Very High for flammability based on an authoritative listing. GreenScreen® criteria classify chemicals as a Very High hazard for flammability when they are classified as GHS Category 1 flammable gases (H220) by the EU (CPA 2018b). The confidence in the score was high as it is based on an authoritative A listing.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU GHS (H-Statements) - H220 - Extremely flammable gas [Flammable gases - Category 1].
  - *Screening:*
    - GHS – Australia - H220 - Extremely flammable gas [Flammable gases - Category 1].
    - GHS – Japan - H220 - Extremely flammable gas [Flammable gases - Category 1].
    - GHS - New Zealand - 2.1.1A - Flammable Gases: high hazard.
    - Québec CSST - WHMIS 1988 - Class B1 - Flammable gases.
- ECHA 2021c
  - Ethylene has an auto-ignition temperature of 450°C.
  - Ethylene has lower and upper explosion limits of 2.7% and 36%, respectively.
- ECB 2000
  - Ethylene is an extremely flammable liquefied gas.
  - Ethylene is very flammable.
- UNEP 2002
  - Ethylene has a flash point of -136.11°C.

**Use of New Approach Methodologies (NAMs)[16] in the Assessment, Including Uncertainty Analyses of Input and Output**

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* genotoxicity assays, *in silico* endocrine activity and skin sensitization assessments, use of structural alerts to evaluate skin and respiratory sensitization, and ECOSAR modeling for acute and chronic aquatic toxicity. 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 2020, 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 5, Type I (input data) uncertainties in ethylene's NAMs dataset include no *in vivo* and/or *in vitro* experimental data for endocrine activity, skin and respiratory sensitization, and acute and chronic aquatic toxicity, and lack of a testing method for skin sensitization for a gas. Ethylene's Type II (extrapolation output) uncertainties include limitations in the applicability domains of the (Quantitative) Structure Activity Relationship ((Q)SAR) models applied in this assessment and exogenous metabolic systems used in *in vitro* genotoxicity tests that do not entirely mirror *in vivo* metabolism. Some of ethylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data in the case of mutagenicity and the use of surrogate *in vivo* data for skin sensitization.

| **Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses** | |
|---|---|
| **Uncertainty Analyses (OECD 2020b)** | |
| **Type I Uncertainty: Data/Model Input** | **Endocrine activity**: No *in vivo* experimental data are available.<br>**Respiratory sensitization**: No experimental data are available and there are no validated test methods.<br>**Skin sensitization:** Testing is not feasible as a gas, data are only available for a weak surrogate.<br>**Acute and chronic aquatic toxicity:** No experimental data are available. |
| **Type II Uncertainty: Extrapolation Output** | **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[17]. |

[16] 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).

[17] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

| | | |
|---|---|---|
| | 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].<br><br>**Endocrine activity:** ToxCast models don't define applicability domain. The *in vivo* relevance of *in silico* modeling by ToxCast, VEGA and Danish QSAR models is uncertain due to lack of consideration of toxicokinetics and other factors.<br><br>**Skin sensitization:** The *in silico* models evaluating key events in the skin sensitization AOP don't typically include metabolism or abiotic transformation to address chemicals that are pro-haptens or pre-haptens, respectively.[19]<br><br>**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. |
| **Endpoint** | **NAMs Data Available and Evaluated? (Y/N)** | **Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)** |
| Carcinogenicity | N | |
| Mutagenicity | Y | *In vitro* data: Bacterial reverse mutation assay/*in vitro* chromosome aberration assay |
| Reproductive toxicity | N | |
| Developmental toxicity | N | |
| Endocrine activity | Y | ToxCast models/ Danish QSAR/VEGA |
| 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 |

[18] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[19] https://www.oecd-ilibrary.org/environment/test-no-442c-in-chemico-skin-sensitisation_9789264229709-en; https://www.oecd-ilibrary.org/environment/test-no-442d-in-vitro-skin-sensitisation_9789264229822-en; https://www.oecd-ilibrary.org/environment/test-no-442e-in-vitro-skin-sensitisation_9789264264359-en

| | | |
|---|---|---|
| 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™ |
| 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 Ethylene (CAS #74-85-1)

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 / Ethylene / 74-85-1 | M | L | *L* | *L* | DG | L | | L | *M* | L | *L* | *L* | *L* | *L* | *M* | *M* | *L* | vL | *L* | vH |

**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 |
|---|---|
| Ethylene | 2 |

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

**Table 6**

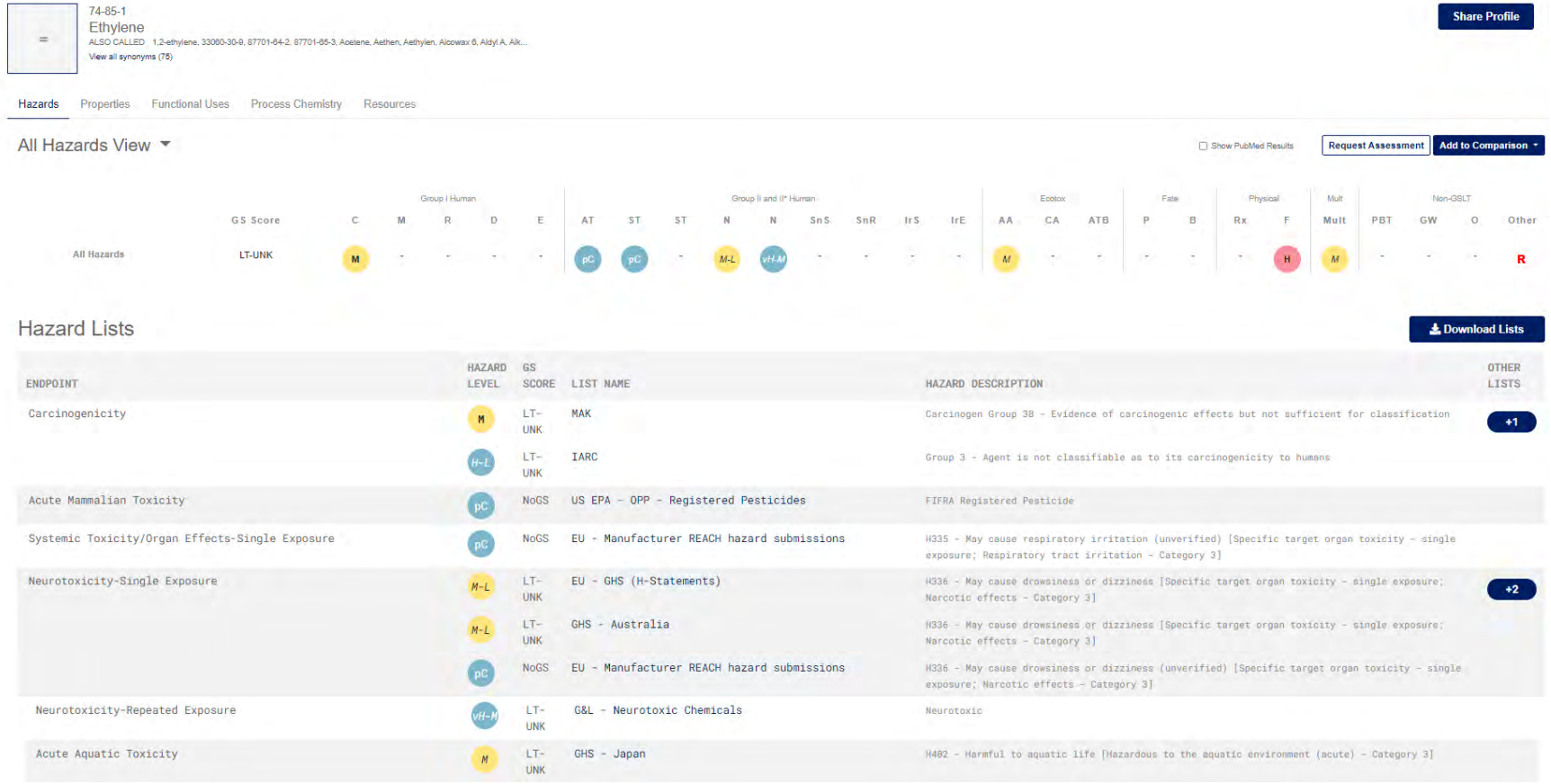
| Chemical Name | Final GreenScreen® Benchmark Score |
|---|---|
| Ethylene | 2 |

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 Ethylene (CAS #74-85-1)



74-85-1
Ethylene
ALSO CALLED 1,2-ethylene, 33080-30-9, 87701-64-2, 87701-65-3, Acetene, Aethen, Aethylen, Alcowax 6, Aldyl A, Alk...
View all synonyms (75)

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-UNK | M | - | - | - | - | pC | pC | - | M-L | vH-M | - | - | - | - | M | - | - | - | - | - | H | M | - | - | - | R |

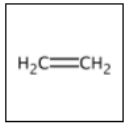
## Hazard Lists

Download Lists

| ENDPOINT | HAZARD LEVEL | GS SCORE | LIST NAME | HAZARD DESCRIPTION | OTHER LISTS |
|---|---|---|---|---|---|
| Carcinogenicity | M | LT-UNK | MAK | Carcinogen Group 3B - Evidence of carcinogenic effects but not sufficient for classification | +1 |
| | H-L | LT-UNK | IARC | Group 3 - Agent is not classifiable as to its carcinogenicity to humans | |
| Acute Mammalian Toxicity | pC | NoGS | US EPA - OPP - Registered Pesticides | FIFRA Registered Pesticide | |
| Systemic Toxicity/Organ Effects-Single Exposure | pC | NoGS | EU - Manufacturer REACH hazard submissions | H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3] | |
| Neurotoxicity-Single Exposure | M-L | LT-UNK | EU - GHS (H-Statements) | H336 - May cause drowsiness or dizziness [Specific target organ toxicity - single exposure; Narcotic effects - Category 3] | +2 |
| | M-L | LT-UNK | GHS - Australia | H336 - May cause drowsiness or dizziness [Specific target organ toxicity - single exposure; Narcotic effects - Category 3] | |
| | pC | NoGS | EU - Manufacturer REACH hazard submissions | H336 - May cause drowsiness or dizziness (unverified) [Specific target organ toxicity - single exposure; Narcotic effects - Category 3] | |
| Neurotoxicity-Repeated Exposure | vH-M | LT-UNK | G&L - Neurotoxic Chemicals | Neurotoxic | |
| Acute Aquatic Toxicity | M | LT-UNK | GHS - Japan | H402 - Harmful to aquatic life [Hazardous to the aquatic environment (acute) - Category 3] | |

| | | | | | |
|---|---|---|---|---|---|
| Flammability | H | LT-UNK | EU - GHS (H-Statements) | H220 - Extremely flammable gas [Flammable gases - Category 1] | +5 |
| | H | LT-UNK | GHS - Australia | H220 - Extremely flammable gas [Flammable gases - Category 1] | |
| | H | LT-UNK | GHS - Japan | H220 - Extremely flammable gas [Flammable gases - Category 1] | |
| | H | LT-UNK | GHS - New Zealand | 2.1.1A - Flammable Gases: high hazard | |
| | H | LT-UNK | Québec CSST - WHMIS 1988 | Class B1 - Flammable gases | |
| | pC | NoGS | EU - Manufacturer REACH hazard submissions | H220 - Extremely flammable gas (unverified) [Flammable gases - Category 1] | |
| 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 | |
| T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)] | U | LT-UNK | GHS - Japan | H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3] | |
| Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure] | M | LT-UNK | GHS - Japan | H335 or H336 [Specific target organs/systemic toxicity following single exposure - Category 3] | |

## APPENDIX D: ToxCast Model Predictions for Ethylene (CAS #74-85-1)



Ethylene

74-85-1 | DTXSID1026378

Searched by CAS-RN.

### ToxCast: Models

ToxCast Model Predictions

Download ToxCast Model Predictions

| Model | Receptor | Agonist | Antagonist | Binding |
|---|---|---|---|---|
| ToxCast Pathway Model (AUC) | Androgen | - | - | - |
| ToxCast Pathway Model (AUC) | Estrogen | - | - | - |
| COMPARA (Consensus) | Androgen | Inactive | Inactive | Inactive |
| CERAPP Potency Level (From Literature) | Estrogen | - | - | - |
| CERAPP Potency Level (Consensus) | Estrogen | Inactive (Inactive) | Inactive (Inactive) | Inactive (Inactive) |

## APPENDIX E: Danish QSAR Endocrine Activity Results for Ethylene (CAS #74-85-1)

| | Exp | Battery | CASE Ultra | Leadscope | SciQSAR |
|---|---|---|---|---|---|
| Estrogen Receptor α Binding, Full training set (Human *in vitro*) | | NEG_OUT | INC_OUT | NEG_OUT | NEG_IN |
| Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*) | | NEG_OUT | INC_OUT | NEG_OUT | NEG_IN |
| Estrogen Receptor α Activation (Human *in vitro*) | | NEG_OUT | INC_OUT | NEG_OUT | NEG_IN |
| Estrogen Receptor Activation, CERAPP data (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Androgen Receptor Inhibition (Human *in vitro*) | | NEG_OUT | INC_OUT | NEG_OUT | NEG_IN |
| Androgen Receptor Binding, CoMPARA data (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Androgen Receptor Inhibition, CoMPARA data (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Androgen Receptor Activation, CoMPARA data (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Thyroid Receptor α Binding (Human *in vitro*) | | | | | |
| - mg/L | | | 4486.76 | 326.0641 | 19.85331 |
| - µM | | | 159955.8 | 11624.39 | 707.7828 |
| - Positive for $IC_{50} \leq 10$ µM | | | | | |
| - Positive for $IC_{50} \leq 100$ µM | | | | | |
| - Domain | | OUT | OUT | OUT | OUT |
| Thyroid Receptor β Binding (Human *in vitro*) | | | | | |
| - mg/L | | | 907.6807 | 5.523864 | 163.0545 |
| - µM | | | 32359.38 | 196.9292 | 5812.996 |
| - Positive for $IC_{50} \leq 10$ µM | | | | | |
| - Positive for $IC_{50} \leq 100$ µM | | | | | |
| - Domain | | OUT | OUT | OUT | OUT |
| Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Pregnane X Receptor (PXR) Binding (Human *in vitro*) | N/A | NEG_OUT | INC_OUT | NEG_OUT | NEG_IN |
| Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW | | N/A | N/A | INC_OUT | N/A |
| Pregnane X Receptor (PXR) Activation (Human *in vitro*) | | N/A | N/A | INC_OUT | N/A |

| | Exp | Battery | CASE Ultra | Leadscope | SciQSAR |
|---|---|---|---|---|---|
| Pregnane X Receptor (PXR) Activation (Rat *in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*) | | N/A | N/A | INC_OUT | N/A |
| | Exp | Battery | CASE Ultra | Leadscope | SciQSAR |
| CYP3A4 Induction (Human *in vitro*) | | N/A | N/A | INC_OUT | N/A |

*DTU-developed models*

| | |
|---|---|
| Estrogen Receptor Binding, alerts in: | |
| - parent only | Non binder, non cyclic structure |
| - metabolites from *in vivo* Rat metabolism simulator only | Non binder, non cyclic structure; Non binder, without OH or NH2 group |
| - metabolites from Rat liver S9 metabolism simulator only | Non binder, non cyclic structure; Non binder, without OH or NH2 group |
| rtER Expert System - USEPA, alerts in: | |
| - parent only | No alert found |
| - metabolites from *in vivo* Rat metabolism simulator only | No alert found |
| - metabolites from Rat liver S9 metabolism simulator only | No alert found |

*OECD QSAR Toolbox v.4.2 profilers*

*Profiler predictions are supporting information to be used together with the relevant QSAR predictions*

## APPENDIX F: VEGA Endocrine Activity Results for Ethylene (CAS #74-85-1)



### 1. Prediction Summary

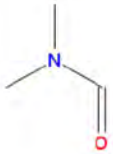
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is Inactive, 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**
**- 3 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set.**

Compound: Molecule 0
Compound SMILES: C=C
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 4
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

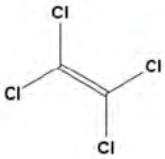
## 3.1 Applicability Domain:
### Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 68-12-2
Dataset id: 23 (Test set)
SMILES: O=CN(C)C
Similarity: 0.481

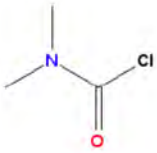
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 127-18-4
Dataset id: 32 (Training set)
SMILES: C(=C(Cl)Cl)(Cl)Cl
Similarity: 0.477

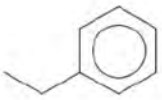
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 79-44-7
Dataset id: 25 (Training set)
SMILES: O=C(N(C)C)Cl
Similarity: 0.445

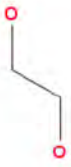
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: 100-41-4
Dataset id: 356 (Test set)
SMILES: c1ccc(cc1)CC
Similarity: 0.445

Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 107-21-1
Dataset id: 22 (Training set)
SMILES: OCCO
Similarity: 0.437

Experimental value: Inactive
Predicted value: Inactive

Compound #6

CAS: 77-73-6
Dataset id: 756 (Training set)
SMILES: C2=CC3C1C=CC(C1)C3(C2)
Similarity: 0.427

Experimental value: Inactive
Predicted value: Inactive

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.479
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 = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

**Model's descriptors range check**
Descriptors range check = False
Explanation: 3 descriptor(s) for this compound have values outside 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

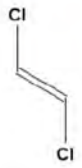
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is Not predicted, 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**
**- 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=C
Experimental value: -
Predicted ER-mediated effect: Not predicted
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 0
No. alerts for possible non-activity: 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

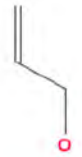
CAS: N.A.
Dataset id: 697 (Training set)
SMILES: C(=CCl)Cl
Similarity: 0.608

Experimental value: NON-active
Predicted value: Not predicted


Compound #2

CAS: N.A.
Dataset id: 418 (Training set)
SMILES: N#CC=C
Similarity: 0.6

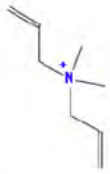
Experimental value: NON-active
Predicted value: Not predicted




Compound #3

CAS: N.A.
Dataset id: 420 (Training set)
SMILES: OCC=C
Similarity: 0.583

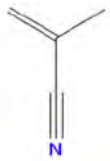
Experimental value: NON-active
Predicted value: Not predicted




Compound #4

CAS: N.A.
Dataset id: 1095 (Training set)
SMILES: C=CC[N+](C)(C)CC=C
Similarity: 0.58

Experimental value: NON-active
Predicted value: Not predicted

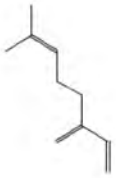



Compound #5

CAS: N.A.
Dataset id: 617 (Training set)
SMILES: N#CC(=C)C
Similarity: 0.576

Experimental value: NON-active
Predicted value: NON-active

Alerts (not found in the target): ER non-activity alert no. 22



Compound #6

CAS: N.A.
Dataset id: 590 (Training set)
SMILES: C=CC(=C)CCC=C(C)C
Similarity: 0.564

Experimental value: NON-active
Predicted value: NON-active

Alerts (not found in the target): ER non-activity alert no. 16

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.597
Explanation: no similar compounds with known experimental value in the training set have been found.

**Accuracy of prediction for similar molecules**
Accuracy index = 0
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

**Concordance for similar molecules**
Concordance index = 0
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

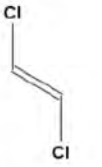
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is NON-active, but the result shows some critical aspects, which require to be checked:**
**- only moderately similar compounds with known experimental value in the training set have been found**

Compound: Molecule 0
Compound SMILES: C=C
Experimental value: -
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 0
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

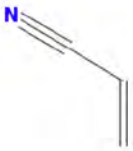



Compound #1

CAS: 156-60-5
Dataset id: 682 (Training set)
SMILES: ClC=CCl
Similarity: 0.608

Experimental value: NON-active
Predicted value: NON-active

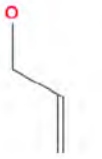
Alerts (not found in the target): ER alert no. 64, inactive




Compound #2

CAS: 107-13-1
Dataset id: 256 (Training set)
SMILES: C=CC#N
Similarity: 0.6

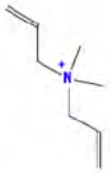
Experimental value: NON-active
Predicted value: NON-active




Compound #3

CAS: 107-18-6
Dataset id: 259 (Training set)
SMILES: C=CCO
Similarity: 0.583

Experimental value: NON-active
Predicted value: NON-active




Compound #4

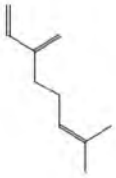
CAS: 7398-69-8
Dataset id: 986 (Training set)
SMILES: C[N+](C)(CC=C)CC=C
Similarity: 0.58

Experimental value: NON-active
Predicted value: NON-active


Compound #5

CAS: 126-98-7
Dataset id: 715 (Training set)
SMILES: CC(=C)C#N
Similarity: 0.576

Experimental value: NON-active
Predicted value: NON-active



Compound #6

CAS: 123-35-3
Dataset id: 837 (Training set)
SMILES: CC(C)=CCCC(=C)C=C
Similarity: 0.564

Experimental value: NON-active
Predicted value: NON-active

Alerts (not found in the target): ER alert no. 30, inactive

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0.777
Explanation: the predicted compound could be out of the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.604
Explanation: only moderately 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 = 1
Explanation: similar molecules found in the training set have experimental values that agree 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

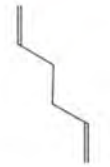
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is Inactive, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal:**
**- only moderately similar compounds with known experimental value in the training set have been found**

Compound: Molecule 0
Compound SMILES: C=C
Experimental value: -
Predicted TR alpha class: Inactive
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

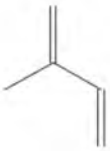
## 3.1 Applicability Domain:
### Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 592-42-7
Dataset id: 127 (Training set)
SMILES: C=CCCC=C
Similarity: 0.707

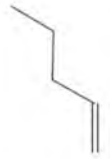
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 78-79-5
Dataset id: 116 (Training set)
SMILES: C=CC(=C)C
Similarity: 0.701

Experimental value: Inactive
Predicted value: Inactive



Compound #3

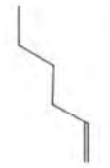
CAS: 109-67-1
Dataset id: 126 (Training set)
SMILES: C=CCCC
Similarity: 0.672

Experimental value: Inactive
Predicted value: Inactive

Compound #4

CAS: 558-37-2
Dataset id: 119 (Training set)
SMILES: C=CC(C)(C)C
Similarity: 0.664

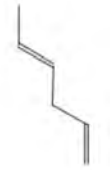
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 592-41-6
Dataset id: 128 (Training set)
SMILES: C=CCCCC
Similarity: 0.634

Experimental value: Inactive
Predicted value: Inactive



Compound #6

CAS: 592-45-0
Dataset id: 125 (Training set)
SMILES: C=CCC=CC
Similarity: 0.631

Experimental value: Inactive
Predicted value: Inactive

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0.832
Explanation: the predicted compound is into the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.692
Explanation: only moderately 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 = 1
Explanation: similar molecules found in the training set have experimental values that agree 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

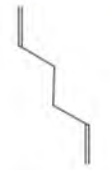
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is Inactive, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections. Anyway some issues could be not optimal:**
**- only moderately similar compounds with known experimental value in the training set have been found**

Compound: Molecule 0
Compound SMILES: C=C
Experimental value: -
Predicted TR beta class: Inactive
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

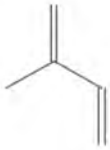
## 3.1 Applicability Domain:
### Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 592-42-7
Dataset id: 127 (Training set)
SMILES: C=CCCC=C
Similarity: 0.707

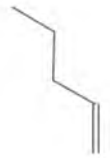
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 78-79-5
Dataset id: 116 (Training set)
SMILES: C=CC(=C)C
Similarity: 0.701

Experimental value: Inactive
Predicted value: Inactive



Compound #3

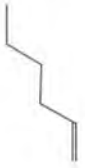
CAS: 109-67-1
Dataset id: 126 (Training set)
SMILES: C=CCCC
Similarity: 0.672

Experimental value: Inactive
Predicted value: Inactive

Compound #4

CAS: 558-37-2
Dataset id: 119 (Training set)
SMILES: C=CC(C)(C)C
Similarity: 0.664

Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 592-41-6
Dataset id: 128 (Training set)
SMILES: C=CCCCC
Similarity: 0.634

Experimental value: Inactive
Predicted value: Inactive

Compound #6

CAS: 592-45-0
Dataset id: 125 (Training set)
SMILES: C=CCC=CC
Similarity: 0.631

Experimental value: Inactive
Predicted value: Inactive

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0.832
Explanation: the predicted compound is into the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.692
Explanation: only moderately 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 = 1
Explanation: similar molecules found in the training set have experimental values that agree 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

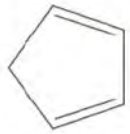
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is Inactive, but the result shows some critical aspects, which require to be checked:**
**- no similar compounds with known experimental value in the training set have been found**

Compound: Molecule 0
Compound SMILES: C=C
Experimental value: -
Aromatase activity: Inactive
Probability(Active Agonist): 0.022
Probability(Active Antagonist): 0.008
Probability(Inactive): 0.97
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

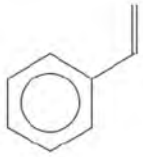
## 3.1 Applicability Domain:
### Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 1738 (Training set)
SMILES: C=1C=CCC=1
Similarity: 0.521

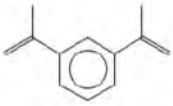
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: N.A.
Dataset id: 2848 (Training set)
SMILES: C=Cc1ccccc1
Similarity: 0.501

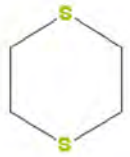
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: N.A.
Dataset id: 113 (Test set)
SMILES: C=C(c1cccc(c1)C(=C)C)C
Similarity: 0.493

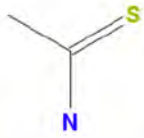
Experimental value: Inactive
Predicted value: Inactive




Compound #4

CAS: N.A.
Dataset id: 136 (Training set)
SMILES: C1CSCCS1
Similarity: 0.479

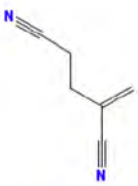
Experimental value: Inactive
Predicted value: Inactive




Compound #5

CAS: N.A.
Dataset id: 2971 (Training set)
SMILES: NC(C)=S
Similarity: 0.474

Experimental value: Inactive
Predicted value: Inactive




Compound #6

CAS: N.A.
Dataset id: 476 (Training set)
SMILES: N#CC(=C)CCC#N
Similarity: 0.468

Experimental value: Inactive
Predicted value: Inactive

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0.715
Explanation: the predicted compound could be out of the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.511
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 = 1
Explanation: similar molecules found in the training set have experimental values that agree 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:

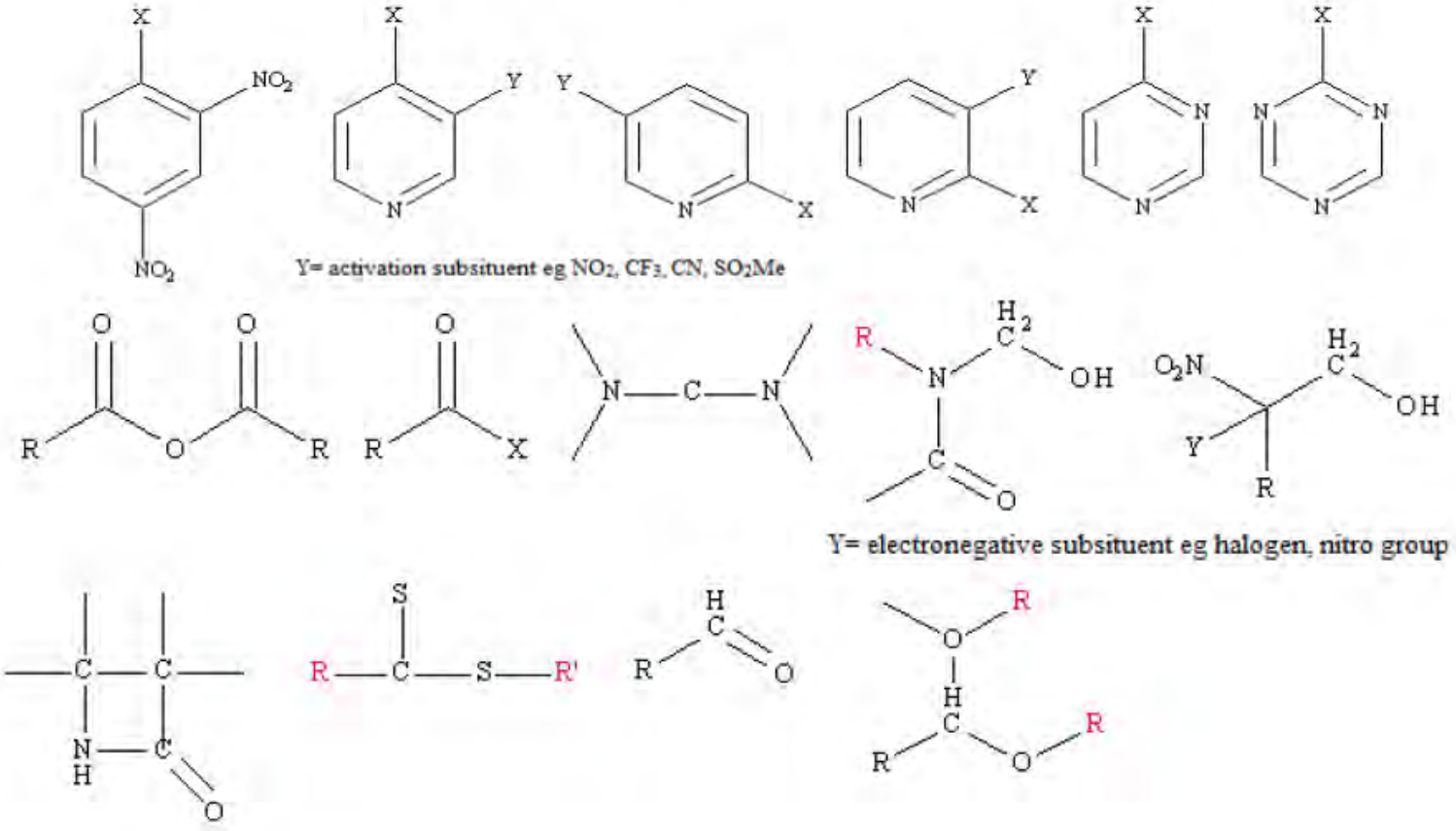
The feature has a good assessment, model is reliable regarding this aspect.

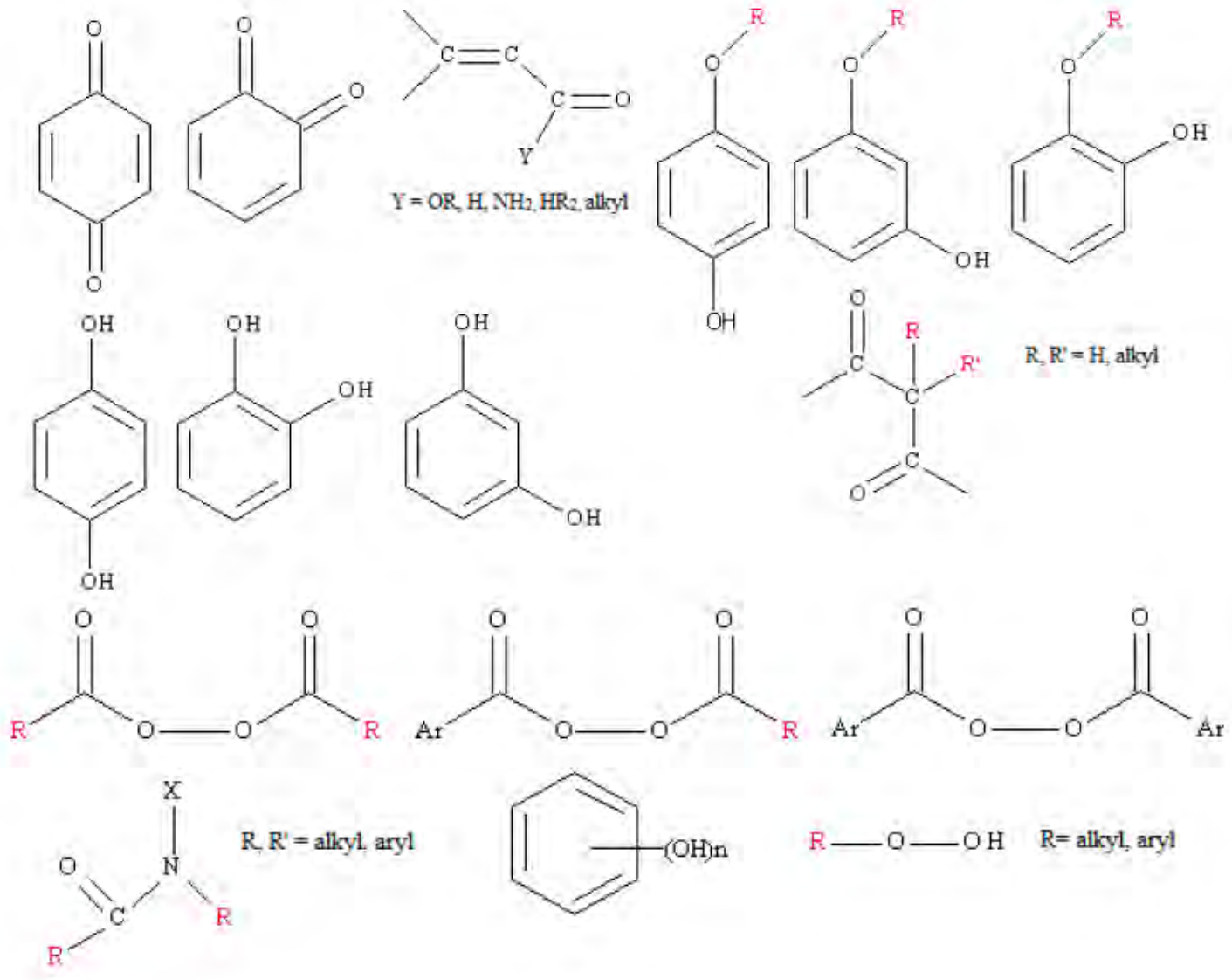
The feature has a non optimal assessment, this aspect should be reviewed by an expert.

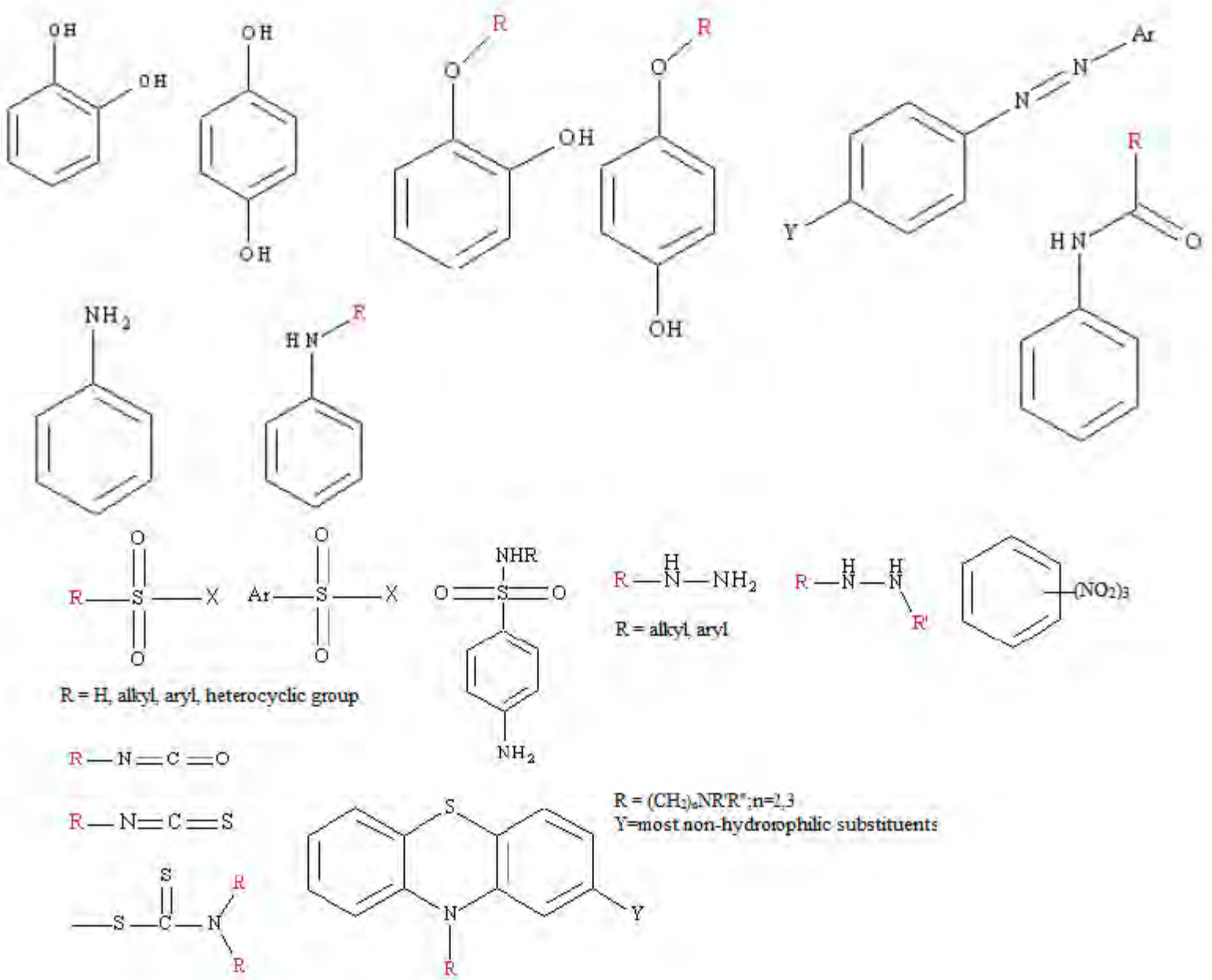
The feature has a bad assessment, model is not reliable regarding this aspect.

## APPENDIX G: Known Structural Alerts for Skin Sensitization

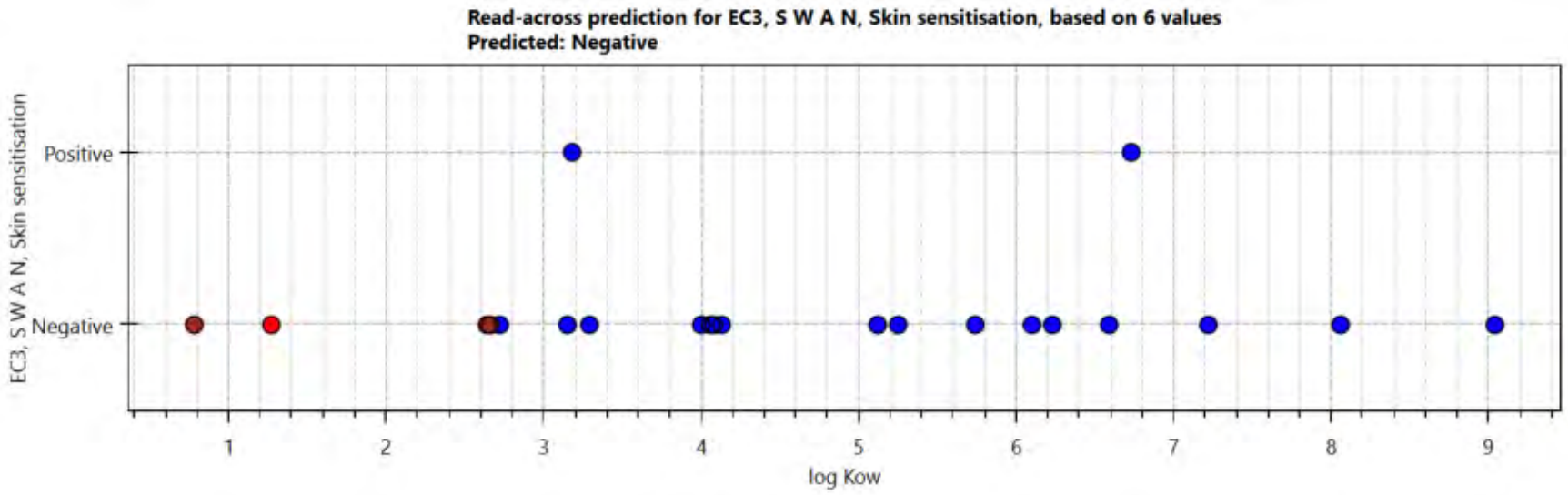
Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Ethylene possesses none of the known structural alerts.

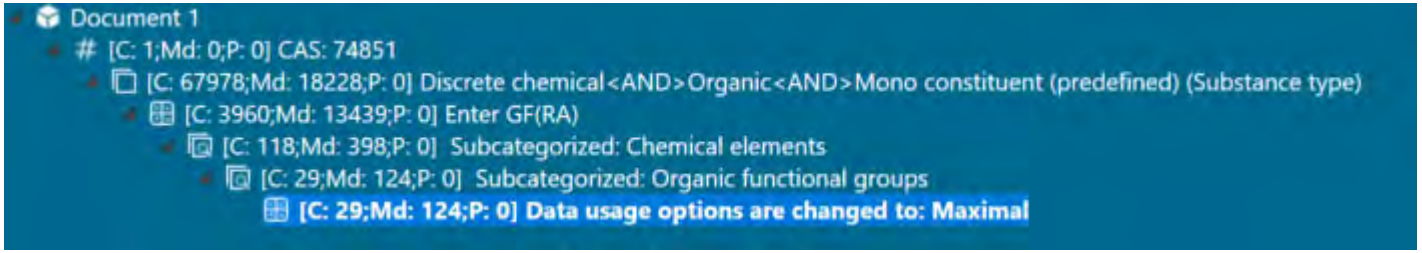




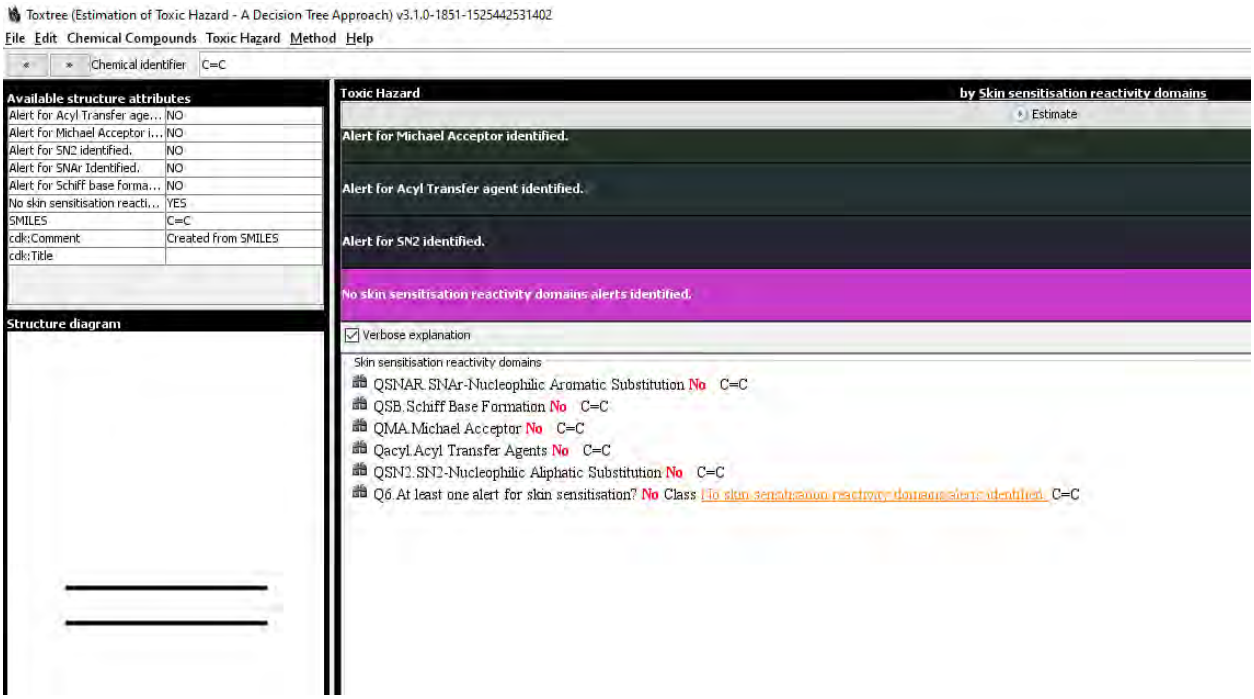


## APPENDIX H: OECD Toolbox Skin Sensitization Results for Ethylene (CAS #74-85-1)



## APPENDIX I: Toxtree Skin Sensitization Results for Ethylene (CAS #74-85-1)



## APPENDIX J: VEGA Skin Sensitization Results for Ethylene (CAS #74-85-1)

VEGA Skin Sensitization model (CAESAR) 2.1.6 page 1

### 1. Prediction Summary

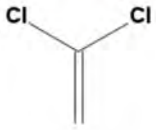
**Prediction for compound Molecule 0**

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**
**- 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=C
Experimental value: -
Predicted skin sensitization activity: NON-Sensitizer
O(Active): 0.14
O(Inactive): 0.86
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: 0.625

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


Compound #2

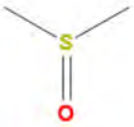
CAS: 50-00-0
Dataset id: 98 (Test set)
SMILES: O=C
Similarity: 0.575

Experimental value: Sensitizer
Predicted value: NON-Sensitizer

Compound #3

CAS: 110-54-3
Dataset id: 105 (Training set)
SMILES: CCCCCC
Similarity: 0.536

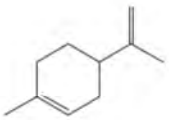
Experimental value: NON-Sensitizer
Predicted value: Sensitizer




Compound #4

CAS: 67-68-5
Dataset id: 84 (Training set)
SMILES: O=S(C)C
Similarity: 0.505

Experimental value: Sensitizer
Predicted value: NON-Sensitizer



Compound #5

CAS: 5989-27-5
Dataset id: 129 (Training set)
SMILES: C=C(C)C1CC=C(C)CC1
Similarity: 0.499

Experimental value: Sensitizer
Predicted value: Sensitizer


Compound #6

CAS: 67-63-0
Dataset id: 122 (Training set)
SMILES: OC(C)C
Similarity: 0.49

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

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0.57
Explanation: the predicted compound is outside the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.599
Explanation: no similar compounds with known experimental value in the training set have been found.

**Accuracy of prediction for similar molecules**
Accuracy index = 0.543
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

**Concordance for similar molecules**
Concordance index = 0.543
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

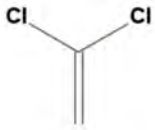
**Prediction for compound Molecule 0**

Prediction: Reliability:

**Prediction is 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**
**- 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**
**- 1 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set.**

Compound: Molecule 0
Compound SMILES: C=C
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: 0.625

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


Compound #2

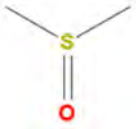
CAS: 50-00-0
Dataset id: 38 (Training set)
SMILES: O=C
Similarity: 0.575

Experimental value: Sensitizer
Predicted value: NON-Sensitizer

Compound #3

CAS: 110-54-3
Dataset id: 193 (Training set)
SMILES: CCCCCC
Similarity: 0.536

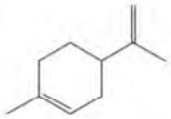
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer




Compound #4

CAS: 67-68-5
Dataset id: 30 (Training set)
SMILES: O=S(C)C
Similarity: 0.505

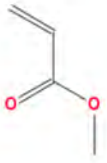
Experimental value: Sensitizer
Predicted value: NON-Sensitizer



Compound #5

CAS: 5989-27-5
Dataset id: 51 (Training set)
SMILES: C=C(C)C1CC=C(C)CC1
Similarity: 0.499

Experimental value: Sensitizer
Predicted value: Sensitizer




Compound #6

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

Experimental value: Sensitizer
Predicted value: Sensitizer

## 3.2 Applicability Domain:
### Measured Applicability Domain Scores

**Global AD Index**
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

**Similar molecules with known experimental value**
Similarity index = 0.599
Explanation: no similar compounds with known experimental value in the training set have been found.

**Accuracy of prediction for similar molecules**
Accuracy index = 0.543
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

**Concordance for similar molecules**
Concordance index = 0.543
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

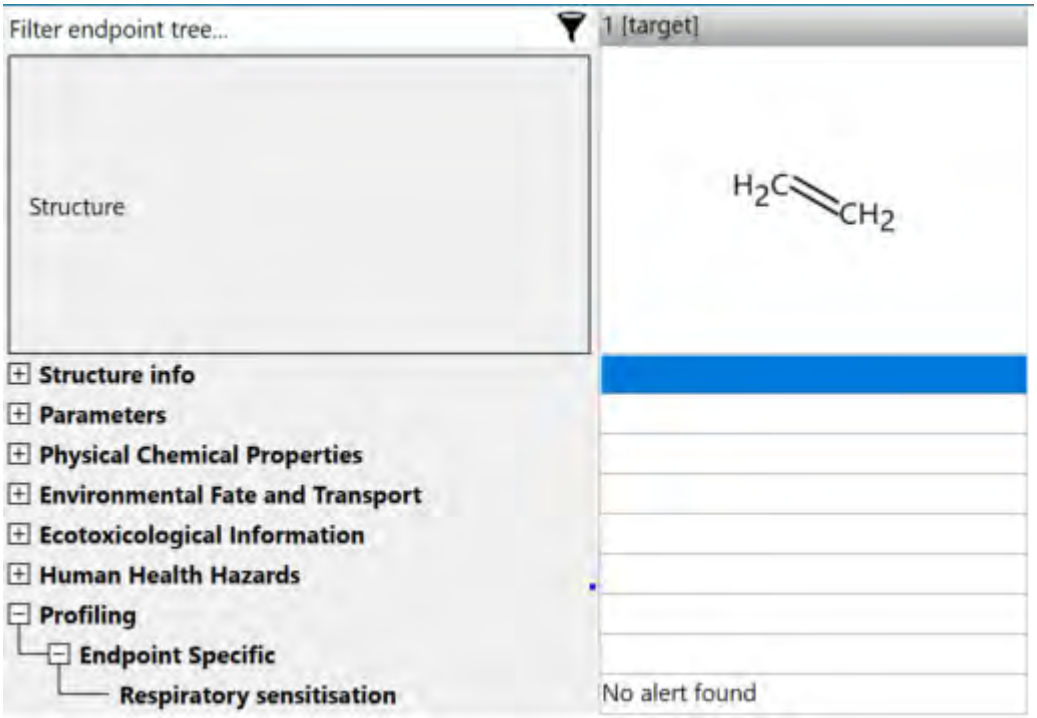
**Model's descriptors range check**
Descriptors range check = False
Explanation: 1 descriptor(s) for this compound have values outside the descriptor range of the compounds of the training set..

**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 K: OECD Toolbox Respiratory Sensitization Results for Ethylene (CAS #74-85-1)



## APPENDIX L: ECOSAR Modeling Results for Ethylene (CAS #74-85-1)

**Neutral Organics**

| Organism | Duration | End Point | Concentration (mg/L) | Max Log Kow | Flags |
|---|---|---|---|---|---|
| Fish | 96h | LC50 | 105 | 5.0 | |
| Daphnid | 48h | LC50 | 55.8 | 5.0 | |
| Green Algae | 96h | EC50 | 31.4 | 6.4 | |
| Fish | | ChV | 9.49 | 8.0 | |
| Daphnid | | ChV | 4.51 | 8.0 | |
| Green Algae | | ChV | 7.07 | 8.0 | |
| **Fish (SW)** | **96h** | **LC50** | **132** | **5.0** | ⚠ |
| **Mysid** | **96h** | **LC50** | **161** | **5.0** | ⚠ |
| Fish (SW) | | ChV | 9.14 | 8.0 | |
| Mysid (SW) | | ChV | 17.3 | 8.0 | |
| Earthworm | 14d | LC50 | 58.1 | 6.0 | |

# Organic Module Report

Results of Organic Module Evaluation

| CAS | Name | SMILES |
|---|---|---|
| 74851 | Ethene | C=C |

| Structure |
|---|

| Details | |
|---|---|
| Mol Wt | 28.05 |
| Selected LogKow | 1.27 |
| Selected Water Solubility (mg/L) | 131 |
| Selected Melting Point (°C) | -169 |
| Estimated LogKow | 1.27 |
| Estimated Water Solubility (mg/L) | 3365.95 |
| Measured LogKow | 1.13 |
| Measured Water Solubility (mg/L) | 131 |
| Measured Melting Point (°C) | -169 |

| Class Results: | |
|---|---|

Neutral Organics

| Organism | Duration | End Point | Concentration (mg/L) | Max Log Kow | Flags |
|---|---|---|---|---|---|
| Fish | 96h | LC50 | 105.19 | 5 | |
| Daphnid | 48h | LC50 | 55.81 | 5 | |
| Green Algae | 96h | EC50 | 31.41 | 6.4 | |
| Fish | | ChV | 9.49 | 8 | |
| Daphnid | | ChV | 4.51 | 8 | |
| Green Algae | | ChV | 7.07 | 8 | |

| Class Results: | |
|---|---|

| Organism | Duration | End Point | Concentration (mg/L) | Max Log Kow | Flags |
|---|---|---|---|---|---|
| Fish (SW) | 96h | LC50 | 131.85 | 5 | • Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported |
| Mysid | 96h | LC50 | 161.13 | 5 | • Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported |
| Fish (SW) | | ChV | 9.14 | 8 | |
| Mysid (SW) | | ChV | 17.31 | 8 | |
| Earthworm | 14d | LC50 | 58.12 | 6 | |

## APPENDIX M: EPI Suite™ Modeling Results for Ethylene (CAS #74-85-1)

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

CAS Number: 74-85-1
SMILES : C=C
CHEM : Ethene
MOL FOR: C2 H4
MOL WT : 28.05
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 1.13
Boiling Point (deg C) : -103.77
Melting Point (deg C) : -169.20
Vapor Pressure (mm Hg) : 52100
Water Solubility (mg/L): 131
Henry LC (atm-m3/mole) : 0.228

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.27
Log Kow (Exper. database match) = 1.13
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): -49.21 (Adapted Stein & Brown method)
Melting Pt (deg C): -150.85 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 3.15E+004 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 4.2E+006 (Mean VP of Antoine & Grain methods)
MP (exp database): -169 deg C
BP (exp database): -103.7 deg C
VP (exp database): 5.21E+04 mm Hg (6.95E+006 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 3366
log Kow used: 1.13 (user entered)
melt pt used: -169.20 deg C
Water Sol (Exper. database match) = 131 mg/L (25 deg C)
Exper. Ref: MCAULIFFE,C (1966)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 770.94 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 9.78E-002 atm-m3/mole (9.91E+003 Pa-m3/mole)
Group Method: 1.62E-001 atm-m3/mole (1.64E+004 Pa-m3/mole)

Exper Database: 2.28E-01 atm-m3/mole (2.31E+004 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: 2.280E-001 atm-m3/mole (2.310E+004 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.141E-001 atm-m3/mole (2.170E+004 Pa-m3/mole)
VP: 5.21E+004 mm Hg (source: User-Entered)
WS: 131 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.13 (user entered)
Log Kaw used: 0.969 (user entered)
Log Koa (KOAWIN v1.10 estimate): 0.161
Log Koa (experimental database): 0.280

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7342
Biowin2 (Non-Linear Model) : 0.9315
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1372 (weeks )
Biowin4 (Primary Survey Model) : 3.8073 (days )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4868
Biowin6 (MITI Non-Linear Model): 0.6918
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.5420
**Ready Biodegradability Prediction: NO**

Hydrocarbon Biodegradation (BioHCwin v1.01):
LOG BioHC Half-Life (days) : 0.4632
BioHC Half-Life (days) : 2.9054

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 6.95E+006 Pa (5.21E+004 mm Hg)
Log Koa (Exp database): 0.280
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 4.32E-013
Octanol/air (Koa) model: 4.68E-013
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.56E-011
Mackay model : 3.45E-011
Octanol/air (Koa) model: 3.74E-011

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 8.5200 E-12 cm3/molecule-sec
Half-Life = 1.255 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 15.065 Hrs
Ozone Reaction:
OVERALL Ozone Rate Constant = 0.175000 E-17 cm3/molecule-sec

Half-Life = 6.549 Days (at 7E11 mol/cm3)
Fraction sorbed to airborne particulates (phi):
2.51E-011 (Junge-Pankow, Mackay avg)
3.74E-011 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 13.22 L/kg (MCI method)
Log Koc: 1.121 (MCI method)
Koc : 9.557 L/kg (Kow method)
Log Koc: 0.980 (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 = 0.413 (BCF = 2.586 L/kg wet-wt)**
**Log Biotransformation Half-life (HL) = -0.8663 days (HL = 0.136 days)**
**Log BCF Arnot-Gobas method (upper trophic) = 0.320 (BCF = 2.087)**
**Log BAF Arnot-Gobas method (upper trophic) = 0.320 (BAF = 2.087)**
**log Kow used: 1.13 (user entered)**

Volatilization from Water:
Henry LC: 0.228 atm-m3/mole (entered by user)
Half-Life from Model River: 0.5418 hours (32.51 min)
Half-Life from Model Lake: 50.32 hours (2.097 days)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 98.88 percent
Total biodegradation: 0.02 percent
Total sludge adsorption: 0.30 percent
Total to Air: 98.57 percent
(using 10000 hr Bio P,A,S)

**Level III Fugacity Model: (MCI Method)**

| | Mass Amount (percent) | Half-Life (hr) | Emissions (kg/hr) |
|---|---|---|---|
| **Air** | **26.9** | **27** | **1000** |
| **Water** | **71.9** | **360** | **1000** |
| **Soil** | **1.04** | **720** | **1000** |
| **Sediment** | **0.172** | **3.24e+003** | **0** |

**Persistence Time: 85.5 hr**

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

| | Mass Amount (percent) | Half-Life (hr) | Emissions (kg/hr) |
|---|---|---|---|
| Air | 26.9 | 27 | 1000 |
| Water | 71.9 | 360 | 1000 |
| water | (71.9) | | |

biota (4.85e-005)
suspended sediment (0.00143)
Soil 1.04 720 1000
Sediment 0.172 3.24e+003 0
Persistence Time: 85.5 hr

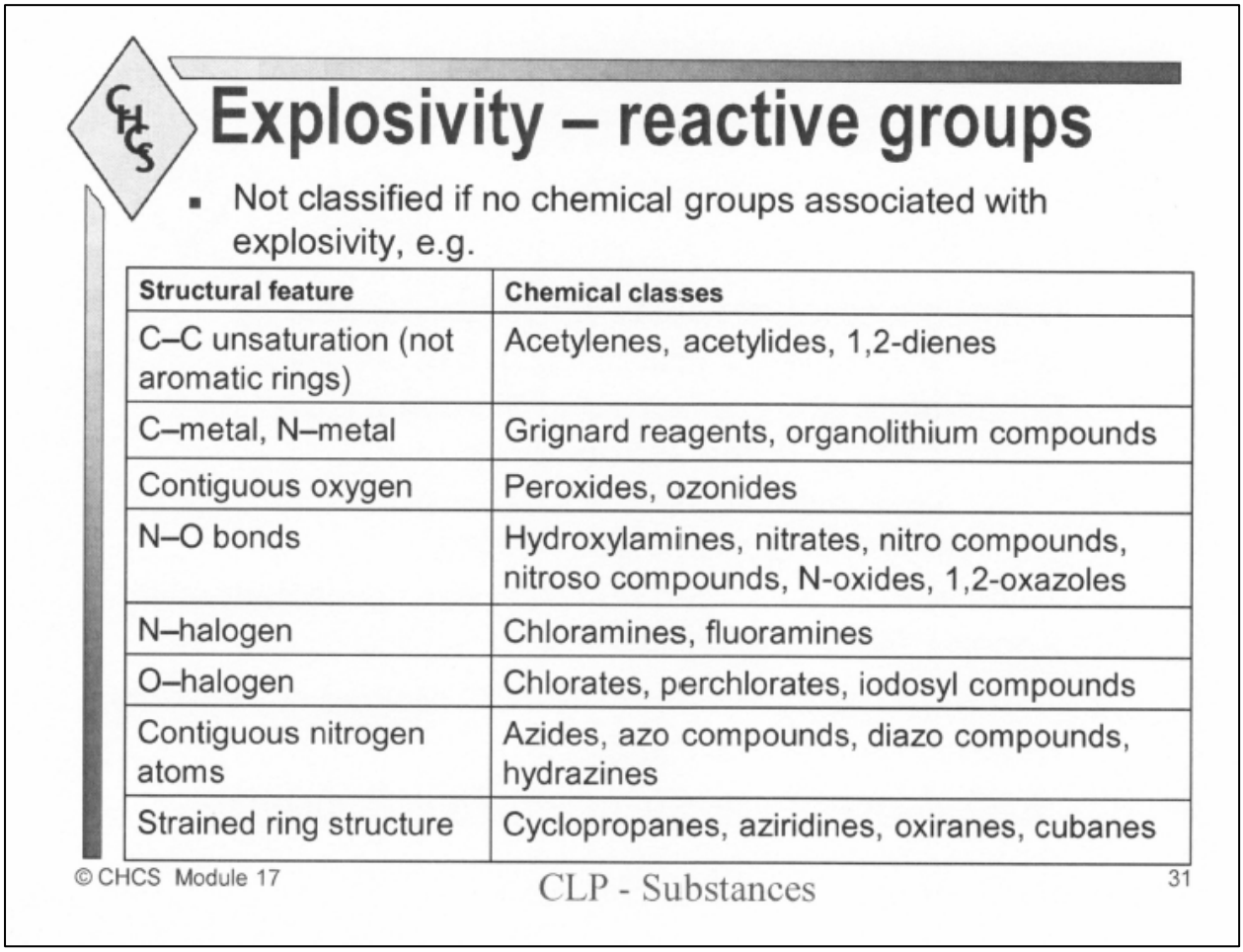
Level III Fugacity Model: (EQC Default)

| | Mass Amount (percent) | Half-Life (hr) | Emissions (kg/hr) |
|---|---|---|---|
| Air | 26.9 | 27 | 1000 |
| Water | 72 | 360 | 1000 |
| water | (72) | | |
| biota | (4.86e-005) | | |
| suspended sediment | (0.000597) | | |
| Soil | 0.964 | 720 | 1000 |
| Sediment | 0.149 | 3.24e+003 | 0 |

Persistence Time: 85.4 hr

## APPENDIX N: Known Structural Alerts for Reactivity

### Explosivity – Abbreviated List



# Explosivity – reactive groups

- Not classified if no chemical groups associated with explosivity, e.g.

| Structural feature | Chemical classes |
|---|---|
| C–C unsaturation (not aromatic rings) | Acetylenes, acetylides, 1,2-dienes |
| C–metal, N–metal | Grignard reagents, organolithium compounds |
| Contiguous oxygen | Peroxides, ozonides |
| N–O bonds | Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles |
| N–halogen | Chloramines, fluoramines |
| O–halogen | Chlorates, perchlorates, iodosyl compounds |
| Contiguous nitrogen atoms | Azides, azo compounds, diazo compounds, hydrazines |
| Strained ring structure | Cyclopropanes, aziridines, oxiranes, cubanes |

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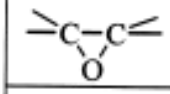
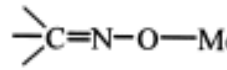
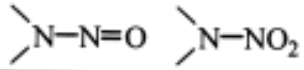
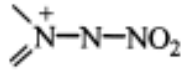
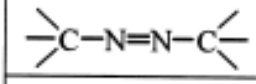
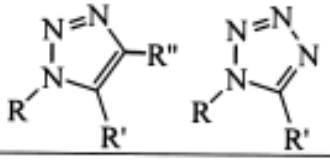
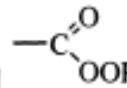
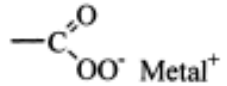
## Explosivity – Full List

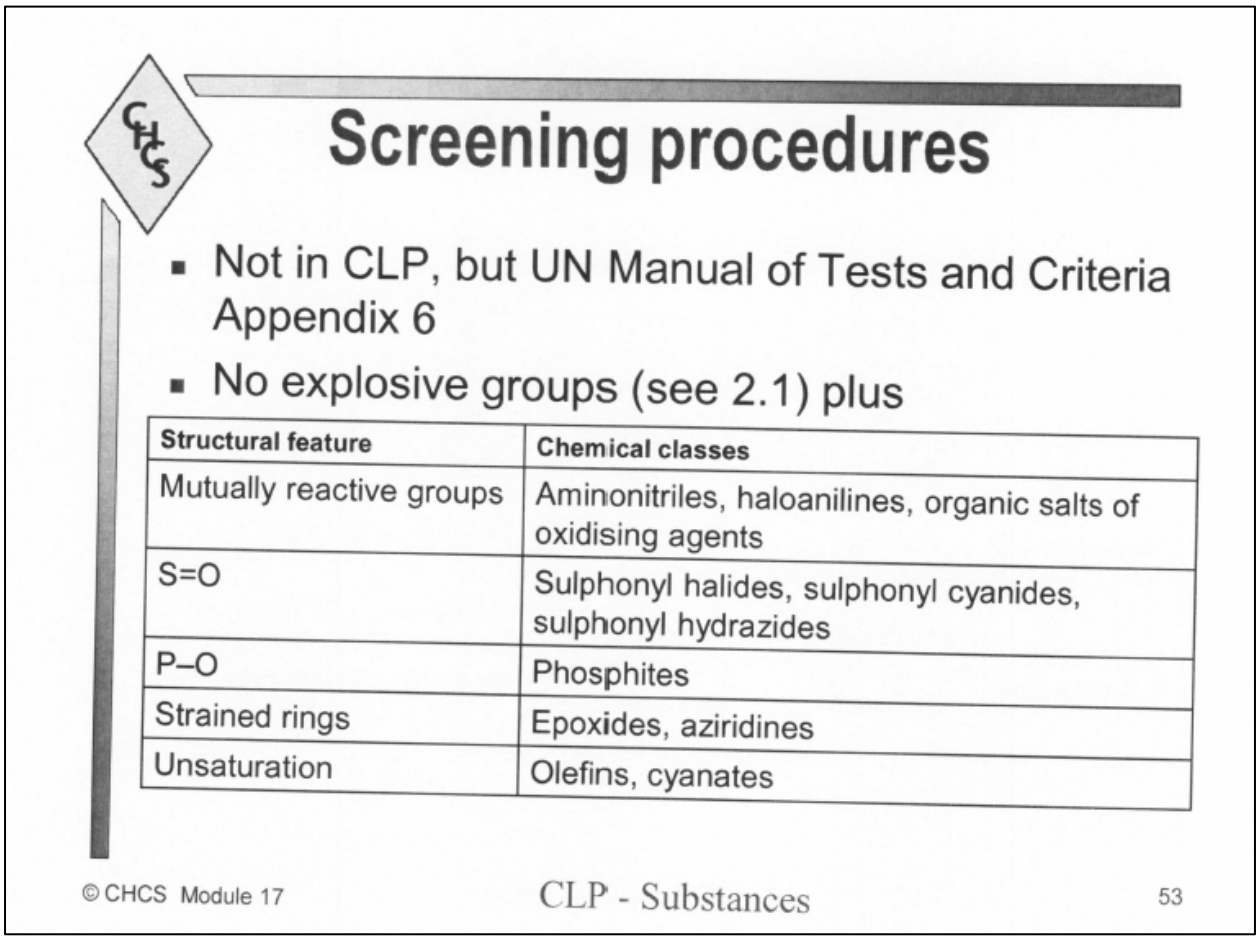
**Table R.7.1-28 Chemical groups associated with explosive properties**

| Chemical group | Chemical Class |
|---|---|
| -C≡C-<br>-C≡C-Metal<br>-C≡C-Halogen | Acetylenic Compounds<br>Metal Acetylides<br>Haloacetylene Derivatives |
|  | Diazo Compounds |
| -N=O -$NO_2$ | Nitroso and Nitro Compounds, |
| R-O-N=O<br>R-O-$NO_2$ | Acyl or Alkyl Nitrites and Nitrates |
|  | 1,2-Epoxides |
|  | Metal Fulminates or *aci*-Nitro Salts |
|  | N-Metal Derivatives (especially heavy metals) |
|  | N-Nitroso and N-Nitro Compounds |
|  | N-Azolium Nitroimidates |
|  | Azo Compounds |
| Ar-N=N-O-Ar | Arene Diazoates |
| $(ArN=N)_2O$, $(ArN=N)_2S$ | Bis-Arenediazo Oxides and Sulfides |
| RN=N-NR'R'' | Triazines |
|  | High-nitrogen Compounds: e.g. Triazoles, Tetrazoles |

| Chemical group | Chemical Class |
|---|---|
| [1] ROOR',<br>[2]  | Peroxy Compounds:<br>[1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic);<br>[2] Peroxo acids (R'=H), Peroxyesters (R'=organic) |
| [1] ROOMetal,<br>[2]  | Metal peroxides, Peroxoacids salts |
| $-N_3$ | Azides e.g. $PbN_6$, $CH_3N_3$ |
| $^{-}O-C-N_2^{+}$ | Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide |
| Ar-N=N-S-<br>Ar-N=N-S-Ar | Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides |
| $XO_n$ | Halogen Oxide: e.g. percholrates, bromates, etc |
| $NX_3$ e.g. $NC1_3$, $RNC1_2$ | N-Halogen Compounds |

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

**Self-Reactive Substances**



## APPENDIX O: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ ethylene. This GreenScreen® has undergone one round of update and the benchmark score remains the same.

**Table 6: Change in GreenScreen® Benchmark™ for Ethylene**

| Date | GreenScreen® Benchmark™ | GreenScreen® Version | Comment |
|---|---|---|---|
| August 10, 2021 | BM-2 | v. 1.4 | New assessment |
| November 12, 2021 | BM-2 | v. 1.4 | Minor updates with no changes in hazard scores for any endpoints |

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