PROPYLENE

(CAS #115-07-1)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 17, 2021

Expiration Date: November 17, 2026

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GreenScreen® Executive Summary for Propylene (CAS #115-07-1)

Propylene is a volatile organic chemical predominately used in the manufacturing of plastics. It is polymerized to polypropylene, ethylene-propylene elastomers, and polymer gasoline for plastic products. Propylene is also used as an aerosol propellant and as a chemical intermediate in the manufacturing of acetone, isopropylbenzene, isopropanol, isopropyl halides, propylene oxide, acrylonitrile and cumene. It is a clear, colorless gas at room temperature, and it is extremely flammable.

Propylene 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 2g
    - Very High Physical hazards (flammability-F)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), propylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if propylene 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 silico* modeling for endocrine activity, skin sensitization, respiratory sensitization, and acute and chronic aquatic toxicity, and *in vitro* testing for genotoxicity. 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 propylene's NAMs dataset include lack of or insufficient experimental data on endocrine activity, skin sensitization, respiratory sensitization, acute aquatic toxicity, and chronic aquatic toxicity, and lack of validated test methods for respiratory sensitization. Propylene's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, uncertain *in vivo* relevance of *in silico* prediction of endocrine receptor binding activities, VEGA and LabMol prediction results that were outside of the applicability domain in predicting skin sensitization, and the lack of a defined applicability domain in prediction of respiratory sensitization in OECD Toolbox. Some of propylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Propylene

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*	*	*								
L	**L**	*L*	**L**	DG	**L**	**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 Propylene (CAS #115-07-1)

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

GreenScreen® Assessment (v.1.2) Prepared By:
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Title: Toxicologist

Organization: ToxServices LLC
Date: February 25, 2013 (Draft); May 29, 2013 (Revision #1)

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GreenScreen® Assessment (v.1.4) Prepared By:
Name: Rachel Galante, M.P.H.
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Date: May 11, 2018

Quality Control (v1.4) Performed By:
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Date: May 22, 2018

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: August 13, 2021, November 16, 2021

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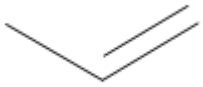
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 13, 2021, November 17, 2021

Expiration Date: November 17, 2026[2]

Chemical Name: Propylene

CAS Number: 115-07-1

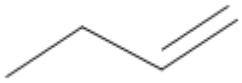
Chemical Structure(s):



Also called: 1-Propene; 1-Propylene; EINECS 204-062-1; Methylethene; Methylethylene; Propene (ChemIDplus 2021)

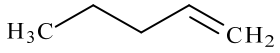
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment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

Suitable surrogates or moieties of chemicals used in this assessment (CAS #s):
In order to address the data gap for reproductive and neurotoxicity, data for 1-butene (CAS #106-98-9) were used. 1-Butene was identified in ECHA's REACH dossier for propylene (ECHA 2021a) as a read-across chemical for this endpoint. Propylene and 1-butene are similar in size and structure (only differing by 1 carbon) and both contain a terminal double bond. Therefore, there toxicities are expected to be similar.



Surrogate: 1-Butene (CAS #106-98-9)

In addition, as propylene is a gas, testing for skin sensitization and irritation and eye irritation is not technically feasible. ToxServices evaluated the potential for the alpha olefin 1-butene to serve as a surrogate for these endpoints but it is also a gas. 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 propylene to address those data gaps. Since pent-1-ene is a liquid while propylene 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:
1. Polymerized to polypropylene base for plastics and carpet fibers.
2. Chemical Intermediate for acetone, isopropylbenzene, isopropanol, isopropyl halides, propylene oxide, acrylonitrile, and cumene.
3. Monomer in polymer gasoline.
4. As aerosol propellant and component.
(HSDB 2018)

Known Impurities[3]:
Polymer grade propylene has typical purities of 95-100%, chemical grade propylene has purities of 90 – 98%, and refinery grade propylene has purities of 50 – 70%. Common impurities in polymer grade and chemical grade propylene are ethane and propane (UNEP 2003). The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Propylene[4,5 6,7]: Propylene 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:

[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.

- Benchmark 2g
    - Very High Physical hazards (flammability-F)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), propylene meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if propylene 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 Propylene

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*	*	*								
L	**L**	*L*	**L**	DG	**L**	**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

Based on its molecular formula, possible combustion products of propylene are CO and CO_2. Although they are feasible environmental transformation products, they are not considered relevant to this GreenScreen® assessment, as they are naturally occurring in the environment, and are not persistent nor bioaccumulative.

Introduction

Propylene is a volatile organic chemical predominately used in the manufacturing of plastics. It is polymerized to polypropylene, ethylene-propylene elastomers, and polymer gasoline for plastic products. Propylene is also used as an aerosol propellant and as a chemical intermediate in the manufacturing of acetone, isopropylbenzene, isopropanol, isopropyl halides, propylene oxide, acrylonitrile and cumene. It is a terminal double bond molecule that is a clear, colorless gas at room temperature, and it is highly flammable (HSBD 2018). Propylene is primarily produced via steam cracking where either propane or naphtha undergoes a dehydrogenation reaction to produce propylene (ICIS 2010).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). 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).

Propylene is not currently on the SCIL.

GreenScreen® List Translator Screening Results

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

- Propylene is a Benchmark U chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Propylene is listed on the U.S. DOT list as a Hazard Class 2.1 chemical.
- Propylene is on the following list for multiple endpoints.
    - EC – CEPA DSL: Inherently toxic to humans (iTH)
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

The following EU harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for propylene, as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below.

Table 1: GHS H Statements for Propylene (CAS #115-07-1) (ECHA 2021b)

H Statement	H Statement Details
H220	Extremely flammable gas

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Propylene (CAS #115-07-1)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Eye/Face protection (face shield and safety glasses); gloves; impervious clothing and shoes; full-face respirators (where risk presents)	HSDB 2018	ACGIH 8hr TWA: 500 ppm	HSDB 2018
		Russia STEL: 100 mg/m^3	HSDB 2018
		Switzerland TWA: 10,000 ppm (11,500 mg/m^3)	HSDB 2018

ACGIH: American Conference of Governmental Industrial Hygienists
STEL: Short-term Exposure Limit
TWA: Time Weighted Average

Physicochemical Properties of Propylene

Propylene is a colorless, odorless gas. It is volatile and moderately soluble in water. Propylene is more soluble in the organic phase than in water, according to the log K_{ow} of 1.77.

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

Table 3: Physical and Chemical Properties of Propylene (CAS #115-07-1)		
Property	**Value**	**Reference**
Molecular formula	C_3H_6	ChemIDplus 2021
SMILES Notation	CC=C	ChemIDplus 2021
Molecular weight	42.0804 g/mol	ChemIDplus 2021
Physical state	Gas	ChemIDplus 2021
Appearance	Colorless, odorless, gas	ECHA 2021a
Melting point	-185°C	ChemIDplus 2021
Boiling point	-47.6°C	ChemIDplus 2021
Vapor pressure	8,690 mm Hg at 25°C	ChemIDplus 2021
Water solubility	200 mg/L at 25°C	ChemIDplus 2021
Dissociation constant	n/a	n/a
Density/specific gravity	0.505 g/cm^3 at 25 °C (pressure >1 atm)	PubChem 2021
Partition coefficient	1.77	ChemIDplus 2021

Toxicokinetics

Absorption

In mice, the rate of uptake of propylene by inhalation is saturable. The maximum rate of uptake was 8 ± 0.5 mg propene/kg bw/h. In Fischer 344 rats exposed by inhalation to 1,000 mg/m^3 propylene, blood concentrations of the metabolite propylene oxide were 740 ng/g blood within 5 minutes of the start of exposure; corresponding values during exposure to 10 mg/m^3 propylene were 160 ng/g after 5-12 minutes. At exposure concentrations that do not saturate the main forms of metabolism, uptake of propylene by inhalation is controlled by the air concentration, the blood:air partition coefficient, and the lung perfusion rate (ECHA 2021a).

Distribution

Levels of DNA adducts resulting from exposure to propylene found in liver, testes, lung, spleen, and kidney were similar indicating an even dose distribution in the tissues studied. Tissue:air partition coefficients for propylene measured *in vitro* indicate a very low potential for accumulation in tissues; values for adipose were approximately 10x greater than that of other tissues (ECHA 2021a).

Metabolism

Two diastereomers of N-(2-hydroxypropyl) histidine were identified in the hydrolysate of hemoglobin from mice exposed by inhalation to propylene (20,000 ppm) (34,400 mg/m^3) showing that propylene is metabolized to the epoxide and that the oxidation is not stereospecific. The levels of adducts in propylene treated mice show that propylene oxide is a major metabolite of propene. The maximum rates of metabolism (Vmax) of propene were 110 and 50.4 µmol/h/kg for mouse and rat respectively; Vmax/2 was reached at 270 ppm and 400 ppm (460 and 690 mg/m^3) in mice and rats respectively. Cytochrome P450 activity in both the liver and the nasal microsomes of rats were initially reduced during exposure to propylene but had returned to approximately their initial values within 6h. In Fischer 344 rats exposed to propylene, concentrations of exhaled propylene oxide decreased during exposure suggesting rapid saturation and subsequent inactivation of propene oxide producing cytochrome species. In male and female rats exposed to propene by inhalation, the presence of HPVal adducts in systemic blood and N7-HPGua adducts in tissue from all treated groups demonstrated internal exposure to

propylene oxide. The number of adducts increased with exposure concentration up to 2,000 ppm (3,440 mg/m^3) reaching a plateau above this concentration (expected to be due to enzyme saturation). The number of N7-HPGua adducts was similar in all tissues examined (ECHA 2021a).

Elimination

Exhalation is the major route of elimination of propylene. During exposure by inhalation to concentrations of propylene that do not result in saturation of metabolism, 92% and 86% of inhaled propene was exhaled unchanged in rat and mouse respectively; this is expected due to the low uptake of propylene from the alveoli into blood (ECHA 2021a).

Relevant Human Information

Following exposure of a healthy male volunteer to propylene by inhalation, propylene concentrations in exhaled air dropped rapidly. A physiological toxicokinetic model predicted that propylene is eliminated so rapidly in humans that it cannot accumulate and that 35% of inhaled propylene enters the blood, 20% of inhaled propylene is metabolized resulting in 7% of inhaled propylene metabolized, while the remainder is exhaled unchanged (ECHA 2021a).

In four male human volunteers exposed by inhalation to propylene for 3 hours, the mean rate of metabolism was 30 µmol/h at an exposure concentration of 25 ppm (43 mg/m^3); the majority of inhaled propene was exhaled unchanged. Mean blood concentrations of propylene oxide calculated assuming a blood:air partition coefficient of 66 were 0.44 and 0.92 nmol/L at mean propylene exposure concentrations of 9.82 and 23.4 ppm (17 and 40 mg/m^3), respectively (ECHA 2021a).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L
Propylene was assigned a score of Low for carcinogenicity based on negative findings in inhalation studies in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative and they are not GHS classified (CPA 2018). Confidence in the score is high as it is based on high quality animal data.

- Authoritative and Screening Lists
  - *Authoritative:* IARC Group 3 – Agent is not classifiable as to its carcinogenicity to humans.
  - *Screening:* Not present on any screening lists for this endpoint.
- HSDB 2018
  - American Conference of Governmental Industrial Hygienists (ACGIH): A4 – not classifiable as a human carcinogen.
- UNEP 2003, ECHA 2021a
  - No evidence of carcinogenicity was found in F344/N rats and B6C3F1 mice exposed to propylene by inhalation at concentrations of 5,000 or 10,000 ppm 6 hours/day 5 days/week for 103 weeks. Propylene induced squamous metaplasia of the respiratory epithelium in male and female rats and epithelial hyperplasia in female rats, but more recent re-evaluation of this study revealed no dose-response for these effects (Klimisch 2, reliable with restrictions).

- Based on the weight of evidence, propylene was assigned a score of Low for carcinogenicity. It is not classifiable as to carcinogenicity, and carcinogenicity studies in both rats and mice were negative.

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

Propylene was assigned a score of Low for mutagenicity/genotoxicity based on mostly negative findings in gene mutation and chromosomal aberration tests *in vivo*. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both mutagenicity and clastogenicity and they are not GHS classified (CPA 2018). Confidence in the score is high as it is based on high quality 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.
- UNEP 2003, ECHA 2021a
  - *In vitro*: Propylene has been tested in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and *Escherichia coli* strain WP_2 *uvr*A (pKM101) under GLP at concentrations up to 10,000 ppm in the presence and absence of metabolic activation. Some mutagenic activity was only observed at concentrations above 2,500 ppm in TA1535 in the presence of S9 (OECD Guideline 471) (Klimisch 1, reliable without restriction).
  - *In vitro:* No evidence of mutagenicity was observed in mouse lymphoma L5178Y cells (GLP unspecified) at concentrations from 2.5 – 50% in the absence of S9, but in the presence of S9 equivocal results were obtained (OECD Guideline 476) (Klimisch 1, reliable without restriction).
  - *In vivo:* Male F344 rats were exposed to 200 – 10,000 ppm propylene by inhalation for 6 hours/day, 5 days/week for a total of 20 exposures under GLP. No increased micronucleus formation was found in bone marrow polychromatic erythrocytes (OECD 474) (Klimisch 1, reliable without restriction).
  - *In vivo:* Male F344 rats were exposed to propylene at 200 – 10,000 ppm for 20 days. The treatments did not produce an increase in *Hprt* mutant frequencies in splenic T-lymphocytes (Klimisch 2, reliable with restrictions).
- Although mutagenic activity was only seen in 1 of 5 bacterial strains tested in the bacterial reverse mutation assay and an *in vitro* mammalian gene mutation assay in the presence of S9, *in vivo* mutagenicity data were negative. In addition, an *in vivo* clastogenicity study was negative. Therefore, the weight of evidence indicates that propylene is not genotoxic *in vivo*.

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

Propylene was assigned a score of Low for reproductive toxicity based on the lack of reproductive effects in a screening test in rats with the surrogate 1-butene and a lack of histological effects on reproductive organs in rats and mice exposed to propylene for 14 and 103 weeks. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative and they are not GHS classified (CPA 2018). Confidence in the score is reduced as it is primarily based on a screening 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.
- U.S. EPA 2010
  - In the repeated dose inhalation toxicity studies in rodents (13-week study in F344 rats; 14-week study in $B6C3F_1$ mice; and 2-year study in F344 rats) described under Systemic

Toxicity/Organ Effects (Repeated Exposure), no treatment-related histological effects were found in reproductive organs (mammary gland, seminal vesicles, prostate, testes, ovaries and uterus) in animals exposed to propylene for 14 and 103 weeks.

- ECHA 2021a
    - *Surrogate: 1-Butene (CAS #106-98-9):* In a GLP-compliant OECD Guideline 422 combined repeated dose toxicity study with reproduction/developmental toxicity screening test, male and female Crl:CD IGS BR rats (12/sex/dose) were exposed via whole body inhalation to 1-butene at concentrations of 0, 500, 2,000 and 8,000 ppm 6 hours/day 7 days/week for two weeks prior to breeding, during breeding, and continuing through day 19 of gestation; the dams were then allowed to deliver their litters, which were retained until lactation day 4. There was no evidence of systemic toxicity in the parents. There were no effects on mating behavior, fertility and gestation indices, the number of implantation sites and corpora lutea per dam, numbers of pups delivered, viability of pups at and after birth and the pup sex ratio when compared to the control group. Based on the lack of effects, the authors established the NOAEC for reproductive toxicity at 8,000 ppm, the highest concentration tested (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, a score of Low was assigned. An OECD Guideline 422 screening test in rats with the surrogate 1-butene identified no effects to reproduction at inhalation exposures of 8,000 ppm. Additionally, there was a lack of histological effects on reproductive organs in rats and mice exposed to propylene for 14 and 103 weeks.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Propylene was assigned a score of Low for developmental toxicity based on negative findings in a prenatal developmental toxicity study with rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and negative, and they are not GHS classified (CPA 2018). Confidence in the score is high as it is based on high quality animal 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.
- U.S. EPA 2010, ECHA 2021a
    - In a GLP-complaint OECD Guideline 414 prenatal developmental toxicity study, pregnant Wistar rats (25/group) were exposed to propylene via whole-body inhalation at concentrations of 0, 200, 1,000, and 10,000 ppm for 6 hours/day on gestation days 6 – 19. There were no changes in food and water consumption, body weight, uterine weights or clinical and necropsy observations in dams. No maternal toxicity or developmental toxicities were observed on conception rate, mean number of corpora lutea, total implantations, pre/post-implantation losses or resorptions, the number of live fetuses, fetal sex ratio, fetal body weights, and external, soft tissue and skeletal abnormalities in the offspring. The NOAEC for maternal and developmental toxicity was 10,000 ppm, which is the highest concentration tested (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, a score of Low was assigned since no effects on a suite of developmental endpoints were observed in rats following gestational exposure.

Endocrine Activity (E) Score (H, M, or L): DG
Propylene was assigned a score of Data Gap for endocrine activity based on insufficient data. There are no robust studies found in which endocrine activity was a key endpoint, thus a Data Gap is assigned.

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

    - *Screening:* TEDX – Potential Endocrine Disruptor
- NTP 1985, ECHA 2021a
    - Toxicology and carcinogenesis studies of propylene (greater than 99% pure) were conducted by exposing groups of 50 F344/N rats and 49 or 50 B6C3F1 mice of each sex to propylene in air by inhalation at concentrations of 5,000 or 10,000 ppm, 6 hours per day, 5 days per week, for 103 weeks. The occurrence of uterine endometrial stromal polyps in female mice showed a positive trend ($P<0.05$; 0/47; 0/47; 3/48); the incidence in the 10,000 ppm group was not significantly greater than that in the concurrent control group, but the incidence was higher than the mean historical control rate (22/2,411, 0.9%) and was within the range (0%-6%) observed in studies throughout the Carcinogenesis Program. The occurrence of endometrial stromal polyps in three high concentration female mice was not considered to be clearly related to exposure to propylene. In addition, histopathology was performed on the mammary gland, thymus, thyroid gland, parathyroid, pancreas, adrenal glands, reproductive organs and pituitary glands and no adverse effects were observed.
- ECHA 2021a
    - In the subchronic NTP inhalation toxicity studies in rats and mice described in the repeated dose toxicity section below, gross pathology and histopathology were performed on the mammary gland, thymus, thyroid gland, parathyroid, pancreas, adrenal glands, reproductive organs and pituitary glands, and no adverse effects were noted.
- U.S. EPA 2021b
    - Propylene was predicted to be inactive for androgen receptor agonism, antagonism and binding by the ToxCast COMPARA (Consensus) model. It was predicted to be inactive for estrogen receptor agonism, antagonism and binding by the ToxCast CERAPP Potency Level (Consensus) model.
- DTU 2021 (only in domain predictions are summarized below)
    - Propylene was predicted to be negative for estrogen receptor α binding (full and balanced training set, human *in vitro*) by the SciQSAR model. It was predicted to be negative for estrogen receptor activation (CERAPP data *in vitro*) by the Leadscope model (Appendix D).
    - Propylene was predicted to be negative for androgen receptor binding (CoMPARA data *in vitro*) by the Leadscope model (Appendix D).

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>
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
Propylene was assigned a score of Low for acute toxicity based on 4h-inhalation LC_{50} of over 120 mg/L in rats. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when 4h-inhalation LC_{50} values for gases are greater than 20 mg/L (CPA 2018). Confidence in the score is high as it is based on 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.
- U.S. EPA 2010
    - *Inhalation* LC_{50} (Sprague-Dawley rats, 4 hours) > 65,000 ppm or 111.87 mg/L[9]. No

[9] (65,000 ppm x 42.0804 g/mol) / 24,450 L/mol = 111.87 mg/L.

mortalities were observed at the only concentration tested.
    - *Inhalation* LC_{50} (male Sprague-Dawley rats, 4 hours) > 50,000 ppm or 86.05 mg/L[10]. No mortalities were observed at the only concentration tested.
- ECHA 2021a
    -
    - All of the studies reported in the REACH dossier are non-standard studies without reporting LC_{50} values. These studies describe evidence of analgesic effects in cats, dogs, mice, and rats exposed to high concentrations of propylene. A few clinical studies on the effects of propylene exposure in humans also describe transient anesthesia following inhalation. Therefore, ToxServices did not include those studies in this report.
- Propylene is a gas at ambient temperature and pressure and therefore ingestion is unlikely and acute dermal studies are technically not feasible to perform. As a result, only acute inhalation toxicity studies were identified. Based on the weight of evidence, propylene is not an acute mammalian toxicant according to GHS classification based on inhalation LC_{50} values in rats.

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

Propylene was assigned a score of Low for systemic toxicity (single dose) based on animal data demonstrating a lack of systemic effects at doses > 20 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when no systemic toxicity is observed below the guidance value of 20 mg/L for a gas inhalation study (CPA 2018b). The confidence in the score is high as it is based on measured animal 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.
- UNEP 2003, ECHA 2021a
    - Dogs could tolerate 50% (926 mg/L) propylene without apparent depression of circulation or respiration while lethal doses of propylene in dogs and cats were between 70 and 80% (1,297 and 1,482 mg/L) (Klimisch 2, reliable with restrictions).
    - 4-Hour inhalation of 50,000 ppm (86.05 mg/L) propylene did not produce death or hepatotoxicity in male Sprague-Dawley rats. Pretreatment with polychlorinated biphenyls (PCBs)[11] caused increased relative liver weight and elevated serum enzyme activities, indicative of liver toxicity (Klimisch 2, reliable with restrictions).
    - No signs of toxicity in cats (details not provided) were observed when anesthesia was maintained at propylene concentrations of 20 – 31% (371-574 mg/L). Some subtle effects were observed at concentrations of 40 – 50% and blood pressure decreases and rapid pulse occurred at a concentration of 70%. Unusual ventricular ectopic beat was observed with exposures from 50 – 80% (Klimisch 2, reliable with restrictions).

[10] (50,000 ppm x 42.0804 g/mol) / 24,450 L/mol = 86.05 mg/L.

[11] The study authors described previous work done by the Chemical Industry Institute of Toxicology (CIIT) (CIIT 1977, 1980) in which exposure to a similar chemical, ethylene (CAS #74-85-1), at up to 9,000 ppm for 90 days or 3,000 ppm for 24 months did not induce any toxic effects. However, research conducted by Conolly et al. (1977) and Guest et al. (1981), demonstrated that pretreatment with polychlorinated biphenyl (PCB) stimulates the metabolism of ethylene and subsequent toxicity (severe hepatic damage) was observed in a single 4-hour inhalation exposure to 25,000 ppm of ethylene in male rats. The metabolism of ethylene has been shown to result in toxic adducts that may explain some of the observed toxicity. Therefore, the study authors expect to observe a similar mechanism of PCB-induced toxicity for propylene and elected to orally pre-treat with PCB (100 mg/kg/day for 3 days) as well as other mixed-function oxidase system (MFOS) inducers (phenobarbital [80 mg/kg/day for 4 days] and β-napthoflavone [60 mg/kg/day for 4 days]) prior to a single treatment with 50,000 ppm of propylene for 4 hours to test for hepatotoxicity (Osimitz and Conolly 1985).

- HSDB 2018
    - In two humans, propylene exposure at the concentrations of 35% and 40% caused vomiting during or after the experiment, and one complained of severe vertigo. Exposure to propylene at 40, 50 and 75% for a few minutes induced initial reddening of eyelids, flushing of face, lacrimation, coughing and sometimes flexing of legs.
- Based on the weight of evidence, a score of Low was assigned. A rat study demonstrated a lack of hepatotoxicity at 86.05 mg/L for 4 hours. A dog study demonstrating a lack of effects on circulation and respiration at a dose of 926 mg/L, and a study in cats demonstrating no toxic effects at a dose of 371-574 mg/L support this classification.

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

Propylene was assigned a score of Low for systemic toxicity (repeated dose) based on subchronic and chronic inhalation NOAECs of greater than 18.5 mg/L in rodents. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when effect levels are greater than 1 mg/L/6h/day for gases in 90-day inhalation toxicity studies (CPA 2018b). The confidence in the score is high as it is based on high quality animal 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.
- UNEP 2003, U.S. EPA 2010, ECHA 2021a
    - *Inhalation:* In a 13-week inhalation toxicity study performed by National Toxicology Program (NTP), male and female F344 rats (9 – 11/sex/group) were exposed to propylene for 6 hours/day, 5 days/week at concentrations of 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm in the air. Clinical observations and body weights were monitored during the study. No treatment-related death or clinical signs occurred during the study. No gross or microscopic pathologic effects (including reproductive organs and nasal cavity changes) were found upon necropsy. Exposed male rats had 4 – 12% higher mean body weights throughout most of the study while no differences in body weight gain was observed in females compared to controls. The mean body weight differences in males were determined not to be related to treatment. The NOAEC was established at 10,000 ppm (equivalent to 17.21 mg/L)[12] (Klimisch 2, reliable with restrictions).
    - *Inhalation:* In a 14-week inhalation toxicity study performed by NTP, male and female $B6C3F_1$ mice (10/sex/group) were exposure to propylene for 6 hours/day, 5 days/week at concentrations of 0, 625, 1,250, 2,500, 5,000 or 10,000 ppm in the air. Clinical observations and body weights were monitored during the study. No gross or microscopic pathologic effects (including reproductive organs and nasal cavity changes) were found upon necropsy. In propylene-exposed females, a 4 – 7% decrease in final weight compared to controls was measured but was determined not to be treatment related. The NOAEC was established at 10,000 ppm (equivalent to 17.21 mg/L)[12] (Klimisch 2, reliable with restrictions).
    - *Inhalation:* In a 2-year inhalation toxicity study performed by NTP, male and female F344 rats (50/sex/group) were exposed to propylene for 6 hours/day, 5 days/week at concentrations of 0, 5,000 or 10,000 ppm in the air (98.6 – 99.7% pure) for 103 weeks. Survival was not affected by the treatment. Mean body weights of exposed animals were 0 – 5% lower than controls without dose-response relationships. No treatment-related adverse clinical signs, gross or microscopic lesions of the reproductive organs were observed. Upon

[12] (10,000 ppm x 42.0804 g/mol) / 24,450 L/mol = 17.21 mg/L.

histopathological examination, portal-of-entry effects of increased incidence of squamous metaplasia in both treatment groups and inflammation of the nasal cavities at 10,000 ppm were observed in females. These effects were not observed in animals exposed to similar concentrations for 14 weeks. The NOAEL was established at 10,000 ppm (equivalent to 17.21 mg/L)[12] by U.S. EPA (2010) while the UNEP (2003) and REACH dossier authors (ECHA 2021a) established the NOAEC at < 5,000 ppm (equivalent to < 8.61 mg/L)[13] based on the local effects of increased squamous metaplasia and inflammation of the nasal cavities (Klimisch 2, reliable with restrictions).

- *Inhalation:* In a 2-year inhalation toxicity study performed by NTP, male and female B3C3F1 mice (50/sex/group) were exposed to propylene for 6 hours/day, 5 days/week at concentrations of 0, 5,000 or 10,000 ppm in the air (98.6 – 99.7% pure) for 103 weeks. Survival rates were not affected by propylene treatments. Slight decrease in mean body weights were measured at 10,000 ppm after week 59. No compound-related clinical signs, gross or microscopic lesions of the reproductive organs or nasal cavity were noted. NOAEC was established at 10,000 ppm (equivalent to 17.21 mg/L)[12] (Klimisch 2, reliable with restrictions).
- *Inhalation:* In a repeated dose biomarker/mutagenicity dose-response study in male F344 rats, animals (8/group) were exposed to propylene at concentrations of 0, 200, 2,000 or 10,000 ppm in the air for 6 hours/day for a total of 1, 3, or 20 exposures. The subgroup receiving 20 exposures included females as well. Sections of the nasal cavity of rats from all groups were microscopically examined and immunohistochemically prepared to identify nasal epithelial cells undergoing DNA synthesis. No propylene-related nasal lesions were microscopically detected in any groups. No exposure-related inflammation (rhinitis) or alterations were noted such as degeneration, necrosis, hyperplasia and metaplasia in the squamous, transitional, respiratory of olfactory epithelium lining in the nasal airways. No apparent exposure-related changes in the number of cells undergoing DNA synthesis were found in the nasal epithelium. No propylene exposure-related effects on cell proliferation were found in the liver or nasal respiratory epithelium. The NOAEC was established at 10,000 ppm (equivalent to 17.21 mg/L)[12] both in males and females (Klimisch 2, reliable with restrictions).

- Based on the weight of evidence, a score of Low was assigned. No adverse systemic effects occurred in rodents at propylene concentrations of 10,000 ppm (17.21 mg/L) in each of the repeated dose inhalation toxicity studies described above.

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

Propylene was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects observed following single exposures in animals and humans. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when a GHS Category 3 classification for transient narcotic effects is warranted (CPA 2018b). The confidence in the score is high as it is based on animal and human data supported by a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan GHS – H335 or H336 (Specific target organ/systemic toxicity following single exposure – Category 3 [narcotic effects])
- UNEP 2003
  - In acute rodent inhalation studies, 30 – 40% (300,000 – 400,000 ppm) of propylene was minimally anesthetic.

[13] (5,000 ppm x 42.0804 g/mol) / 24,450 L/mol = 8.61 mg/L.

  - 37% propylene in oxygen or air induced narcosis in cats. 70% propylene induced anesthesia in cats within 2 minutes of exposure, but the animals recovered quickly with no apparent lasting effects. No signs of toxicity were observed when anesthesia was maintained at propylene concentrations of 20 – 31%. In conclusion, 40 – 50% propylene was narcotic to cats (Klimisch 2, reliable with restrictions).
  - It has been estimated that narcotic concentration of propylene in humans is 46% (46,000 ppm), which is above the lower flammability level (20,000 ppm) for the chemical, meaning that the explosive range of airborne concentrations of propylene will be reached before any physiologic effects can be manifested.
- HSDB 2018
  - In humans, propylene exposure at the concentration of 6.4% (6,400 ppm or 11.8 mg/L) for 2.25 minutes produced mild intoxication, paresthesia and inability to concentrate without memory impairment. Exposure at 12.8% for 1 minute induced the same but markedly accentuated symptoms. Exposures at 24% and 33% for 3 minutes caused unconsciousness. Exposure to 23% for 3 – 4 minutes did not produce unconsciousness.
  - In 2 humans, propylene exposure at the concentrations of 35% and 40% caused vomiting during or after the experiment, and one complained of severe vertigo. 50% propylene prompted anesthesia in two minutes followed by complete recovery without any physiological indications.
- Based on the weight of evidence, propylene can induce narcosis in humans at concentrations as low as 6.4 % (11.8 mg/L). However, these effects are reversible at concentrations up to 50% (92.5 mg/L). According to GHS classification criteria, propylene can be classified as a Category 3 chemical under specific target organ toxicity (single exposure) based on transient narcotic effects (UN 2019).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Propylene was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of neurobehavioral effects observed following repeated exposures of the surrogate 1-butene rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and GHS classification is not warranted (CPA 2018b). The confidence in the score is high as it is based on animal for a strong structural surrogate, 1-butene.

- 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 2021b
  - In the 2-year NTP inhalation toxicity studies in rats and mice described in the repeated dose toxicity section, histopathology was performed on sternebrae, vertebrae, bone marrow, brain and spinal cord and no adverse effects were observed.
  - In the subchronic NTP inhalation toxicity studies in rats and mice described in the repeated dose toxicity section, gross pathology and histopathology were performed on sciatic nerve, sternebrae, vertebrae, bone marrow, brain and spinal cord, and no adverse effects were noted.
- ECHA 2021d
  - <u>*Surrogate: 1-Butene (CAS #106-98-9):*</u> In a GLP-compliant OECD Guideline 422 combined inhalational repeat dose toxicity study with the reproduction/developmental screening test, Sprague-Dawley rats (12/sex/dose) were exposed to 0, 500, 2,000, or 8,000 ppm (nominal) (0, 524, 2,062, or 8,271 ppm analytical concentrations) of 1-butene gas (≥ 99% purity) via whole body inhalation 6 hours/day, 7 days/week for 28 days. Neurobehavioral examinations including sensory activity, grip strength, motor activity, and rectal temperature were not

impacted by treatment in any dosed animals (Klimisch 1, reliable without restriction).

- Based on the weight of evidence, a Low was assigned for this endpoint. No neurobehavioral effects were observed in a series of motor and functional observation battery tests in rats exposed to up to 8,271 ppm (equivalent to 18.98 mg/L/6h/day)[14] of the surrogate 1-butene for 28 days. This NOAEC is greater than the duration-adjusted GHS Category 2 guidance value of 3 mg/L for vapors (i.e., 1 mg/L x 3 months/1 month). Therefore, the chemical is not classified under GHS.

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

Propylene was assigned a score of Low for skin sensitization based on negative results in four out of five predictive modeling programs supported by negative experimental data on the weak surrogate pent-1-ene. 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 experimental data on 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
  - Propylene is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh (1994). See Appendix E for complete list of structural alerts.
- OECD 2020a
  - OECD Toolbox predicted that propylene is not a skin sensitizer by using the read-across method. See Appendix F for details.
- Toxtree 2018
  - Propylene is not predicted to be a skin sensitizer using the Toxtree model v2.6.0 using decision tree methodology. This chemical has not been identified as a substrate for any of the 5 electrophilic mechanisms known to produce a skin sensitization reaction. See Appendix G for modeling output.
- VEGA 2021
  - Propylene is predicted to not be a skin sensitizer using the VEGA model, although it is outside of the applicability domain for the model (Global AD Index = 0.563). Therefore, this prediction is not reliable. See Appendix H for justification.
- LabMol 2020
  - Propylene is predicted to be a skin sensitizer based on the Bayesian consensus model outcome with high confiability. Four out of five models predicted propylene to be positive for skin sensitization with high confiability except for the *in vitro* cellular response prediction h-CLAT model that had a 61.7% confiability; however, propylene was outside of the applicability domain for all models tested. Therefore, these predictions are not reliable. See Appendix I for details.
- ECHA 2021c
  - *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

[14] (8,271 ppm x 56.1072 g/mol (molecular weight of 1-butene)) / 24,450 L/mol = 18.98 mg/L.

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

- Based on the weight of evidence, a score of Low was assigned. All but one predictive modeling output indicated that propylene is not expected to be sensitizing to the skin. The Bayesian consensus model outcome run in LabMol predicted propylene to be positive for skin sensitization, but all models used in building the consensus model were outside the respective applicability domains. In addition, the weak surrogate pent-1-ene is not a dermal sensitizer in a reliable LLNA.

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

Propylene was assigned a score of Low for respiratory sensitization based on ECHA's guidance on respiratory sensitization evaluation. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The 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
  - Propylene does not contain any structural alerts for respiratory sensitization (Appendix J)
- 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 propylene is not expected sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by propylene, and as propylene does not contain any structural alerts for respiratory sensitization (OECD 2020a), propylene is not expected to be a respiratory sensitizer.

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

Propylene 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.
- ECB 2000
  - Although rapid evaporation of liquid propylene may freeze the skin and cause "frost bite", the gas produces little or no irritation in animals and humans.
- UNEP 2003
  - Two humans were anesthetized by 35 or 40% propylene without disagreeable sensations. Information about the route of exposure was not available.
- ECHA 2021c
  - *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*

Propylene 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 2003
  - In a human study, volunteers were exposed to mixtures of propylene (1 – 8 ppm) and nitric oxide (0 – 4 ppm). A reduction in propylene concentration led to a direct decline in eye irritation (Klimisch 3, not reliable).
  - In another human study, a mixture of 1 ppm propylene and 0.25 ppm nitric oxide resulted in slight irritation, and when the propylene concentration increased to 2 – 3 ppm, moderate irritation was reported. Study authors attributed eye irritation to formation of formaldehyde (Klimisch 3, not reliable).
  - Two humans were anesthetized by 35 or 40% propylene without disagreeable sensations.
- ECHA 2021c
  - *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 (Klimisch 2, reliable with restrictions).
- 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 propylene, as an ocular irritant under GHS criteria.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *M*
Propylene was assigned a score of Moderate for acute aquatic toxicity based on predicted an acute aquatic toxicity EC_{50} of 21.10 mg/L in green algae. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity values are between 10 and 100 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.
- U.S. EPA 2017a
  - No measured data are available and therefore ECOSAR was used to model the aquatic toxicity of propylene. Propylene is designated to the neutral organics ECOSAR chemical class with predicted L/EC_{50} values of 55.62 mg/L in fish (96h), 30.92 mg/L in daphnia (48h) and 21.10 mg/L in green algae (Appendix K).
- Based on the weight of evidence, a score of Moderate was assigned. Propylene is highly volatile and will not remain in water for long periods of time. ECOSAR modeling indicates that propylene is expected to have moderate acute aquatic toxicity.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
Propylene was assigned a score Moderate for chronic aquatic toxicity based on predicted a chronic toxicity value of 2.84 mg/L in daphnia. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are between 1.0 and 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.
- U.S. EPA 2017a
  - No measured data are available and therefore ECOSAR was used to model the aquatic toxicity of propylene. This chemical has predicted chronic values of 5.30 mg/L in fish, 2.84 mg/L in daphnia and 5.27 mg/L in green algae (Appendix K).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *L*
Propylene was assigned a score of Low for persistence based on its half-life in water and air. GreenScreen® criteria classify chemicals as a Low hazard for persistence when the half-life in air is < 2 days and in water is < 16 days (CPA 2018b). The confidence in the score is low as it is based on modeled half-life 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.
- UNEP 2003
  - Although no standard aquatic biodegradation tests were found for propylene because it presents severe technical challenges to achieve aqueous concentrations due to its potential to rapidly partition from water to air, it was scientifically judged[15] to have aerobic, aqueous

[15] Where no data were available to assess the inherent biodegradability, validated estimation methods described in Howard et al.'s Handbook of Environmental Degradation Rates were used to estimate the half-life of propylene (Howard et al. 1991).

biodegradation half-lives of between 7 and 28 days. There is also sufficient information in the literature that demonstrates its potential to be metabolized by selected bacteria in the environment, although no information is available on the degradation rate.
    - Propylene will partition negligibly to the water compartment and the low levels in the water are unlikely to degrade by hydrolysis.
    - Propylene may degrade in soil but microbial degradation is likely to have little influence on the fate of propylene in the environment because propylene does not partition to soil.
    - Propylene is highly volatile and will partition predominantly to the atmosphere.
    - Propylene reacts readily with OH^- and O_3 in the air, and has half-lives between 15.1-23.8 hours based on reactions with OH^- and O_3, respectively.
- U.S. EPA 2017b
    - BIOWIN predicts that propylene is readily biodegradable. Fugacity modeling (MCI method) predicts 88.3% will partition to water with a half-life of 15 days, 10% will partition to air with a half-life of 6.46 hours and 1.45% will partition to soil with a half-life of 30 days (Appendix L).

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Propylene was assigned a score of Very Low for bioaccumulation based on estimated BCF values and a log K_{ow} of 1.77. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF/BAF values are less than 100 and log K_{ow} values are less than 4 (CPA 2018b). The confidence in the score is high as it is based on an experimental log K_{ow}.
- 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 2017b
    - BCFBAF predicted a BCF of 6.837 for propylene using the regression-based method, and a BCF of 6.398 for the upper trophic level using the Arnot-Gobas method, taking metabolism into consideration, based on a measured log K_{ow} of 1.77 (Appendix K).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Propylene 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.
- ICSC 1998
    - Gas/air mixtures of propylene are explosive when heated.
- HSDB 2018
    - Propylene is explosive in the form of vapor when exposed to heat or flame. Under unusual conditions (i.e., 955 atm pressure and 327℃), it has been known to explode.
    - Lower explosive limit: 2.4%; upper explosive limit: 10.1%
    - Liquid propylene will explode on contact with water at 42-75°C.
    - Cylinders exposed to fire may vent and release flammable gas. Containers may explode when heated. Ruptured cylinders may rocket.

- Despite the characteristics described for propylene vapor/gas exposed to heat or liquid propylene exposed to water and heat, these features are not classifiable for reactivity under GHS (UN 2019).
    - Propylene is not considered an explosive substance because, alone, it is not capable of creating a chemicals reaction of gas at a high temperature and pressure at a speed that would damage surroundings (UN 2019 Chapter 2.1 Explosives).
    - Propylene is not a pyrotechnic substance. That is, alone, it is not capable of producing heat, light, sound, gas, or smoke as a result of a non-detonative self-staining exothermic chemical reaction (UN 2019 Chapter 2.1 Explosives).
    - Propylene is not a substance which on contact with water emits a flammable gas. The flammability of propylene on contact with water must involve the addition of heat into the system. That is, water and propylene alone cannot ignite a flame (UN 2019 Chapter 2.12 Substances and mixtures which, in contact with water, emit flammable gas).
    - As propylene gas and liquid require the addition of heat (and water in some circumstances) to ignite or explode, the substance is not considered readily reactive.
- Screening procedures for explosivity were used here to estimate the reactivity property of propylene. These procedures are listed in the GHS (UN 2019).
    - Based on the structure of its components or moieties, propylene is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix M).
    - Based on the structure of its components or moieties, propylene 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.

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

Propylene was assigned a score of Very High for flammability based on association with EU harmonized Hazard Statement of H220. GreenScreen® criteria classify chemicals as a Very High hazard for flammability when they are associated with H220 (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 – H220: Extremely flammable gas
    - *Authoritative:* U.S. DOT Class 2.1 chemical
    - *Screening:* Quebec CSST – WHMIS 1988 – Class B1 – Flammable gases
    - *Screening:* Australia GHS – H220: Extremely flammable gas
    - *Screening:* Japan GHS – Flammable Gases – Category 1
    - *Screening:* New Zealand GHS – 2.1.1A: Flammable gases – high hazard
- ECHA 2021a
    - Propylene is an extremely flammable gas with lower and upper explosion limits of 2% and 11%, respectively.
    - Propylene is classified as a GHS Category 1 flammable gas as it is ignitable when present at ≤13% in the air.
    - Propylene has a self-ignition temperature of 455°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 silico* modeling for endocrine activity, skin sensitization, respiratory sensitization, and acute and chronic aquatic toxicity, and *in vitro* testing for genotoxicity. 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 4, Type I (input data) uncertainties in propylene's NAMs dataset include lack of or insufficient experimental data on endocrine activity, skin sensitization, respiratory sensitization, acute aquatic toxicity, and chronic aquatic toxicity, and lack of validated test methods for respiratory sensitization. Propylene's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, uncertain *in vivo* relevance of *in silico* prediction of endocrine receptor binding activities, VEGA and LabMol prediction results that were outside of the applicability domain in predicting skin sensitization, and the lack of a defined applicability domain in prediction of respiratory sensitization in OECD Toolbox. Some of propylene's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Endocrine activity**: No experimental data are available that examined endocrine levels. **Skin sensitization**: Experimental data are available only for a weak surrogate, and testing is not feasible as propylene is a gas. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Acute Aquatic Toxicity**: No experimental data are available. **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

[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).

	non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[17]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[18] **Endocrine activity:** ToxCast models don't define applicability domain. The *in vivo* relevance of *in silico* modeling by ToxCast and Danish QSAR models is uncertain due to lack of consideration of toxicokinetics and other factors. **Skin sensitization:** The *in silico* and *in vitro* assays 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] In addition, the VEGA and LabMol models implemented were outside of the applicability domain of the prediction model. **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* gene mutation assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: ToxCast/Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	

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

Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	Y	*In silico* modeling: VEGA/Payne and Walsh (1994) structural alerts/ /Toxtree/OECD Toolbox/LabMol
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	N	
Bioaccumulation	N	

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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 Propylene (CAS #115-07-1)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

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 / Propylene / 115-07-1	L	L	*L*	L	DG	L	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	No	No	Yes
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Propylene	2

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

Table 6

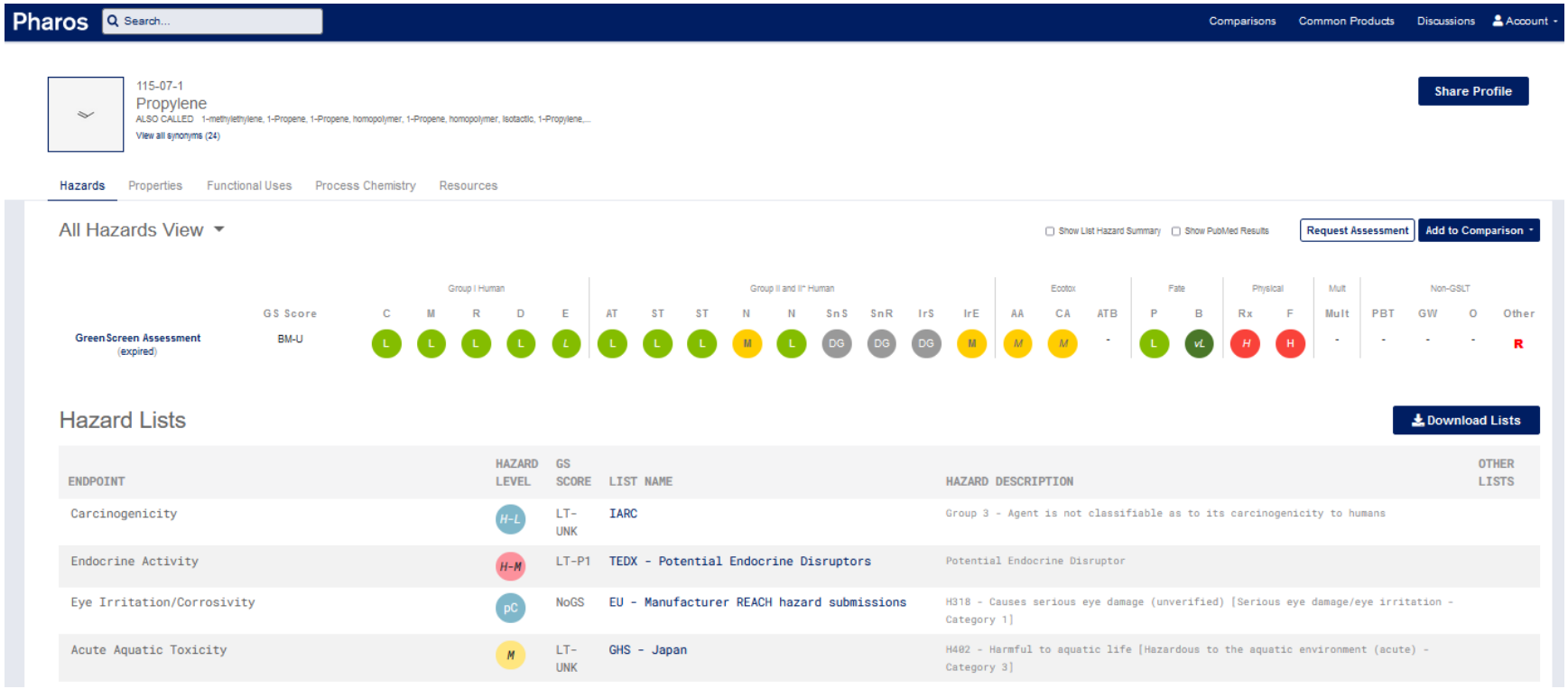
Chemical Name	Final GreenScreen® Benchmark Score
Propylene	2

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 Propylene (CAS #115-07-1)



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]	
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]	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (iTH)	

Restricted Substance Lists (3)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- MA Toxics Use Reduction Act (TURA) listed substances: Reportable Chemicals

Positive Lists (1)

- German FEA - Substances Hazardous to Waters: Non-Hazardous to Water (Water Hazard Class 0 NWG)

APPENDIX D: Danish QSAR Endocrine Activity Output for Propylene (CAS #111-07-1)

Endocrine and Molecular Endpoints

	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*)		INC_OUT	INC_OUT	NEG_OUT	POS_OUT
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	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	NEG_IN	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	NEG_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			6730.94	399.9868	62.91813
- µM			159955.8	9505.389	1495.203
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			1361.683	6.068841	233.118
- µM			32359.38	144.2215	5539.875
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 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 –		N/A	N/A	INC_OUT	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Random final model (Human *in vitro*)					
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
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	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	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	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	INC_OUT	N/A

DTU-developed models

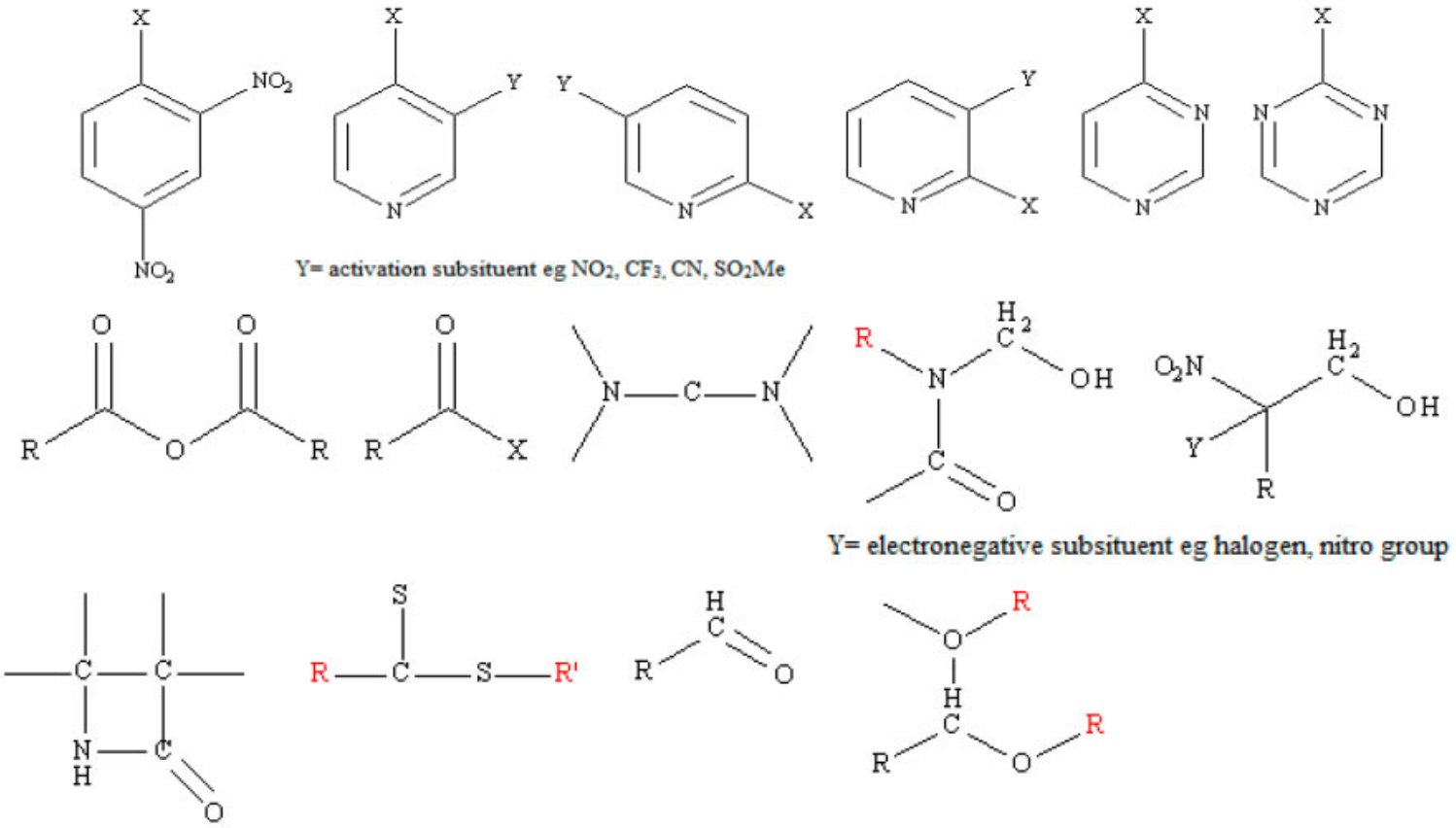
Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, non cyclic structure
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, non cyclic structure; Non binder, without OH or NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Non binder, non cyclic structure; 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

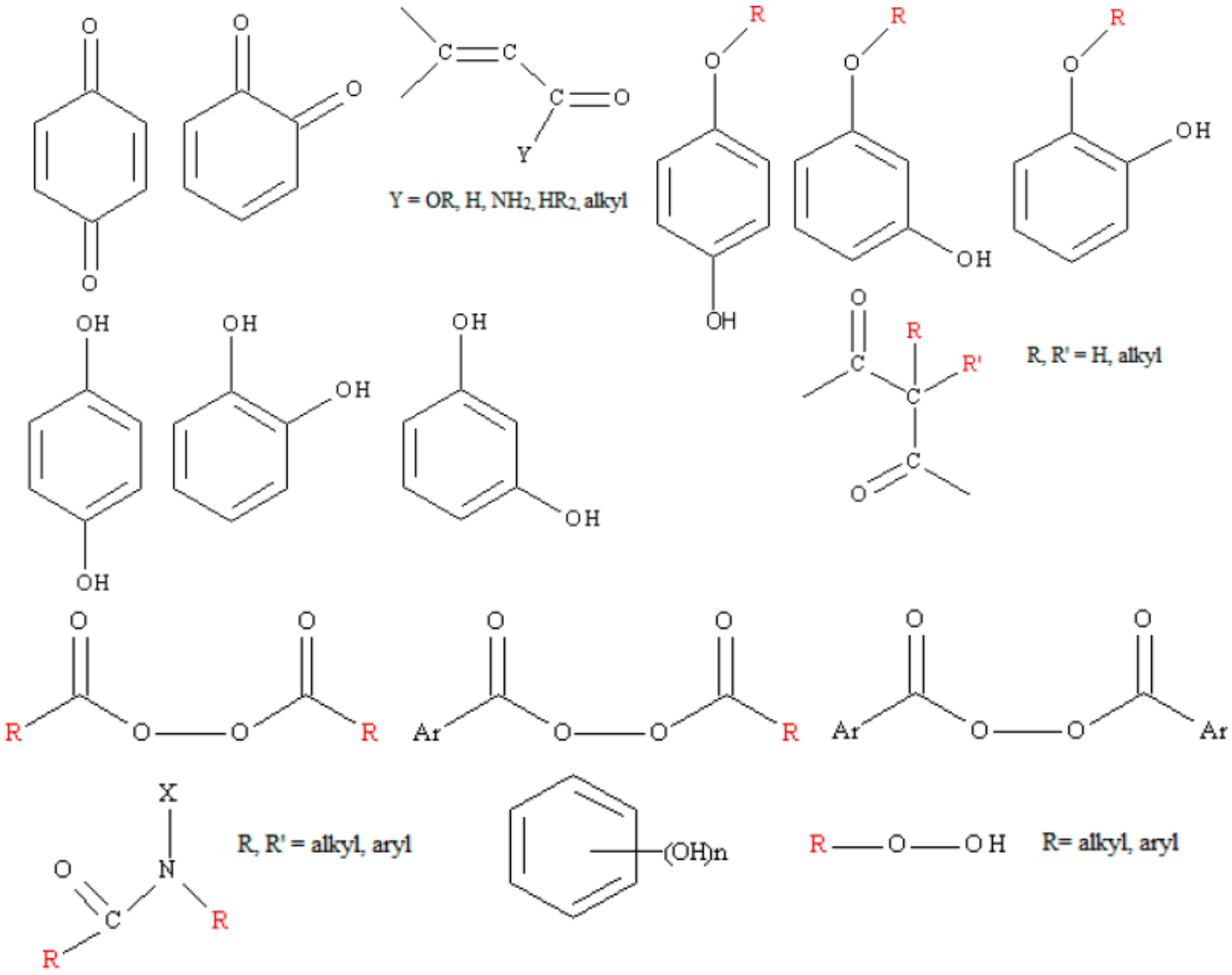
OECD QSAR Toolbox v.4.2 profilers

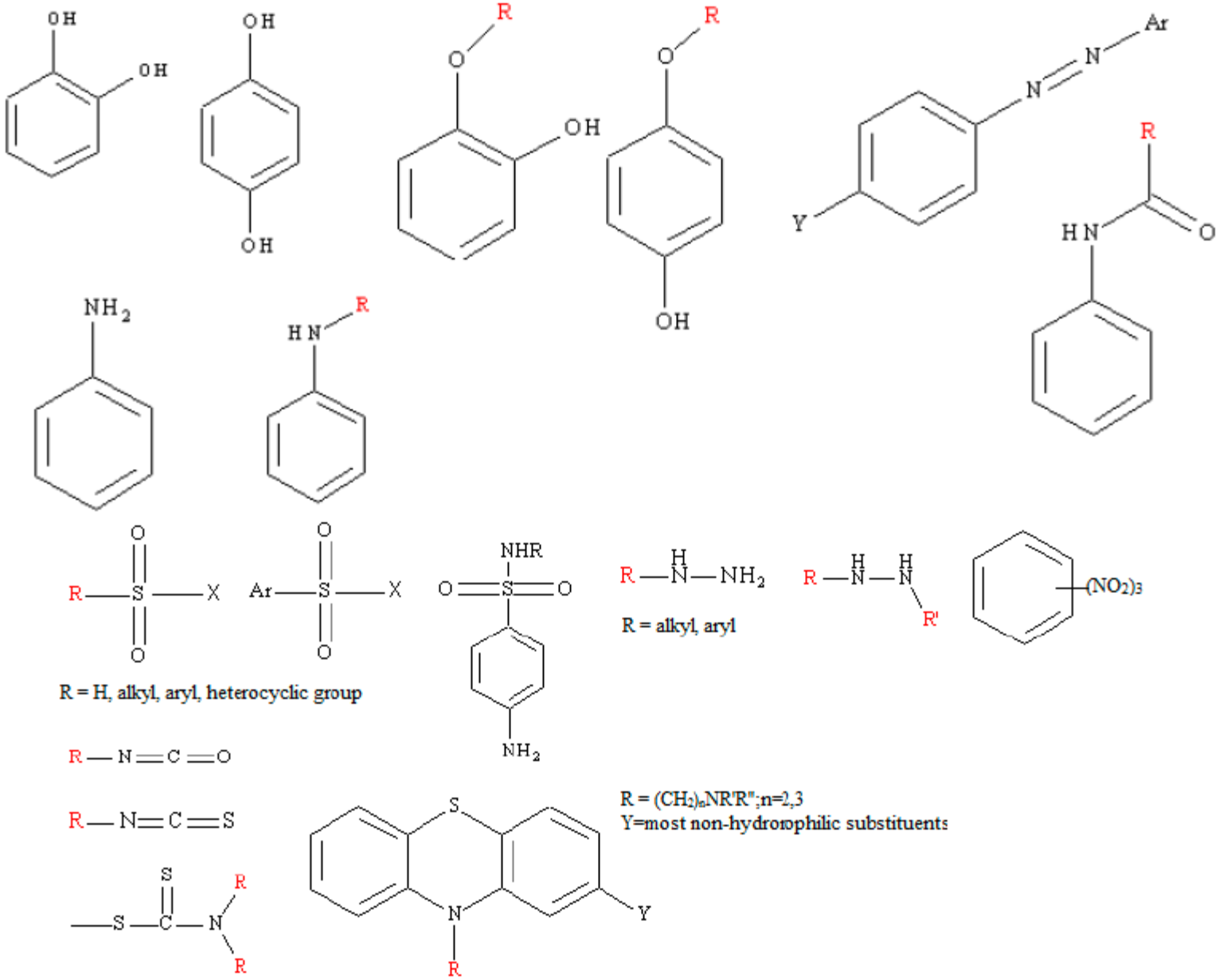
Profiler predictions are supporting information to be used together with the relevant QSAR predictions

APPENDIX E: Known Structural Alerts for Skin Sensitization

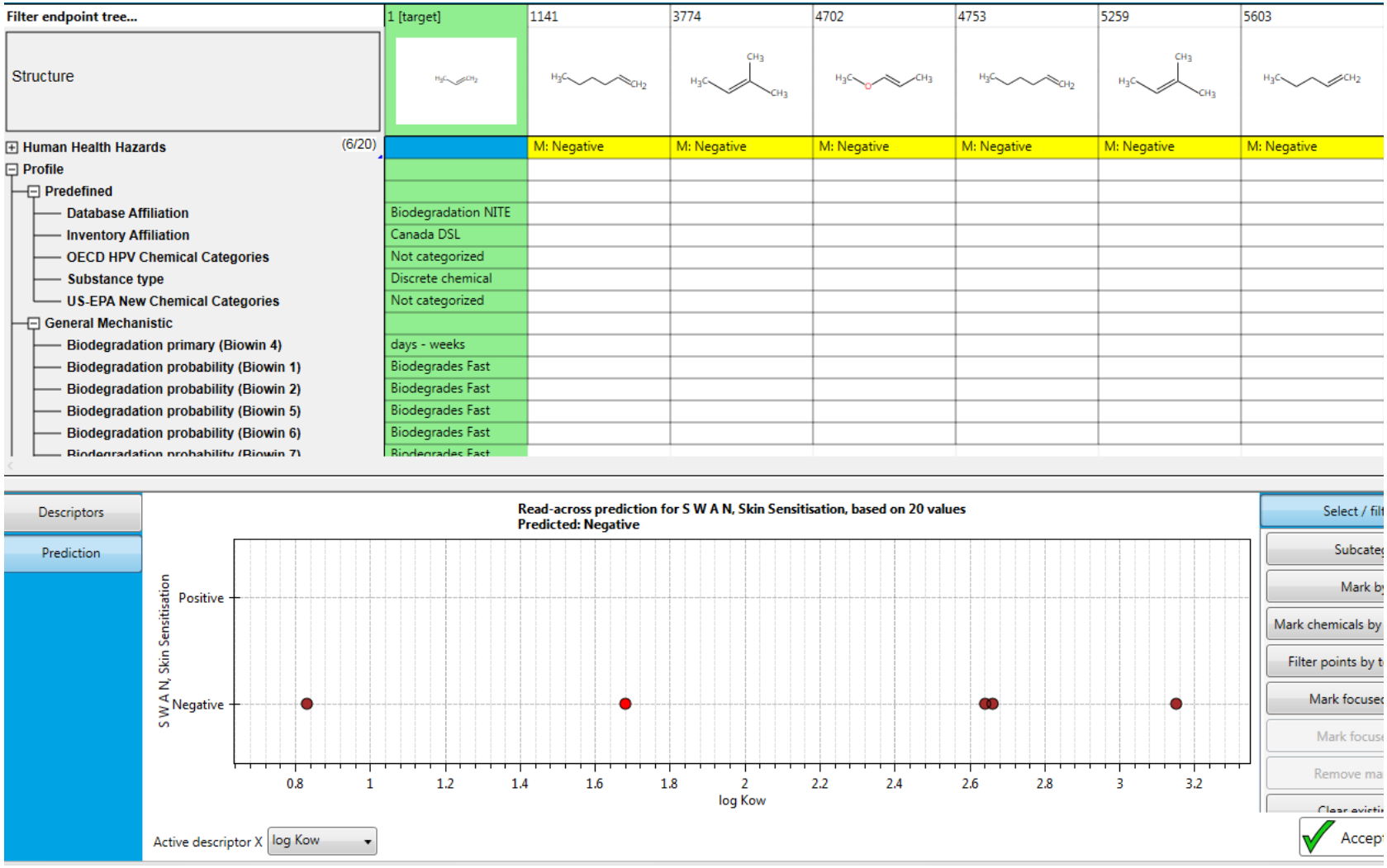
Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Propylene does not possess any of the below structural alerts.



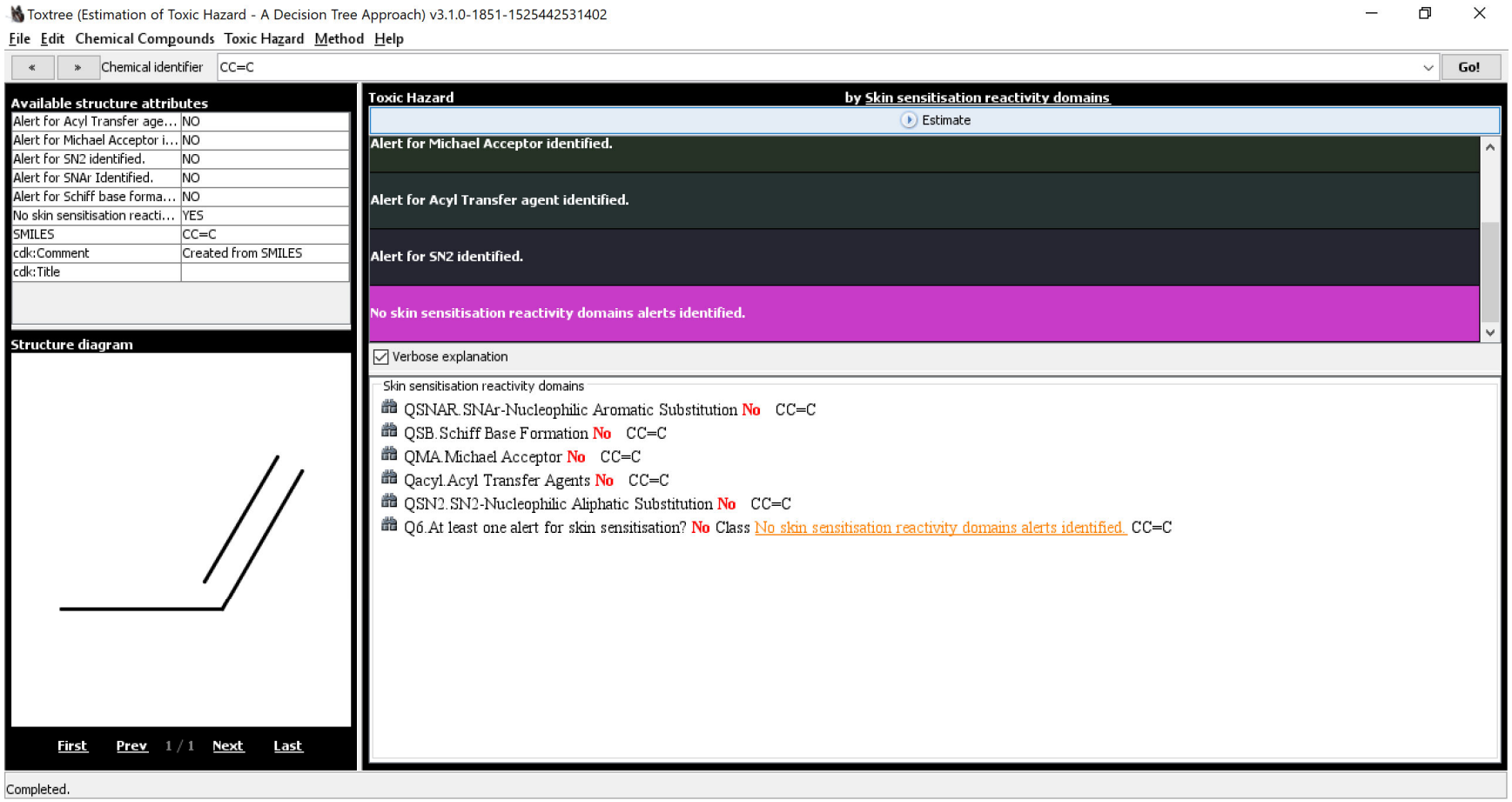




APPENDIX F: OECD Toolbox Skin Sensitization Results for Propylene (CAS #115-07-1)



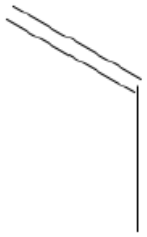
APPENDIX G: Toxtree Skin Sensitization Results for Propylene (CAS #115-07-1)



APPENDIX H: VEGA Skin Sensitization Results for Propylene (CAS #115-07-1)

1. Prediction Summary

Prediction for compound Molecule 0

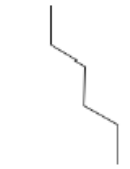
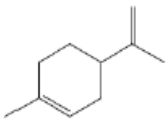
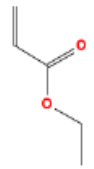
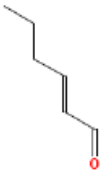
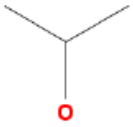
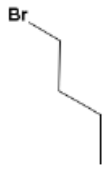


Prediction: Reliability:

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:
- only moderately 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=CC
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: 110-54-3 Dataset id: 105 (Training set) SMILES: CCCCCC Similarity: 0.64 Experimental value: NON-Sensitizer Predicted value: Sensitizer
	Compound #2 CAS: 5989-27-5 Dataset id: 129 (Training set) SMILES: C=C(C)C1CC=C(C)CC1 Similarity: 0.627 Experimental value: Sensitizer Predicted value: Sensitizer
	Compound #3 CAS: 140-88-5 Dataset id: 88 (Training set) SMILES: O=C(OCC)C=C Similarity: 0.601 Experimental value: Sensitizer Predicted value: Sensitizer
	Compound #4 CAS: 6728-26-3 Dataset id: 106 (Training set) SMILES: O=CC=CCCC Similarity: 0.594 Experimental value: Sensitizer Predicted value: Sensitizer
	Compound #5 CAS: 67-63-0 Dataset id: 122 (Training set) SMILES: OC(C)C Similarity: 0.584 Experimental value: NON-Sensitizer Predicted value: NON-Sensitizer
	Compound #6 CAS: 109-65-9 Dataset id: 23 (Training set) SMILES: CCCCBr Similarity: 0.56 Experimental value: NON-Sensitizer Predicted value: NON-Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.563 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.633 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.491 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0.509 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

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

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

APPENDIX I: LabMol Modeling Results for Propylene (CAS #115-07-1)

Chemical Exposure	**Molecular initiating event** *in chemico*	**Cellular response** *in vitro*		**Tissue / Organ response** *in vivo*	**Organism response** *in vivo*	**Pred-Skin 3.0 Outcome** *in silico*
•Skin Penetration •Electrophilic substance: directly or via auto-oxidation or metabolism	Covalent interaction with proteins in the skin (OECD442C) Haptenation: covalent modification of epidermal proteins	Keratinocyte responses (OECD442D) • Activation of inflammatory cytokines •Induce cytoprotective genes	Dendritic cells (DCs) (OECD442E) • Induction of inflammatory cytokines •Mobilization of DCs	Proliferation of antigen-specific T cells (OECD429) •Histocompatibility complex representation by DCs •Activation of T cells •Proliferation of activated T cells	Inflammation upon challenge allergen To maximise the use of existing knowledge, we also incorporate historical HRIPT (human repeated insult patch test) and HMT (human maximization test)	The Bayesian model is a consensus model integrating predictions from all the other assays for an integrative qualitative risk assessment (QRA) of skin sensitization based on the weight of evidence (WoE).
•Exposure consideration ? •Physicochemical and Biopharmaceutical properties ? •Skin Penetration ? •Skin Metabolism ? 	**Prediction DPRA** Sensitizer (+) (AD, Confiability) (Outside , 91.8%) Probability map 	**Prediction KeratinoSens** Sensitizer (+) (AD, Confiability) (Outside, 94.9%) Probability map 	**Prediction h-CLAT** Sensitizer (+) (AD, Confiability) (Outside, 61.7%) Probability map 	**Prediction LLNA** Sensitizer (+) (AD, Confiability) (Outside, 98.6%) Probability map 	**Prediction HRIPT/HMT** Sensitizer (+) (AD, Confiability) (Outside, 97.9%) Probability map 	**Bayesian Outcome** Sensitizer (+) (Confiability) (High)

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

APPENDIX J: OECD Toolbox Respiratory Sensitization Results for Propylene (CAS #115-07-1)

Filter endpoint tree...	1 [target]
Structure	
Toxic hazard classification by Cramer	Low (Class I)
Toxic hazard classification by Cramer (extended)	Low (Class I)
Endpoint Specific	
Acute aquatic toxicity classification by Verha ...	Class 1 (narcosis or baseline toxicity)
Acute aquatic toxicity MOA by OASIS	Basesurface narcotics
Aquatic toxicity classification by ECOSAR	Neutral Organics
Bioaccumulation - metabolism alerts	-C=CH [alkenyl hydrogen]
Bioaccumulation - metabolism half-lives	Fast
Biodegradation fragments (BioWIN MITI)	-C=CH [alkenyl hydrogen]
Carcinogenicity (genotox and nongenotox) al ...	No alert found
DART scheme v.1.0	Not known precedent reproductive and c
DNA alerts for AMES by OASIS v.1.4	No alert found
DNA alerts for CA and MNT by OASIS v.1.1	No alert found
Eye irritation/corrosion Exclusion rules by BfR	(Undefined) Group All Lipid Solubility < C
Eye irritation/corrosion Inclusion rules by BfR	Inclusion rules not met
in vitro mutagenicity (Ames test) alerts by ISS	No alert found
in vivo mutagenicity (Micronucleus) alerts by ISS	No alert found
Keratinocyte gene expression	Not possible to classify according to thes
Oncologic Primary Classification	Not classified
Protein binding alerts for Chromosomal aberra ...	No alert found
Protein binding alerts for skin sensitization ...	No alert found
Protein Binding Potency h-CLAT	No alert found
Respiratory sensitisation	No alert found
Retinoic Acid Receptor Binding	Not possible to classify according to thes
rtER Expert System ver.1 - USEPA	No alert found
Skin irritation/corrosion Exclusion rules by BfR	(Undefined) Group All Lipid Solubility < C
Skin irritation/corrosion Inclusion rules by BfR	Inclusion rules not met
Empiric	
Chemical elements	Group 14 - Carbon C
Groups of elements	Non-Metals
Lipinski Rule Oasis	Bioavailable
Organic functional groups	Alkene

APPENDIX K: ECOSAR Modeling Results for Propylene (CAS #115-07-1)

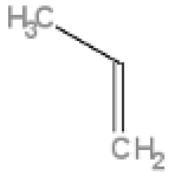
Created on Aug 12, 2021 9:52:41 PM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
115071	1-Propene	C(=C)C

Structure



Details	
Mol Wt	42.08
Selected LogKow	1.77
Selected Water Solubility (mg/L)	200
Selected Melting Point (°C)	-185
Estimated LogKow	1.68
Estimated Water Solubility (mg/L)	1108.55
Measured LogKow	1.77
Measured Water Solubility (mg/L)	200
Measured Melting Point (°C)	-185

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	55.62	5	
Daphnid	48h	LC50	30.92	5	
Green Algae	96h	EC50	21.1	6.4	
Fish		ChV	5.3	8	
Daphnid		ChV	2.84	8	
Green Algae		ChV	5.27	8	
Fish (SW)	96h	LC50	69.93	5	
Mysid	96h	LC50	60.73	5	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)		ChV	6.6	8	
Mysid (SW)		ChV	5.62	8	
Earthworm	14d	LC50	77.29	6	

APPENDIX L: EPI Suite™ Modeling Results for Propylene (CAS #115-07-1)

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

CAS Number: 115-07-1
SMILES : CC=C
CHEM :
MOL FOR: C3 H6
MOL WT : 42.08
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 1.77
Boiling Point (deg C) : -47.60
Melting Point (deg C) : -185.00
Vapor Pressure (mm Hg) : 8690
Water Solubility (mg/L): 200
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.68
Log Kow (Exper. database match) = 1.77
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): -9.84 (Adapted Stein & Brown method)
Melting Pt (deg C): -135.38 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 6.98E+003 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 9.31E+005 (Mean VP of Antoine & Grain methods)
MP (exp database): -185 deg C
BP (exp database): -48 deg C
VP (exp database): 8.69E+03 mm Hg (1.16E+006 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1109
log Kow used: 1.77 (user entered)
melt pt used: -185.00 deg C
Water Sol (Exper. database match) = 200 mg/L (25 deg C)
Exper. Ref: MCAULIFFE,C (1966)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 717.99 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.53E-001 atm-m3/mole (1.55E+004 Pa-m3/mole)

Group Method: 1.58E-001 atm-m3/mole (1.60E+004 Pa-m3/mole)
Exper Database: 1.96E-01 atm-m3/mole (1.99E+004 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.104E-001 atm-m3/mole (2.132E+004 Pa-m3/mole)
VP: 8.69E+003 mm Hg (source: User-Entered)
WS: 200 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.77 (user entered)
Log Kaw used: 0.904 (exp database)
Log Koa (KOAWIN v1.10 estimate): 0.866
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7275
Biowin2 (Non-Linear Model) : 0.9177
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1062 (weeks)
Biowin4 (Primary Survey Model) : 3.7870 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5105
Biowin6 (MITI Non-Linear Model): 0.7095
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.5359
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
LOG BioHC Half-Life (days) : 0.3730
BioHC Half-Life (days) : 2.3603

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.16E+006 Pa (8.69E+003 mm Hg)
Log Koa (Koawin est): 0.866
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.59E-012
Octanol/air (Koa) model: 1.8E-012
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 9.35E-011
Mackay model : 2.07E-010
Octanol/air (Koa) model: 1.44E-010

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 26.4360 E-12 cm3/molecule-sec
Half-Life = 0.405 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 4.855 Hrs
Ozone Reaction:

OVERALL Ozone Rate Constant = 1.200000 E-17 cm3/molecule-sec
Half-Life = 0.955 Days (at 7E11 mol/cm3)
Half-Life = 22.920 Hrs
Fraction sorbed to airborne particulates (phi):
1.5E-010 (Junge-Pankow, Mackay avg)
1.44E-010 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 21.73 L/kg (MCI method)
Log Koc: 1.337 (MCI method)
Koc : 34.34 L/kg (Kow method)
Log Koc: 1.536 (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 = 0.835 (BCF = 6.837 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.5593 days (HL = 0.2758 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.806 (BCF = 6.398)
Log BAF Arnot-Gobas method (upper trophic) = 0.806 (BAF = 6.398)
log Kow used: 1.77 (user entered)

Volatilization from Water:
Henry LC: 0.196 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 0.6639 hours (39.83 min)
Half-Life from Model Lake : 61.64 hours (2.568 days)

Removal In Wastewater Treatment (recommended maximum 95%):
Total removal: 98.70 percent
Total biodegradation: 0.02 percent
Total sludge adsorption: 0.41 percent
Total to Air: 98.27 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**10**	**6.46**	**1000**
Water	**88.3**	**360**	**1000**
Soil	**1.45**	**720**	**1000**
Sediment	**0.242**	**3.24e+003**	**0**

Persistence Time: 69.7 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	10	6.46	1000

Water	88.3	360	1000
water	(88.3)		
biota	(0.00026)		
suspended sediment	(0.00288)		
Soil	1.45	720	1000
Sediment	0.242	3.24e+003	0

Persistence Time: 69.7 hr

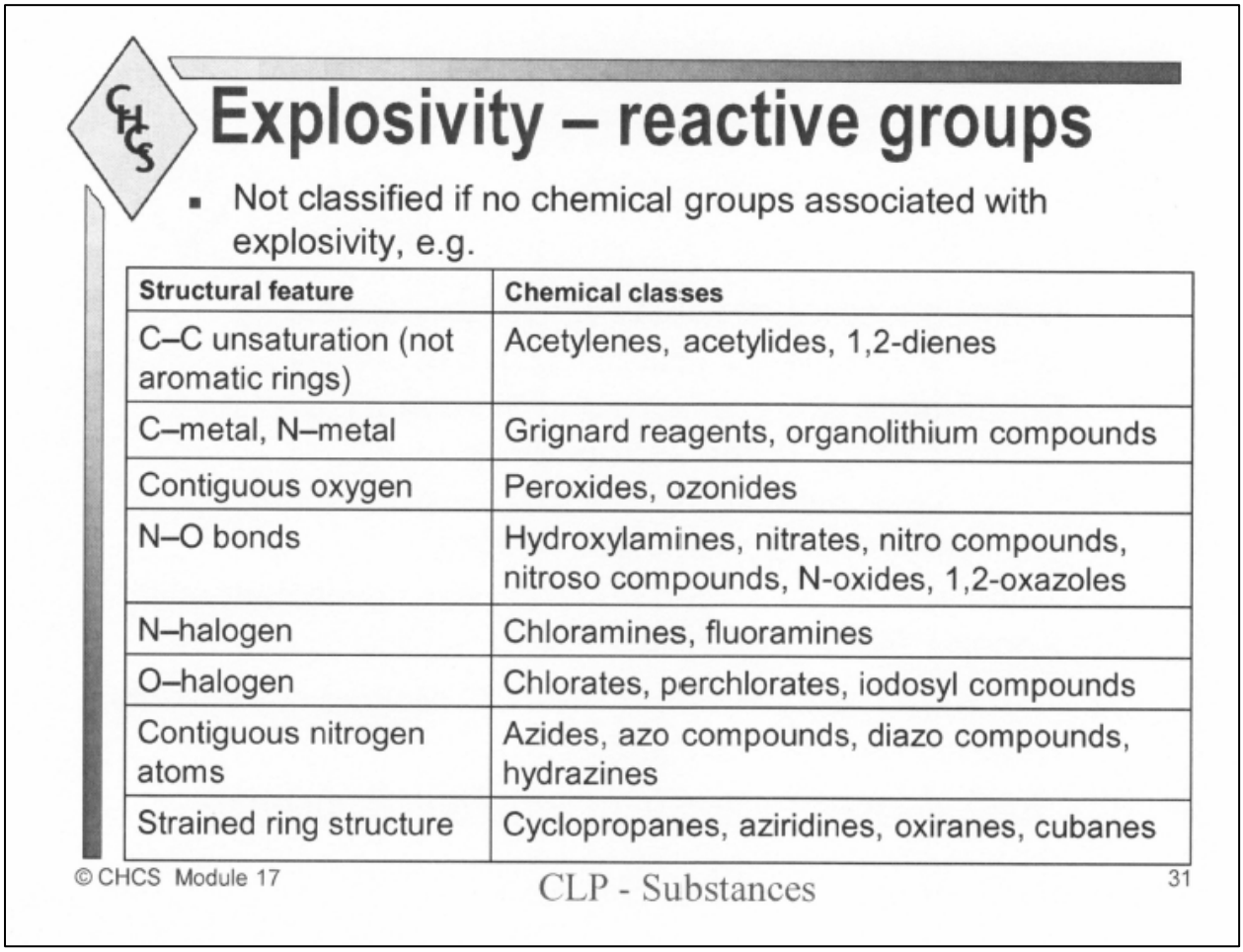
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	10	6.46	1000
Water	88.2	360	1000
water	(88.2)		
biota	(0.00026)		
suspended sediment	(0.0032)		
Soil	1.48	720	1000
Sediment	0.251	3.24e+003	0

Persistence Time: 69.7 hr

APPENDIX M: 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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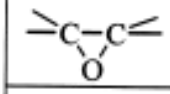
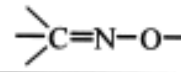
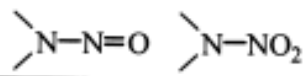
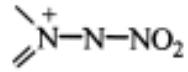
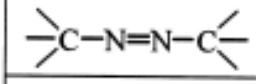
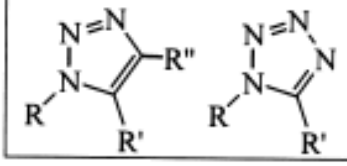
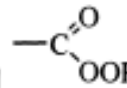
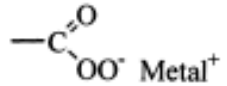
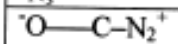
Explosivity – Full List

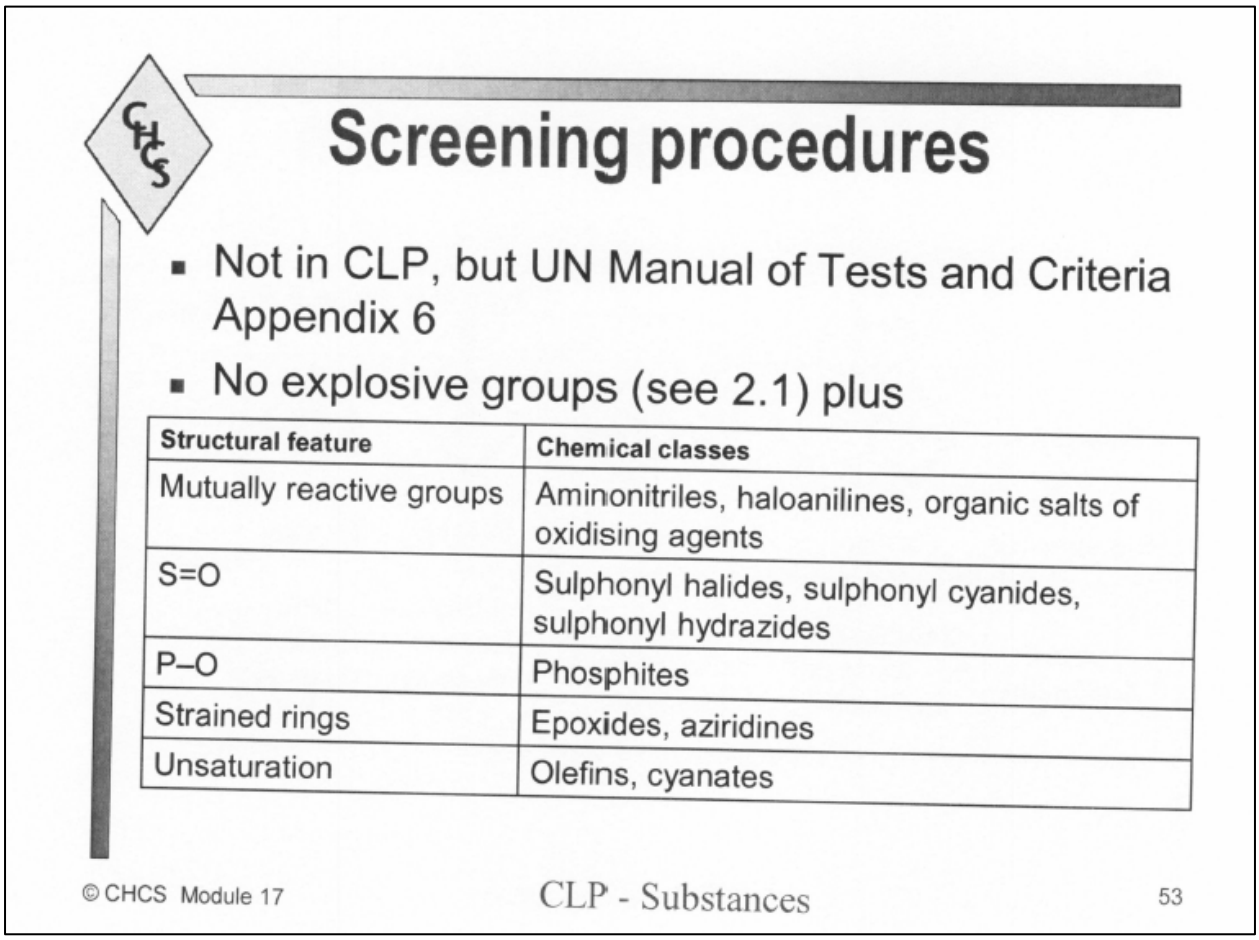
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O 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', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- 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 N: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for propylene. This benchmark score of propylene has changed over time from BM-U to BM-2.

Table 5: Change in GreenScreen® Benchmark™ for Propylene

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
April 11, 2013	BM-U	v. 1.2	New assessment
June 3, 2013	BM-U	v. 1.2	Minor updates without changing hazard scores
October 15, 2013	BM-U	v. 1.2	Verified by Clean Production Action; hazard scores for the following endpoints were changed: Single dose systemic toxicity: **M** to **L** Skin irritation: **M** to DG Persistence: *vL* to **L**
May 22, 2018	BM-2	v. 1.4	Updated to v. 1.4; hazard scores for the following endpoints were changed: Endocrine activity: *L* to DG Repeated dose neurotoxicity: **L** to DG Skin sensitization: DG to *L* Flammability: **H** to **vH**
August 13, 2021	BM-2	v. 1.4	Minor updates; hazard scores for the following endpoints were changed: Respiratory sensitization: DG to *L* Skin irritation: DG to *L* Eye irritation: *M* to *L* Reactivity: *H* to *L*
November 17, 2021	BM-2	v. 1.4	Minor updates; hazard score for the following endpoint was changed: Repeated dose neurotoxicity: DG to **L**

Licensed GreenScreen® Profilers

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