ETHYL ACETATE

(CAS #141-78-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 3, 2023

Expiration Date: April 3, 2028

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GreenScreen® Executive Summary for Ethyl Acetate (CAS #141-78-6)

Ethyl acetate is a clear, volatile liquid with an ether-like odor reminiscent of pineapple. It is highly flammable, but not reactive. Ethyl acetate is used as a solvent in surface coatings (60%), organic synthesis and pharmaceutical manufacture (15%), inks (15%) and other products such as adhesives and cosmetics (10%). It is also used as a flavoring and fragrance agent, and the United States Food and Drug Administration granted ethyl acetate generally recognized as safe (GRAS) status when used as a synthetic flavorant (21 CFR §182.60). Use levels in food are up to 2,302 ppm. When used as a solvent in personal care products such as nail polish removers, use concentrations >50% were reported.

Ethyl acetate occurs naturally during the fermentation process of ethanol by the action of acetyl coenzyme A. It is produced commercially by the Tishchenko condensation of acetaldehyde using an aluminum ethoxide catalyst; as a co-product of butane oxidation to acetic acid in the presence of catalytic cobalt or chromium ions; as a co-product in the ethanolysis of polyvinyl acetate to polyvinyl alcohol; and by heating acetic acid and ethanol in the presence of sulfuric acid and distilling. Commercial grades of ethyl acetate include 85-88%, 95-98%, and 99%, with ethanol as the major impurity. The U.S. EPA reported the National Production Volume at 226,925,660 pounds per year in 2014. Similarly, the total tonnage band report in the REACH Dossier for ethyl acetate in Europe was 100,000 – 1,000,000 tons per year as of November 2022.

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

- Benchmark 2g
    - High 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), ethyl acetate meets the requirements for a GreenScreen Benchmark™ Score of 2 despite the data gap. In a worst-case scenario, if ethyl acetate were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 chemical.

The GreenScreen® Benchmark Score for ethyl acetate has not changed over time. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017, and version 1.4 updates in 2019 and in this 2023 report.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, and persistence, and *in vitro* assays for genotoxicity and endocrine activity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

Type I (input data) uncertainties in ethyl acetate's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Ethyl acetate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to

evaluate ethyl acetate's carcinogenic potential, the non-transparency of VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in silico* prediction and *in vitro* testing of endocrine receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of ethyl acetate'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 Ethyl Acetate

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**	**M**	**M**	**M**	**L**	**L**	*L*	**L**	**H**	**L**	**M**	**vL**	**vL**	**L**	**H**

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

GreenScreen® Chemical Assessment for Ethyl Acetate (CAS #141-78-6)

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

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Organization: ToxServices LLC
Date: January 25, 2023; April 3, 2023

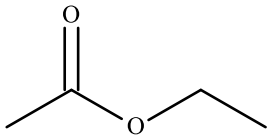
Expiration Date: April 3, 2028[2]

Chemical Name: Ethyl acetate

CAS Number: 141-78-6

[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).

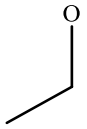
Chemical Structure(s):



Also called: Acetic acid, ethyl ester; Acetic acid, ethyl ester; Acetic ether; Acetidin; Acetoxyethane; Ethyl acetic ester; Ethyl ester; Ethyl ethanoate; Acetic acid ethyl ester; Ethyl acetate (PubChem 2023).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Ethyl acetate did not have a complete dataset and data gaps existed for carcinogenicity and reproductive and developmental toxicities. The OECD SIDS Dossier identified ethanol as a surrogate because ethyl acetate is rapidly hydrolyzed to form ethanol and acetic acid (OECD 2007). Acetic acid is a commonly consumed food ingredient with a long history of safe use. Ethanol is expected to be more toxic than acetic acid. Therefore, studies using ethanol were considered applicable in assessing carcinogenicity and reproductive and developmental toxicities.

Hydrolysis of ethyl acetate to equimolar amounts of ethanol and acetate by endogenous esterases occurs in many tissues including the skin, lungs, and gastrointestinal tract. Data from rats suggest esterases are not saturated at levels as high as 10,000 ppm (approximately 36.6 mg/L), and ester hydrolysis is faster than ethanol metabolism. In humans, alcohol dehydrogenase (ADH) is the principal enzyme involved in hepatic metabolism of ethanol to acetaldehyde, and acetaldehyde is rapidly converted to acetate and acetyl-CoA, which is then oxidized to carbon dioxide or utilized for the biosynthesis of lipids and fatty acids (OECD 2008).



Surrogate #1: Ethanol (CAS# 64-17-5)

Identify Applications/Functional Uses: (OECD 2008, HSDB 2015)
1. Solvent in surface coatings (60%), in organic synthesis and pharmaceutical manufacture (15%), in inks (15%) and in other products such as adhesives and cosmetics (nail polish remover) (10%).
2. Flavoring and fragrance agent (minor use).

Known Impurities[3]:
Commercial grades of ethyl acetate include 85-88%, 95-98%, and 99%, with ethanol as the major impurity (HSDB 2015).

[3] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.

GreenScreen® Summary Rating for Ethyl Acetate[4,5 6,7]: Ethyl acetate 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:

- Benchmark 2g
  - High 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), ethyl acetate meets the requirements for a GreenScreen Benchmark™ Score of 2 despite the data gap. In a worst-case scenario, if ethyl acetate 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 Ethyl Acetate

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**	**M**	**M**	**M**	**L**	**L**	*L*	**L**	**H**	**L**	**M**	**vL**	**vL**	**L**	**H**

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). Ethyl acetate may undergo hydrolysis to form ethanol and acetic acid (see Toxicokinetics section). However, ethyl acetate is readily biodegradable in the environment (see Persistence section below), and therefore the expected hydrolysis products are not considered relevant to this assessment due to their transient nature.

[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.

Table 1: Environmental Transformation Product Summary						
Life Cycle Stage	**Transformation Pathway**	**Environmental Transformation Product**	**CAS #**	**Feasible (Yes or No)**	**Relevant (Yes or No)**	**GreenScreen® List Translator Score or GreenScreen Benchmark™ Score[8,9]**
N/A	Hydrolysis	Ethanol	64-17-5	Yes	No	LT-1
N/A	Hydrolysis	Acetic acid	64-19-7	Yes	No	LT-U

Introduction

Ethyl acetate is a clear volatile liquid with an ether-like odor reminiscent of pineapple. It is highly flammable, but not reactive. Ethyl acetate is used as a solvent in surface coatings (60%), organic synthesis and pharmaceutical manufacture (15%), inks (15%) and other products such as adhesives and cosmetics (10%) (OECD 2008). It is also used as a flavoring and fragrance agent, and the U.S. Food and Drug Administration granted ethyl acetate generally recognized as safe (GRAS) status when used as a synthetic by (21 CFR §182.60). Use levels in food are up to 2,302 ppm (HSDB 2015). When used as a solvent in personal care products such as nail polish removers, use concentrations >50% have been reported (CIR 1989).

Ethyl acetate occurs naturally during the fermentation process of ethanol by the action of acetyl coenzyme A. It is produced commercially by the Tishchenko condensation of acetaldehyde using an aluminum ethoxide catalyst; as a co-product of butane oxidation to acetic acid in the presence of catalytic cobalt or chromium ions; as a co-product in the ethanolysis of polyvinyl acetate to polyvinyl alcohol; and by heating acetic acid and ethanol in the presence of sulfuric acid and distilling (HSDB 2015). Commercial grades of ethyl acetate include 85-88%, 95-98%, and 99%, with ethanol as the major impurity. The U.S. EPA reported the National Production Volume at 226,925,660 pounds per year in 2014. Similarly, the total tonnage band report in the REACH Dossier for ethyl acetate in Europe was 100,000 – 1,000,000 tons per year in August 2019 (HSDB 2015, OECD 2008).

ToxServices assessed ethyl acetate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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 2023a). 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).

Ethyl acetate is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2019) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[10] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for ethyl acetate can be found in Appendix C.

- Ethyl acetate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Ethyl acetate is listed on the U.S. DOT list as a Hazard Class 3, Packing Group II.
- Ethyl acetate is on the following list for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - German FEA – Substances Hazardous to Waters: Class 1 – Low Hazard to Waters

Hazard Statement and Occupational Control

Harmonized H Statements from ECHA's C&L Inventory are included in Table 2, below. Occupational exposure limits and recommended personal protection equipment are listed in Table 3.

Table 2: GHS H Statements for Ethyl Acetate (CAS #141-78-6) (ECHA 2023a)

H Statement	H Statement Details
H225	Highly flammable liquid and vapor
H319	Causes serious eye irritation
H336	May cause drowsiness or dizziness

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Ethyl Acetate (CAS #141-78-6)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Organic vapor canister or air mask; goggles or face shield; protective gloves and clothing	HSDB 2015	OSHA PEL: TWA 400 ppm (1,400 mg/m^3)	NIOSH 1997
		NIOSH REL: TWA 400 ppm (1,400 mg/m^3)	
		NIOSH IDLH: 2,000 ppm 10% LEL	
		ACGIH TLV: 400 ppm as TWA	
		MAK: 400 ppm (1,500 mg/m^3)	

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

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

Physicochemical Properties of Ethyl Acetate

Ethyl acetate is a colorless liquid at room temperature. It is highly soluble in water and its high vapor pressure indicates it is likely to volatize. Ethyl acetate has an ether-like odor reminiscent of pineapple. Its low log K_{ow} indicates it is hydrophilic and unlikely to bioaccumulate.

Table 4: Physical and Chemical Properties of Ethyl Acetate (CAS #141-78-6)

Property	Value	Reference
Molecular formula	$C_4H_8O_2$	PubChem 2023
SMILES Notation	O(C(=O)C)CC	PubChem 2023
Molecular weight	88.1052 g/mol	PubChem 2023
Physical state	Liquid	ECHA 2023b
Appearance	Colorless liquid	ECHA 2023b
Melting point	-83.6°C	PubChem 2023
Boiling point	77.1°C	PubChem 2023
Vapor pressure	93.2 mm Hg at 25ºC	PubChem 2023
Water solubility	80,000 mg/L at 25ºC	PubChem 2023; ECHA 2023b
Dissociation constant	Not applicable (no ionic structure)	ECHA 2023b
Density/specific gravity	900.63 kg/m^3	ECHA 2023b
Partition coefficient	Log K_{ow} = 0.68 at 25ºC	ECHA 2023b

Toxicokinetics

Numerous *in vivo* studies in animals and humans have demonstrated rapid absorption of ethyl acetate following oral, inhalation, and dermal exposures. Due to its high volatility, inhalation is the primary route of absorption for humans (HSDB 2015). Inhalation absorption was 63.2% and 56.7% in men and women after 4-hour exposures to 0.344 – 0.501 mg/L ethyl acetate (OECD 2008, ECHA 2023b).

No data were available on the distribution of ethyl acetate. Upon, or even before absorption into the systemic circulation, ethyl acetate is rapidly hydrolyzed with an elimination half-life of 33 – 37 seconds in the blood of rats. No ethyl acetate was detected in expired air one hour after inhalation exposure to 0.344 – 0.501 mg/L for 4 hours, or in the urine within 2 hours after a 4-hour inhalation exposure to 1.45 mg/L in humans. Hydrolysis of ethyl acetate to equimolar amounts of ethanol and acetate by endogenous esterases occurs in many tissues including the skin, lungs, and gastrointestinal tract. Data from rats suggest esterases are not saturated at levels as high as 10,000 ppm (approximately 36.6 mg/L), and ester hydrolysis is faster than ethanol metabolism. In humans, alcohol dehydrogenase (ADH) is the principal enzyme involved in hepatic metabolism of ethanol to acetaldehyde, acetaldehyde is rapidly converted to acetate and acetyl-CoA, which is then oxidized to carbon dioxide or utilized for the biosynthesis of lipids and fatty acids (OECD 2008, ECHA 2023b).

Based on the metabolic pathways described above, ethyl acetate and its metabolites are eliminated via urine and expired air.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*

Ethyl acetate was assigned a score of Low for carcinogenicity based on limited negative carcinogenicity data on itself, and negative weight of evidence from modeling. Although its metabolite ethanol is an IARC group I carcinogen when consumed in alcoholic beverages, it is only considered carcinogenic following excessive alcohol consumption which is not reasonably anticipated for ethyl acetate under its known uses, therefore hazards associated with excessive ethanol exposure do not apply. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score was low as it was based on limited experimental data and modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - *Intraperitoneal:* A/He mice (a mouse pulmonary tumor model according to the method of Andervant and Shimkin, non-GLP) were administered doses of 150 or 750 mg/kg/injection intraperitoneally three times a week for eight weeks and observed for 16 weeks. Treatment did not cause an increase in lung tumor formations (Authors of the REACH dossier assigned a Klimisch score of 2 (reliable with restrictions) on the basis that the study was well documented and meets basic scientific principles).
- U.S. EPA 2013
  - U.S. EPA concluded there are "inadequate information to assess carcinogenic potential" for ethyl acetate.
  - *Dermal:* Female CD-1 mice (8 animals) were exposed to ethyl acetate as a solvent control in an initiation/promotion carcinogenicity study. Mice were initiated by applying a single 0.2 mL dose of the test compound to shaved dorsal skin. Four days later, mice were exposed to the promoter chemical, or the solvent control ethyl acetate, 2x/week for 22 weeks. Ethyl acetate-exposed mice did not develop papillomas after 22 weeks of exposure, and there were no adverse effects on body weight or body weight gain for treated animals. No further details were provided.
- U.S. EPA 2019, 2021
  - An attempt was made to use EPA's OncoLogic (v 8.0 and v 9.0) to evaluate this chemical, but it does not fit into any of the existing chemical classes. Therefore, it cannot be assessed by OncoLogic.
- Toxtree 2018
  - Ethyl acetate does not have structural alerts for genotoxic carcinogenicity or non-genotoxic carcinogenicity (Appendix D).
- DTU 2023
  - Ethyl acetate was modeled in the Danish QSAR Database. The E Ultra model predicted ethyl acetate would be non-carcinogenic based on data from all 7 FDA rodent databases, and the compound was within the applicability domain for all 7 predictions. The Leadscope model predicted ethyl acetate would be non-carcinogenic based on data from 3 of the FDA rodent databases for which the compound was within the applicability domain, and with the remaining 4 databases the predictions were negative or inconclusive but the compound was outside the applicability domain. The model output also noted no structural alerts for

genotoxic or nongenotoxic carcinogenicity using the alerts by ISS and OECD QSAR Toolbox v.4.2. Lastly, ethyl acetate was predicted to be negative for liver specific cancer in rats or mouse according to the model battery consisted of CASE Ultra, Leadscope, and SciQSAR models, and ethyl acetate was in domain for all predictions (Appendix E).

- VEGA 2021
  - The CAESAR model predicted ethyl acetate as a carcinogen with strong reliability (Global applicability domain (AD) Index = 0.944) (Appendix F). *However, an examination of chemicals in the training set reveals that most of them contain additional structural alerts for carcinogenicity that are not present in ethyl acetate. Therefore, ToxServices did not heavily weigh this positive prediction in the weight of evidence evaluation.*
  - The ISS model predicted ethyl acetate as a NON-carcinogen with low reliability (Global AD Index = 0). The 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, and the predicted compound is outside of the applicability domain (Appendix F).
  - The IRFMN/Antares model predicted ethyl acetate as a possible NON-carcinogen, however the reliability is low (Global AD Index = 0). The 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, and the predicted compound is outside of the applicability domain (Appendix F).
  - The IRFMN/ISSCAN-CGX model predicted ethyl acetate as a possible NON-carcinogen, however the reliability is low (Global AD Index = 0). The 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, and the predicted compound is outside of the applicability domain (Appendix F).
  - The IRFMN oral classification model predicted ethyl acetate as a NON-carcinogen with good reliability based on experimental data (Global AD index = 1) (Appendix F).
  - The IRFMN inhalation classification model predicted ethyl acetate as a NON-carcinogen with good reliability based on experimental data (Global AD index = 1) (Appendix F).
- Pharos 2023
  - *Surrogate: Ethanol (CAS# 64-17-5):* The surrogate ethanol is classified as Group 1 carcinogen by IARC (alcoholic beverages) and Group 5 carcinogen by German MAK.
- Based on limited evidence, a score of Low was assigned. In a limited cancer initiation/promotion study, ethyl acetate was not carcinogenic when evaluated as a control substance. A limited intraperitoneal study using a mouse pulmonary tumor model was also negative. Mixed results were obtained using modeling. Toxtree did not identify any structural alerts for genotoxic or non-genotoxic carcinogenicity. Danish QSAR modeling also predicted a lack of carcinogenicity. VEGA predicted positive results in one model with high confidence but negative in five models with good to low confidence. However, only positive prediction was based on chemicals with additional structural alerts for carcinogenicity. Therefore, ToxServices did not consider this prediction reliable. The hydrolysis product ethanol is a known carcinogen (digestive tract, liver, and lung), and ethyl acetate has been demonstrated to be rapidly hydrolyzed in the body. It should be noted that the form of alcohol that is classified as carcinogenic is alcoholic beverage, for which high exposure levels are expected. Ethyl acetate is not directly consumed as a beverage, and its most common use is as an industrial solvent. Therefore, the carcinogenicity hazard associated with excessive alcohol consumption is irrelevant to the intended uses of ethyl acetate.

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

Ethyl acetate was assigned a score of Low for mutagenicity/genotoxicity based on mostly negative results in *in vitro* and *in vivo* genotoxicity assays. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available for both gene mutation and clastogenicity and negative and it is not GHS classified (CPA 2018b). The confidence in the score was high as it was based on well-conducted studies of good quality.

- 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 2023b (Only studies designated by the REACH dossier authors as Klimisch scores 1 (reliable without restriction) and 2 (reliable with restrictions) were included below. Studies conducted on read-across chemicals were not included due to availability of high quality data on the target chemical).
  - *In vitro:* Negative in an Ames assay performed according to OECD 471 (GLP not specified) (>99% purity) in *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535, and TA1537, with and without metabolic activation at concentrations up to 10,000 µg/mL (Klimisch 2, reliable with restrictions, published study that was sufficiently documented but strain TA102 was not included).
  - *In vitro:* Negative in an Ames assay performed according to OECD 471 (GLP not specified) (99% purity) in *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537, with metabolic activation at concentrations up to 5 mg/plate (Klimisch 2, reliable with restrictions due to lack of details on number of concentrations tested and only tested in the presence of metabolic activation).
  - *In vitro:* Negative in an Ames assay performed according to OECD 471 (non-GLP) (99.9% purity) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538, with and without metabolic activation at concentrations up to 1,000 µg/plate (Klimisch 2, reliable with restrictions due to lack of details on methods, but detailed results were available in an original test report, and study did not appear to use a positive control without metabolic activation)
  - *In vitro:* Negative in a chromosome aberration assay performed according to OECD 473 (GLP not specified) (99% purity) in Chinese hamster ovary (CHO) cells, at concentrations up to 5,000 µg/mL without activation and concentrations of 5,020 with metabolic activation (Klimisch 2, reliable with restrictions. This study was well reported but deviated from the method guideline by not using replicates).
  - *In vitro:* Ambiguous results were reported in a chromosome aberration study, equivalent or similar to OECD 473 (GLP not specified) (99.9% purity) in Chinese hamster lung fibroblasts. Cells were treated with up to 9 mg/mL ethyl acetate without metabolic activation. At the maximum tolerated dose of 9 mg/mL the frequency of chromosomal aberrations was equivocal at 24 hours and marginally positive at 48 hours (Klimisch 2, reliable with restrictions due to lack of details on the number of concentrations tested, only results for the maximum dose were reported, and no replicates were used).
  - *In vitro:* CHO cells were tested for sister chromatid exchange (SCE) induction in a non-guideline study (non-GLP) (99% purity). CHO cells were treated with up to 1,500 µg/mL ethyl acetate in the absence of metabolic activation and 5,000 µg/mL in the presence of metabolic activation. Treatment with ethyl acetate in the absence of metabolic activation did not increase the frequency of sister chromatid exchange. Treatment in the presence of metabolic activation produced equivocal results in one trial, and a weak positive in a second trial. The authors noted that the concentrations tested are above the maximum normally

recommended for testing (Klimisch 2, reliable with restrictions due to lack of replicates, and study was non-GLP).
    - *In vivo:* Negative in a hamster micronucleus assay equivalent or similar to OECD 474 (GLP not specified) (purity not specified). Chinese hamsters (10/group) received a single oral dose of 2,500 mg/kg via oral gavage and bone marrow was collected 12, 24, 28, and 72 hours later and the frequency of micronucleated polychromatic erythrocytes were quantified. Treatment did not increase the frequency of micronucleated polychromatic erythrocytes in the bone marrow of hamsters (Klimisch 2, reliable with restrictions. Study is well documented, meets basic scientific principles. No data on replicates. No data on necropsy, slide preparation or clinical observations).
    - *In vivo:* Negative in a mouse micronucleus assay equivalent or similar to OECD 474 (GLP not specified) (99.9% purity in 0.5% carboxymethylcellulose sodium salt). Male ddY mice received a single dose of 0, 100, 200, 400, or 800 mg/kg and one group received 200 mg/kg/day for four days. Treatment did not increase the frequency of micronucleated polychromatic erythrocytes in any treatment group (Klimisch 2, reliable with restrictions. Single sampling time of 24 hours was used. Individual animal data were not presented but statistics for each dose level were presented in tabular form).
    - *In vivo:* Negative in a hamster micronucleus assay equivalent or similar to OECD 474 (GLP not specified) (purity not specified). Chinese hamsters received 473 mg/kg via a single intraperitoneal injection. Treatment did not increase the frequency of micronucleated polychromatic erythrocytes in the bone marrow of treated hamsters (Klimisch 2, reliable with restrictions. Well documented publication which meets basic scientific principles. No data on replicates, slide preparation, necropsy or clinical observations reported in the reference, although study cross-referenced another publication for details).
- Based on the weight of evidence, a score of Low was assigned. Ethyl acetate was negative in multiple Ames assays, one *in vitro* chromosome aberration assay, and three *in vivo* micronucleus assays. Ambiguous results were reported when cells were treated with concentrations at or above the maximum tolerated dose in an *in vitro* sister chromatid exchange assay and an *in vitro* chromosome aberration assay. Therefore, ToxServices did not consider these results to be toxicologically relevant.

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

Ethyl acetate was assigned a score of Low for reproductive toxicity based on measured data on ethyl acetate from a repeated dose toxicity study supported by very high NOAELs for the surrogate ethanol in reproductive toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative and they are not classified under GHS (CPA 2018b). The confidence in the score was high as it was based on well-conducted studies of good quality on a conservative 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.
- ECHA 2023b,c
    - *Inhalation:* Male Sprague-Dawley rats were tested in a sub-chronic toxicity study with fertility endpoints according to EPA OTS 798.2450, and to GLP. Animals were exposed to 0, 350, 750, or 1,500 ppm (equivalent to 1.26, 2.7, 5.4 mg/L[11]) ethyl acetate (purity not

[11] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(350\ ppm)(88.1052)}{24,450} = 1.26$ mg/L.

specified) by inhalation for 6 hours per day, 5 days per week, for 94 days. Treatment did not alter the number or concentration of spermatids in the testes, the number or concentration of sperm in the epididymides, sperm motility, or sperm morphology (Klimisch 1, reliable without restriction).

- *Inhalation: Surrogate: Ethanol (CAS #64-17-5):* In a one-generation reproduction toxicity study equivalent or similar to OECD Guideline 415 (GLP not specified), male and female Sprague-Dawley rats were exposed to 0, 10,000 or 16,000 ppm (equivalent to 18.8 and 30.1 mg/L[12]) ethanol (>95% purity, with reminder primarily water) by whole body inhalation for 7 hours/day. Males were exposed 6 weeks before mating, and females were exposed on gestation days 1-19. Females were allowed to deliver litters. Treatment with ethanol did not affect the weight gain of parental animals. Incidence of fertility did not differ from controls and no group differences were found for litter size, number of dead pups, or length of pregnancy. Offspring survival and weight gain was not affected by ethanol treatment, either. A NOAEC of > 16,000 ppm (> 30.1 mg/L) was established for this study (Klimisch 2, reliable with restrictions. Published study that contained sufficient details and was scientifically rigorous, however limited experimental details were reported, and some elements of the protocol were not included).
- *Oral: Surrogate: Ethanol (CAS #64-17-5):* In a two-generation reproduction toxicity study equivalent or similar to OECD 416 (GLP not specified), CD-1 mice were exposed to 0, 6,900, 13,800, or 20,700 mg/kg/day ethanol (92% purity) in their drinking water. Treatment began one week prior to mating and continued for a 14-week breeding period followed by a 21-day holding period. Dams were continuously exposed through gestation and lactation, treatment continued in F1 offspring from weaning though postnatal days (PNDs) 74-84. F1 males in the high dose group had a significant decrease in percent motile sperm but there were no changes in sperm concentration, percent abnormal sperm, or percent tailless sperm. Treatment did not alter mating or fertility; however, adjusted live pup weight was significantly reduced in the high dose group. The authors noted this was likely due to generalized maternal toxicity and concluded that ethanol had no demonstrable effect on fertility. The authors identified a NOAEL of 13,800 mg/kg/day based on decreased sperm motility in F1 males (Klimisch 1, reliable without restriction).

- Based on the weight of evidence, a score of Low was assigned. Subchronic inhalation exposure to ethyl acetate had no effect on the number or concentration of sperm, sperm motility, or sperm morphology in rats. A one-generation inhalation toxicity study with ethanol in rats reported no effects on fertility at concentrations up to 16,000 ppm (30.1 mg/L). A two-generation study in mice reported decreased sperm motility in males treated with 20,700 mg/kg/day ethanol and the NOAEL was 13,800 mg/kg/day. This is much higher than the limit dose of 1,000 mg/kg/day specified by OECD for repeated dose oral toxicity studies (UN 2021). GHS guidance does not specify a guidance dose for classification for this endpoint. However, GHS suggests that a limit dose of 1,000 mg/kg unless expected human response indicates a higher dose level, for evaluation of this endpoint. A limit dose refers to a dose level above which adverse effects do not lead to classification (UN 2021).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L

Ethyl acetate was assigned a score of Low for developmental toxicity based on measured data from studies using ethanol demonstrating effects only at extremely high exposure levels. GreenScreen®

[12] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(10{,}000\ ppm)(46.0684)}{24{,}450} = 18.8\ mg/L.$

criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and negative and it is not GHS classified (CPA 2018b). The confidence in the score was high as it was based on well-conducted studies of good quality and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* MAK - Pregnancy Risk Group C.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - *Inhalational: Surrogate: Ethanol (CAS #64-17-5):* Ethanol was evaluated in the previously described one-generation reproduction toxicity study performed in a manner equivalent or similar to OECD Guideline 415 (GLP not specified). Male and female Sprague-Dawley rats were exposed to 0, 10,000 or 16,000 ppm (equivalent to 18.8 and 30.1 mg/L[13]) ethanol (>95% purity, with reminder primarily water) by whole body inhalation for 7 hours/day. Males were exposed 6 weeks before mating, and females were exposed on gestation days 1-19. Females were allowed to deliver litters. Treatment with ethanol did not affect the weight gain of parental animals. No group differences were found for litter size, number of dead pups, or length of pregnancy. Offspring survival and weight gain was not affected by ethanol treatment, either. A NOAEC of >16,000 ppm (> 30.1 mg/L) was established for this study (Klimisch 2, reliable with restrictions. Published study that contained sufficient details and was scientifically rigorous, however limited experimental details were reported, and some elements of the protocol were not included).
- OECD 2007 (Studies with Klimisch score of 4 (reliability not assignable) were not included in this assessment)
  - *Surrogate: Ethanol (CAS #64-17-5):* In humans, ethanol is known to cause adverse developmental effects collectively called "fetal alcohol syndrome". The blood concentration leading to these effects are commonly achievable in alcoholics.
  - *Inhalation: Surrogate: Ethanol (CAS #64-17-5):* Pregnant Sprague-Dawley rats were exposed to 0, 10,000, 16,000, or 20,000 ppm ethanol (equivalent to 18.8, 30.1, 37.6 mg/L[13]) via inhalation 7 hours per day during gestation days 1 – 19. Treatment had no effect on the percentage of implants resorbed. Litter sizes, litter weights, and sex ratio were not affected by treatment. The authors reported there were no significant differences in the frequency of abnormalities; however, litters exposed to 37.6 mg/L had more abnormal fetuses. The authors identified a teratogenicity NOEL of 37.6 mg/L. ToxServices identified a developmental LOAEL of 37.6 mg/L based on an increased incidence of abnormal fetuses (Klimisch 1, valid without restriction).
  - *Oral: Surrogate: Ethanol (CAS #64-17-5):* In the previously described two-generation reproduction toxicity study, CD-1 mice were exposed to 0, 6,900, 13,800, or 20,700 mg/kg/day ethanol in their drinking water. Parental animals were treated one week prior to mating, during a 98-day cohabitation exposure, and a 21-day segregation exposure. Dams were continuously exposed through gestation and lactation, treatment continued in F1 offspring from weaning though PND 74-84. Treatment with 20,700 mg/kg/day caused a reduction in the number of live pups per litter. F1 offspring exposed to 20,700 mg/kg/day had reduced body weights at weaning and study termination, reduced fertility and mating index, reduced F2 pup weights, reduced body weights for F1 dams, reduced parental F1 body weights at necropsy, and increased relative liver, kidney, and adrenal weights. F1 males exposed to 20,700 mg/kg/day had decreased body weight and decreased weights of

[13] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
(10,000 ppm)(46) = 18.8 mg/L.
24,450

the left testis/epididymis, the right epididymis, and seminal vesicles. After adjustment for body weight, these changes were not significantly different from controls. F2 females exposed to 20,700 mg/kg/day had increased relative liver and kidney/adrenal weights. The authors identified an offspring toxicity NOEL of 13,800 mg/kg/day and a LOEL of 20,700 mg/kg/day. ToxServices identified a developmental LOAEL of 20,700 mg/kg/day based on a reduction in the number of live pups per litter (Klimisch 1, valid without restriction).

- *Oral: Surrogate: Ethanol (CAS #64-17-5):* Pregnant C57BL/6J mice were exposed to ethanol in the diet at 0, 17%, 25% and 30% on gestational days 4 to 9. The study record indicates that these doses are equivalent to approximately 0, 17, 29 and 28 g/kg. Maternal toxicity was observed at 25% and 30% as demonstrated by increased fetal resorption. Significantly increased malformation was found in the offspring at doses of 25% and 30%. Study authors identified a NOAEL and LOAEL of 17,000 and 29,000 mg/kg, respectively, for both maternal toxicity and teratogenicity (Klimisch 2, valid with restrictions, justification not provided).
- *Oral: Surrogate: Ethanol (CAS #64-17-5):* Pregnant CBA/J mice were orally exposed to ethanol in a liquid diet at concentrations of 15, 20, 25, or 30% ethanol derived calories for up to 80 days and through gestation. Treatment produced skeletal abnormalities in all treatment groups and decreased fetal weights. Treatment caused increased resorption at all dose levels. The authors identified a LOAEL of 15% ethanol (lowest dose tested) based on decreased fetal weight and increased skeletal abnormalities (Klimisch 2, valid with restrictions, justification not provided).
- *Oral: Surrogate: Ethanol (CAS #64-17-5):* Pregnant CH3/IG mice were orally exposed to ethanol in a liquid diet at concentrations of 20, 25, 30, or 35% of ethanol derived calories for up to 80 days and through gestation. Treatment caused increased resorption at all dose levels. Treatment produced skeletal abnormalities and decreased fetal weights in all treatment groups. The authors identified a teratogenicity LOAEL of 20% (lowest dose tested) based on decreased fetal weight and increased skeletal abnormalities (Klimisch 2, valid with restrictions, justification not provided).
- *Oral: Surrogate: Ethanol (CAS #64-17-5):* Pregnant CD-1 mice were exposed to 200 proof ethanol by gavage at 0, 2,200, 3,600, 5,000, 6,400 and 7,800 mg/kg on gestational days 8 to 14. A maternal NOAEL of 2,200 mg/kg and LOAEL of 3,600 mg/kg was identified based on 1/6 death and clinical signs of toxicity (lethargy and labored breathing). Increased resorption and decreased live fetuses per litter were found at 5,000 mg/kg only without dose-response. Study authors concluded that ethanol had no clear effects on fetuses in the presence of clear maternal toxicity. A teratogenicity NOAEL of 6,400 mg/kg (all dams died pre-maturely at 7,800 mg/kg, the highest dose tested and fetuses at this dose were not examined) (Klimisch 2, valid with restrictions, justification not provided).
- *Oral: Surrogate: Ethanol (CAS #64-17-5):* In a study of male-mediated developmental toxicity, male Swiss Webster mice were given 0 or 6.3% ethanol in liquid diet for 28 days and then mated to untreated females for up to 11 days. Females were terminated on gestational day 18. Only pregnancy and resorptions were examined. Only one of the nine matings 3 – 5 days after exposure resulted in a litter, while fertilization rates during days 6 to 11 were not affected. Decreased rump length was found in the single litter produced during 3 – 5 days after exposure. There were no treatment related effects on paternal toxicity weight. A NOAEL could not be determined based on information provided in this study (Klimisch 2, valid with restrictions, justification not provided).

- Based on the weight of evidence, a score of Low was assigned. No developmental studies were identified for ethyl acetate, therefore studies with the surrogate ethanol were used to fill the data gap.

Ethanol is a known developmental toxicant with human evidence. Prenatal exposure to ethanol produced decreased fetal weight and skeletal abnormalities in rats and mice. The two-generation study in rats reported a reduction in the number of live pups born in animals treated with 20,700 mg/kg/day. Inhalation exposure to ethanol during gestation produced an increased incidence in abnormal fetuses at 37.6 mg/L. Two studies which sought to simulate human chronic alcoholism in mice identified LOAEL values of 15% and 20% ethanol based on reduced fetal weight and increased skeletal abnormalities. As ethyl acetate is rapidly hydrolyzed to ethanol, these studies were considered applicable in assessing the developmental toxicity of ethyl acetate. However, the effects were only reported in the presence of maternal toxicity at extremely high exposure levels, much higher than the 1,000 mg/kg/day limit dose specified by OECD guideline for repeated dose oral toxicity studies (UN 2021). Such high levels of exposure to ethanol are unlikely to occur with the current use patterns of ethyl acetate. If standard developmental toxicity studies were to be conducted on ethyl acetate, no effects would have been observed at the limit dose of 1,000 mg/kg. Therefore, a score of Low was assigned.

Endocrine Activity (E) Score (H, M, or L): DG
Ethyl acetate was assigned a score of Data Gap for endocrine activity based on insufficient data available.

- 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 2023b
  - *Intraperitoneal*: In a lung tumor study in A/He mice administered doses of 150 or 750 mg/kg/injection intraperitoneally three times a week for eight weeks, followed by 16 weeks observation, examinations at necropsy included gross examination of the thymus, endocrine, and salivary glands. No adverse effects on the endocrine glands were reported. The specific endocrine glands examined were not reported (Klimisch score of 2, reliable with restrictions).
- U.S. EPA 2023b
  - Within the EDSP21 database, 1 of 8 high throughput screening assays demonstrated estrogen receptor (ER) activity; 0 of 9 assays demonstrated androgen receptor (AR) activity; 0 of 10 assays demonstrated thyroid receptor activity, and 0 of 2 assays demonstrated steroidogenesis.
  - Ethyl acetate was predicted to be inactive for estrogen receptor agonism, antagonism and binding using the CERAPP Potency Level (Consensus and From literature) models. It was also predicted to be inactive for androgen receptor agonism, antagonism and binding using the COMPARA (Consensus) model in ToxCast (Appendix G).
- DTU 2023 (only predictions that are within their applicability domains are reported below)
  - Ethyl acetate is predicted to be negative by the Battery, CASE Ultra, and SciQSAR models for the estrogen receptor α binding, full and balanced training sets. It is also predicted to be negative by the CASE Ultra model as well as the SciQSAR model for estrogen receptor α activation (Appendix H).
  - Ethyl acetate is predicted to be negative by the Battery, CASE Ultra, Leadscope, and SciQSAR models for androgen receptor inhibition (Appendix H).
  - Ethyl acetate and its predicted metabolites are predicted to be non-binders for estrogen receptor binding (Appendix H).
  - Ethyl acetate is predicted to be negative for TPO inhibition QSAR2 by the Leadscope model (Appendix H).

- VEGA 2021
    - Ethyl acetate was predicted to be inactive in the Estrogen Receptor Relative Binding Affinity model (IRFMN) with strong reliability (Global AD Index = 0.865) (Appendix I).
    - Ethyl acetate was predicted to be possibly non-active in the Estrogen Receptor-mediated effect (IRFMN/CERAPP) 1.0.0 model with strong reliability (Global AD Index = 0.972) (Appendix I).
    - Ethyl acetate was predicted to be non-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with strong reliability (Global AD Index = 0.976) (Appendix I).
- Pharos 2023
    - *Surrogate: Ethanol (CAS #64-17-5):* Ethanol is listed by TEDX as a potential endocrine disruptor.
- The following studies were used to support the TEDX listing of ethanol as a potential endocrine disruptor:
    - Badr et al. 1977
        - *Surrogate: Ethanol (CAS #64-17-5):* Adult male mice (strain and number not specified) were administered gavage doses of ethyl alcohol at 1,240 mg/kg and peripheral plasma samples were obtained 30, 60, 90, and 120 minutes after dosing. Plasma testosterone levels decreased significantly at 30, 60, and 90 minutes but were considered normal 120 minutes after dosing. One hour after dosing, testicular concentrations of testosterone were also significantly depressed. The addition of ethyl alcohol to incubation medium at 5, 10, 20, or 50 µL/mL medium had no significant effect on the accumulation of testosterone in decapsulated testes. In contrast, addition of similar concentrations of acetaldehyde, a metabolite of ethyl alcohol, elicited a pronounced inhibition of testosterone production. Therefore, the study authors postulated that the decreased plasma testosterone levels detected after oral administration of ethyl alcohol *in vivo* may be related to a direct inhibition of testicular testosterone production by the metabolite acetaldehyde.
    - Clark and Gerend 1986
        - *Surrogate: Ethanol (CAS #64-17-5):* The authors evaluated the effects of 3-9% ethyl alcohol on the binding efficiency of ^{125}I-labeled bovine thyroid stimulating hormone (^{125}I-bTSH) to its receptor in normal and neoplastic thyroid tissue. Additionally, ethyl alcohol's effect on adenylate cyclase (AC) stimulation was investigated in an 8,000 × g particulate fraction from normal and neoplastic non-medullary thyroid tissue isolated from 10 patients (20 specimens total) and AC activity in 16 other non-thyroidal tissues consisting of 5 parathyroid adenoma, 1 pheochromocytoma, 1 sarcoma, and normal and neoplastic breast, kidney, parotid, and colon tissues. Ethyl alcohol exposure increased the binding of ^{125}I-bTSH to normal and neoplastic thyroid tissue and increased AC activity in 17/20 thyroid tissues (20.9±7.1 for basal tissue activity and 45.9±12.3 for ethyl alcohol treatment) and 13/16 non-thyroid tissues (83.0 ±21.5 for non-thyroid basal activity and 137±31.1 for ethyl alcohol treatment) (activity values in picomoles/30 min per mg protein]. The increase was dose-dependent over the range of concentrations tested. No difference in the degree of ethyl alcohol stimulation of AC was detected between normal and neoplastic thyroid or normal and neoplastic non-thyroid tissues. An increase in AC activity was detected when 5% ethyl alcohol was combined with TSH, sodium fluoride, Gpp(NH)p, or forskolin relative to the treatments without ethyl alcohol. Additionally, the combined effect of TSH and ethyl alcohol was

comparable or greater than the result when TSH and ethyl alcohol were added separately. The authors concluded that ethyl alcohol stimulates TSH binding and activates AC in nearly all normal and neoplastic human tissues.

- Furuya et al. 1996
  - *Surrogate: Ethanol (CAS #64-17-5):* Pregnant female rats (strain and number not specified) were provided drinking water containing ethyl alcohol at 0%, 5%, 10%, or 20% during the gestation period (specific days not identified). Brain function, as learning ability (Sidman avoidance behavior) and levels of monoamines (noradrenalin, dopamine, and serotonin), and metabolites (3,4-dihydroxyphenyl acetic acid [DOPAC], homovanillic acid [HVA], and 5-hydroxyindole acetic acid [5-HIAA]) in whole brain samples were evaluated. *In utero* exposure to ethyl alcohol was not associated with alterations in avoidance behavior in 56-day old offspring, but changes in the levels of monoamines and their metabolites were identified in the brains of treated 66-day old offspring (no further details were available).

- IARC 2012
  - *Surrogate: Ethanol (CAS #64-17-5):* Consumption of alcohol beverages has been shown to increase estrogen levels and androgen (not specified) in women. This process is thought to contribute to the development of breast cancer. A mechanism suggested to explain the alcohol-mediated increase in steroid levels includes alcohol dehydrogenase (ADH)-mediated alcohol oxidation which increases the hepatic redox state and inhibits catabolism (break-down) of sex steroids.
- UNEP 2004
  - *Surrogate: Ethanol (CAS #64-17-5):* Chronic ingestion of alcohol is associated with decreased secretion of testosterone and oxytocin and increased secretion of aldosterone, cortisol, and insulin.
- OECD 2007
  - *Surrogate: Ethanol (CAS #64-17-5):* In a previously described two-generation reproduction toxicity study, CD-1 mice were exposed to 0, 6,900, 13,800, or 20,700 mg/kg/day ethanol in their drinking water. Parental animals were treated one week prior to mating, during a 98-day cohabitation exposure, and a 21-day segregation exposure. Dams were continuously exposed through gestation and lactation, treatment continued in F1 offspring from weaning though PND 74-84. F1 offspring exposed to 20,700 mg/kg/day had increased relative adrenal weights. F2 females exposed to 20,700 mg/kg/day had increased relative kidney/adrenal weights were increased. No pathological effects were identified (Klimisch 1, reliable without restriction).
- *In vivo* data for ethyl acetate are limited to a 16-week lung tumor study in mice injected intraperitoneally, in which there were no adverse effects on the endocrine system identified at necropsy. *In vitro* high throughput screening data for ethyl acetate demonstrated potential for estrogen receptor binding in 1 of 8 assays, and no activity towards androgen receptor binding, thyroid receptor binding, or steroidogenesis; however, these assays are qualitative and have limited utility at this time. Evidence of endocrine effects exists for surrogate compound/ hydrolysis product ethanol in animals and humans with a possible endocrine mode of action for breast cancer in women. While all of the *in vivo* studies used very high dose levels consistent with addictive alcohol consumption patterns, which as mentioned previously, is beyond the anticipated use levels for ethyl acetate, there remain some concerns. In particular, no information is available regarding the tested concentrations of ethanol in *in vitro* studies in relation to *in vivo* concentrations. Collectively, data are insufficient to determine if ethyl acetate is endocrine active.

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

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

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

Ethyl acetate was assigned a score of Low for acute toxicity based on measured data. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation (vapor) LC_{50} values are greater than 20 mg/L (CPA 2018b). The confidence in the score was high as it was based on measured data of good quality for all three routes of exposure.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan - GHS - Acute toxicity (inhalation: vapor) - Category 4.
- ECHA 2023b
  - *Oral:* LD_{50} (rat) = 5,620 mg/kg (pre-guideline, pre-GLP) (Klimisch 2, reliable with restrictions. Original study cited not available for review, derived from a secondary source).
  - *Oral:* LD_{50} (rat) = 6,100 mg/kg (guideline and GLP not specified) (Klimisch 2, reliable with restrictions. Original study cited not available for review, derived from a secondary source).
  - *Oral:* LD_{50} (female Carworth Wistar rat) = 11.3 mL/kg (10,200 mg/kg) (pre-guideline, pre-GLP) (Klimisch 2, reliable with restrictions. Study is sufficiently detailed, meets basic scientific principles, no information on doses was provided).
  - *Oral:* LD_{50} (mouse) = 4,100 mg/kg (guideline and GLP not specified) (Klimisch 2, reliable with restrictions. Original study cited not available for review, derived from a secondary source).
  - *Oral:* LD_{50} (guinea pig) = 5,500 mg/kg (guideline and GLP not specified) (Klimisch 2, reliable with restrictions. Original study cited not available for review, derived from a secondary source).
  - *Oral:* LD_{50} (rabbit) = 7,650 mg/kg (guideline and GLP not specified) (Klimisch 2, reliable with restrictions. Original study cited not available for review, derived from a secondary source).
  - *Oral:* LD_{50} (rabbit) = 4,934 mg/kg (OECD 401, GLP not specified) (Klimisch 2, reliable with restrictions due to lack of info on number of animals tested, actual doses, rabbits are not normally one of the preferred species for oral toxicity, and there was only a 24-hour observation period).
  - *Dermal:* LD_{50} (male New Zealand White rabbit) > 20,000 mg/kg (pre-guideline, pre-GLP) (Klimisch 2, reliable with restrictions. Study meets basic scientific principles, but is lacking some observational details).
  - *Inhalation (vapor):* 6hr LC_0 (male and female Sprague-Dawley rat) > 6,000 ppm (22.5 mg/L) (Multi-Substance Rule for the Testing of Neurotoxicity 40 CFR Part 799 (58 FR 40262), and to GLP) (Klimisch 1, reliable without restriction).
  - *Inhalation (vapor):* 4hr LC_{50} (albino rat) > 8,000 ppm (29 mg/L) (pre-guideline, pre-GLP) (Klimisch 2, reliable with restrictions. Documented publication meets key scientific principles, but derived from a secondary source).
  - *Inhalation (unspecified):* 1hr LC_{50} (male rat) = 200 mg/L (non-guideline, GLP not specified) (Klimisch 4, not assignable because it is derived from a secondary source).
  - *Inhalation (unspecified):* 2hr LC_{50} (mouse) = 33.5 mg/L (non-guideline, GLP not specified) (Klimisch 4, not assignable because it is derived from a secondary source).

  - *Inhalation (unspecified):* 4hr LC_{50} (mouse) > 18 mg/L (non-guideline, GLP not specified) (Klimisch 4, not assignable because it is derived from a secondary source).
- PubChem 2023
  - *Oral:* LD_{50} (guinea pig) = 5,500 mg/kg.
  - *Oral:* LD_{50} (mouse) = 4,100 mg/kg.
  - *Oral:* LD_{50} (rabbit) = 4,935 mg/kg.
  - *Oral:* LD_{50} (rat) = 5,620 mg/kg.
  - *Dermal:* LD_{50} (rabbit) > 20 mL/kg.
  - *Inhalation:* 2-hr LC_{50} (mouse) = 45,000 mg/m^3 (equivalent to 45 mg/L[14]).
  - *Inhalation:* LC_{50} (rat) = 200,000 mg/m^3 (equivalent to 200 mg/L[15]).
- NITE 2009, 2019
  - Ethyl acetate is classified to a GHS Category 4 (inhalation: vapor) in Japan based on LC_{50} values of 16,000 ppm (4-hour equivalence: 19,600 ppmV), 14,640 mL/m^3 (13,176 g/m^3: 3,658 ppmV), and 16,000 ppm (4-hour equivalence: 13,856 ppmV) in rats. Since saturated vapor pressure concentration was 123,289 ppmV, the classification criteria for gas was adopted.
- Based on a weight of evidence, a score of Low was assigned. Ethyl acetate was classified to GHS Category 4 (inhalation: vapor) in Japan, which corresponds to a score of Moderate. However, measured data for all routes of exposure are greater than the acute toxicity guidance values. Therefore, ToxServices placed more weight in the measured data over the screening list, and a score of Low was assigned.

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

Ethyl acetate was assigned a score of Moderate for systemic toxicity (single dose) based on transient respiratory irritation in two studies in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 (CPA 2018b). The confidence in the score was high as it was based on human and animal data of good quality with support from a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan GHS – Specific target organs/systemic toxicity following single exposure – Category 3 (H335).
- ECHA 2023b
  - *Inhalation (vapor):* Male and female Sprague-Dawley rats (14/sex/group) were exposed to 0, 2.25, 11.25, or 22.5 mg/L ethyl acetate for 6 hours (Multi-Substance Rule for the Testing of Neurotoxicity 40 CFR Part 799 (58 FR 40262), GLP-compliant). Following treatment animals were observed for an additional 15 days. The authors noted that all treated animals had transient decreases in body weight following the day of exposure. No other effects on terminal body weight were reported. The authors identified a NOEC of 2.25 mg/L/6h based on transient decreases in body weight (Klimisch 1, reliable without restriction).
- NITE 2009, 2019
  - Ethyl acetate is classified as a GHS Category 3 following single exposure in Japan based on reports that exposure of volunteers for 4 hours to 400 ppm (equivalent to 1.44 mg/L[16]) of the

[14] 45,000 mg/m^3 * (1 m^3 / 1,000 L) = 45 mg/L.
[15] 200,000 mg/m^3 * (1 m^3 / 1,000 L) = 200 mg/L.
[16] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(400\ ppm)(88.1052)}{}$ = 1.44 mg/L.

substance led to slight irritation of the eyes, nose, and throat. Based on the data, the substance was classified into Category 3 (respiratory tract irritation).

- EC 2008
  - Volunteers reported mild irritation of the eyes, throat, and nose after exposure to 1,468 mg/m^3 (equivalent to 1.468 mg/L[17]) via inhalation for 4 hours and 2,202 mg/m^3 (equivalent to 2.202 mg/L[18]) via inhalation for 15 minutes.
- Based on the weight of evidence, a score of Moderate was assigned. An acute inhalation toxicity study in rats identified a NOEC of 2.25 mg/L based on transient decreases in body weight on the day following treatment. No other changes in body weight were reported during the 15-day observation period; therefore, ToxServices did not consider the transient changes in body weight to be toxicologically relevant. Ethyl acetate is classified as GHS Category 3 by Japan based on reports of respiratory irritation in humans. This classification also corresponds to a score of Moderate. Additionally, study descriptions of inhalation exposure to ethyl acetate (described in the neurotoxicity endpoint) describe its effects to be transient with recovery occurring shortly after treatment. Therefore, ToxServices classified ethyl acetate as GHS Category 3 based on transient respiratory tract irritation, and a score of Moderate was assigned.

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

Ethyl acetate was assigned a score of Moderate for systemic toxicity (repeated dose) based on decreased body weight gain in rats in subchronic inhalation studies with the lowest LOAEC of 0.9 mg/L in a subchronic study (No NOAECs identified below this LOAEC). GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when inhalation (gas or vapor, mg/L/6h/day) LOAEC values are between 0.2 and 1 mg/L (CPA 2018b). The confidence in the score was high as it was based on well conducted studies of good quality with support from a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* New Zealand - Harmful to human target organs or systems (GHS Cat. 2).
- ECHA 2023b (Studies with Klimisch scores of 4 (reliability not assignable) were not included in this assessment)
  - *Oral:* In a GLP-compliant subchronic oral study equivalent or similar to EPA OTS 795.2600, male and female Sprague-Dawley rats (30/sex/dose) received 0, 300, 900, or 3,600 mg/kg/day ethyl acetate (99.9% purity) via gavage for 90-92 days. Gavage trauma appeared to cause the death of one male and female in the 900 mg/kg/day group and five males and two females in the 3,600 mg/kg/day group. Treatment with 3,600 mg/kg/day caused significantly decreased body weight gain and reduced food consumption in male rats. Males and females in the 3,600 mg/kg/day group had an increased frequency of salivation, irregular breathing, and lethargy. The authors identified a NOAEL of 900 mg/kg/day and a LOAEL of 3,600 mg/kg/day based on clinical signs, decreased body weights, and decreased food consumption (Klimisch 2, reliable with restrictions. Comparable to guideline study. Mortality attributed to gavage trauma but does not influence the reliability of the NOAEL).
  - *Inhalation:* In a GLP-compliant subchronic inhalation study equivalent or similar to EPA OTS 798.2450, male and female Crl:CD BR rats (10/sex/concentration) were exposed to 0, 350, 750, or 1,500 ppm (reported in ECHA as equivalent to 1.28, 2.75 and 5.49 mg/L, respectively) ethyl acetate (99.92% purity) via inhalation 6 hours per day, 5 days per week

24,450

[17] 1,468 mg/m^3 / 1,000 = 1.468 mg/L.
[18] 2,202 mg/m^3 / 1,000 = 2.202 mg/L.

for 94 days. Treatment did not cause mortality at any concentration. No significant toxic effects were reported. Treatment with 750 and 1,500 ppm caused diminished response to an alerting stimulus which was attributed to the sedative properties of ethyl acetate. Animals treated with 750 and 1,500 ppm had reduced food consumption and body weight gain, and lower serum triglycerides. The authors reported there was some evidence of nasal mucosa degeneration at 350 ppm. The authors identified a systemic NOAEC of 350 ppm (1.28 mg/L or 0.914 mg/L/day after adjustment for a 7-day exposure[19]) and a LOAEC of 750 ppm (2.75 mg/L or 1.96 mg/L/day[20]) based on reduced food consumption, reduced body weight gain, and lower serum triglycerides. They identified a LOEC of 350 ppm (1.28 mg/L or 0.914 mg/L/day after adjustment for a 7-day exposure[21]) based on nasal irritation (Klimisch 1, reliable without restriction).

- EC 2008, ECHA 2023b
    - *Inhalation:* Rats were exposed to 0, 350, 750, or 1,500 ppm (equivalent to 1.26, 2.7, 5.4 mg/L[22]) via inhalation 6 hours per day, 5 days per week for 13 weeks. The neurobehavioral effect of treatment with ethyl acetate was evaluated using motor activity tests and a functional observational battery (FOB) test on non-exposure days during weeks 4, 8, and 13. Upon completion of the treatment period, tissues were microscopically examined for neuropathology. Treatment with 2.7 and 5.4 mg/L caused decreased body weight, body weight gain, food consumption, and feed efficiency. These effects were fully or partially reversible after a 4-week recovery period. Treatment with 1.26 mg/L also caused decreased body weight gain and feed efficiency in male rats. The authors identified a systemic LOEC of 1.26 mg/L (0.9 mg/L after adjustment for a 7-day exposure[23]) based on decreased body weight gain in male rats (Klimisch 2, reliable with restrictions, well-documented published study that meets basic scientific principles).
- U.S. EPA 2013
    - Female CD-1 mice (8 animals) were exposed to ethyl acetate as a solvent control in a previously described initiation/promotion carcinogenicity study. Mice were initiated by applying a single 0.2 mL dose of the test compound to shaved dorsal skin. Four days later, mice were exposed to the promoter chemical, or the solvent control ethyl acetate, 2x/week for 22 weeks. Ethyl acetate-exposed mice did not develop papillomas after 22 weeks of exposure, and there were no adverse effects on body weight or body weight gain for treated animals.
- CCID 2023
    - Ethyl acetate is classified as Category 6.9B in New Zealand, which corresponds to a GHS Category 2. This classification is based on a 90-day inhalation study in which a NOAEC of 0.002 mg/L and LOAEC of 0.01 mg/L were identified based on significantly increased number of leukocytes; increased motoric chronaxie; decreased cholinesterase activity; significantly reduced body weight; pathological changes of the cerebral cortex (swelling, hyperchloremia), liver (decreased glycogen and lipid level), thyroid gland (follicle

[19] To calculate a daily exposure level, adjustment was made to account for 5 days of exposure per week: 1.28 mg/L x 5/7 = 0.914 mg/L/6h/day.
[20] To calculate a daily exposure level, adjustment was made to account for 5 days of exposure per week: 2.75 mg/L x 5/7 = 1.96 mg/L/6h/day.
[21] To calculate a daily exposure level, adjustment was made to account for 5 days of exposure per week: 1.28 mg/L x 5/7 = 0.914 mg/L/6h/day.
[22] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(350\ ppm)(88.1052)}{24,450} = 1.26\ mg/L$
[23] To calculate a daily exposure level, adjustment was made to account for 5 days of exposure per week: 1.26 mg/L x 5/7 = 0.9 mg/L/6h/day.

degeneration, infiltration) and adrenal gland (hypertrophy of the cortex). *ToxServices noted that OECD (2008) assigned a reliability score of 4 (not assignable) for this study presumably due to insufficient documentation (i.e., no information on purity, a continuous exposure [6 hour exposure period daily is required for classification], an unspecified post exposure observation period, and a lack of GLP status). Therefore, ToxServices did not weigh this classification heavily in the evaluation.*

- Based on the weight of evidence, a score of Moderate was assigned. The data indicate that oral exposure to doses up to 900 mg/kg/day does not cause systemic toxicity in rats. Although an inhalation LOAEC of 0.01 mg/L served as the basis for the New Zealand GHS Category 2 classification, this study had reduced reliability due to insufficient documentation. Therefore, the repeated inhalation exposure studies in rats that identified LOAEC values of 0.9 and 1.96 mg/L based on reversible decreased body weight gain in rats in reliable studies served as the basis for classification. Based on the most conservative reliable LOAEC of 0.9 mg/L a score of Moderate was assigned.

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

Ethyl acetate was assigned a score of Moderate for neurotoxicity (single dose) based on evidence of transient narcotic effects in humans and mice. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when a GHS Category 3 classification is warranted (CPA 2018b). The confidence in the score was high as it was based on both animal and human data of good quality with support from authoritative B lists and screening lists.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS (H Statement) – H336: May cause drowsiness or dizziness.
  - *Screening:* Korea - GHS - Specific target organ toxicity - Single exposure - Category 3 [H336 - May cause drowsiness or dizziness].
  - *Screening:* Australia - GHS - H336 - May cause drowsiness or dizziness.
  - *Screening:* Malaysia - GHS - H336 - May cause drowsiness or dizziness.
  - *Screening:* Japan - GHS - H336 - May cause drowsiness or dizziness.
  - *Screening:* G&L – Neurotoxic chemicals - Neurotoxic.
- ECHA 2023b, UNEP 2004
  - LD_{50} (rabbit) = 56 mMol/kg, equivalent to 4,934 mg/kg (OECD 401, GLP not specified). At 51 mMol/kg, approximately 4,493 mg/kg, narcotic effects were observed in 50% of the animals based on stupor and loss of voluntary movements. Additional symptoms at higher doses included disappearance of corneal reflexes, shortness of breath, involuntary eye movements and slowed hearth rates (doses unspecified) (Klimisch 2, reliable with restrictions due to lack of info on number of animals tested, actual doses, rabbits are not normally one of the preferred species for oral toxicity, and there was only a 24-hour observation period).
- ECHA 2023b
  - Male and female Sprague-Dawley rats (14/sex/group) were exposed to 0, 600, 3,000, and 6,000 ppm (equivalent to 0, 2.25, 11.25, and 22.5 mg/L, respectively) ethyl acetate (vapor) for 6 hours (Multi-Substance Rule for the Testing of Neurotoxicity 40 CFR Part 799 (58 FR 40262), GLP-compliant). Decreased motor activity was observed in both sexes at 3,000 and 6,000 ppm within 1 hour post exposure, and for the 6,000 ppm group, persisted until the next morning. Following treatment animals were observed for an additional 15 days. There were no treatment related clinical signs of toxicity. Authors noted all treated animals had transient decreases in body weight following the day of exposure. No effects on terminal body weight were found. The authors identified a NOEC of 600 ppm/6h (equivalent to 2.25 mg/L/6h) and

a LOAEL of 3,000 ppm/6h (equivalent to 11.25 mg/L/6h) based on transient decreases in body weight (Klimisch 1, reliable without restriction).

- EC 2008
  - Volunteers reported mild irritation of the eyes, throat, and nose, and headache and distraction after exposure to 1,468 mg/m^3 (equivalent to 1.468 mg/L[24]) via inhalation for 4 hours and 2,202 mg/m^3 (equivalent to 2.202 [25]) via inhalation for 15 minutes.
  - Mice (8/group) were exposed to 0, 500, 1,000, or 2,000 ppm (equivalent to 1.8, 3.6, 7.2 mg/L[26]) via inhalation for 20 minutes. Following exposure, acute neurobehavioral effects were evaluated using locomotor activity and a FOB test. Treatment caused significant decreases in locomotor activity, arousal, rearing, and handling-induced convulsions at 7.2 mg/L. Treatment with greater than 1.8 mg/L produced clonic movements; however, it was noted that these data were not presented by the authors and could not be evaluated. Treatment-induced effects were reversible and recovery began within minutes of removing the animals from the treatment chamber.
- NITE 2009, 2019
  - Ethyl acetate is classified as a GHS Category 3 following single exposure in Japan based on narcotic effects in animals. There is a report that the inhalation exposure to cats and mice and the oral exposure to rabbits caused narcotic effects at dose levels of equal to or less than the LD_{50} value. The effects are transient, however. Based on the data, the substance was classified into Category 3 (narcotic effects).
- Based on the weight of evidence, a score of Moderate was assigned. Ethyl acetate is present on the G&L Neuro: Known to be neurotoxic in man screening list. Association with this screening list warrants a Very High to Moderate score. In addition, ethyl acetate is associated with the authoritative EU harmonized H336, which translates to a Low to Moderate score. Acute exposure to ethyl acetate caused headaches and distraction in human volunteers. Acute exposure in mice caused decreased locomotor activity, arousal, rearing, and handling induced convulsions. These effects were transients and recovery began shortly after animals were removed from the treatment chamber. These observations suggest transient narcotic effects, which warrant a GHS Category 3 classification.

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

Ethyl acetate was assigned a score of Low for neurotoxicity (repeated dose) based on measured data indicating no additional neurotoxicity (other than transient narcotic effects already classified under single exposure neurotoxicity) seen in rats after repeated inhalation exposures. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and negative and it is not GHS classified (CPA 2018b). The confidence in the score is high as it is based on a well conducted study of good quality.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* G&L – Neurotoxic Chemicals - Neurotoxic.
- EC 2008, ECHA 2023b
  - *Inhalation:* In a previously described neurotoxicity study, rats were exposed to 0, 350, 750,

[24] 1,468 mg/m^3 / 1,000 = 1.468 mg/L.
[25] 2,202 mg/m^3 / 1,000 = 2.202 mg/L.
[26] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(500\ ppm)(88.1052)}{24,450}$ = 1.8 mg/L.

or 1,500 ppm ethyl acetate (equivalent to 1.26, 2.7, 5.4 mg/L[27]) via inhalation 6 hours per day, 5 days per week for 13 weeks. The neurobehavioral effect of treatment with ethyl acetate was evaluated using motor activity tests and an FOB test on non-exposure days during weeks 4, 8, and 13. Upon completion of the treatment period, tissues were microscopically examined for neuropathology. Treatment with ≥ 2.7 mg/L caused a diminished behavioral response to unexpected auditory stimuli during exposure, which appeared to be an acute sedative effect. Females treated with 5.4 mg/L had reduced motor activity, which was not present after a 4-week recovery period. Treatment did not affect any other FOB or motor activity parameters, and there were no pathological changes to nervous system tissues (Klimisch 2, reliable with restrictions).

- ECHA 2023b
  - *Oral:* In a GLP-compliant subchronic oral study equivalent or similar to EPA OTS 795.2600, male and female Sprague-Dawley rats (30/sex/dose) received 0, 300, 900, or 3,600 mg/kg/day ethyl acetate (99.9% purity) via gavage for 90-92 days. Gavage trauma appeared to cause the death of one male and female in the 900 mg/kg/day group, and five males and two females in the 3,600 mg/kg/day group. Treatment with 3,600 mg/kg/day caused significantly decreased body weight gain and reduced food consumption in male rats. Males and females in the 3,600 mg/kg/day group had an increased frequency of salivation, irregular breathing, and lethargy. The authors identified a NOAEL of 900 mg/kg/day and a LOAEL of 3,600 mg/kg/day based on clinical signs, decreased body weights, and decreased food consumption (Klimisch 2, reliable with restrictions. Comparable to guideline study. Mortality attributed to gavage trauma does not influence the reliability of the NOAEL).
- Based on the weight of evidence, a score of Low was assigned. Ethyl acetate is listed on the G&L Neuro: Known to be neurotoxic in man screening list which warrants a Moderate to Very High score for repeated dose neurotoxicity. Repeated exposure to ethyl acetate caused diminished behavioral response to auditory stimuli and depressed motor activity, which indicates that treatment produces sedation (narcotic effects). These effects were reversible and occurred at concentrations higher than 1 mg/L/6h/day for GHS category 2 classification. Narcotic effects were discussed and included in the neurotoxicity single dose section above, and therefore, a score of Low was assigned for this endpoint.

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

Ethyl acetate was assigned a score of Low for skin sensitization based on the lack of positive skin sensitization reactions in a guinea pig maximization test. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and it is not GHS classified (CPA 2018b). The confidence in the score was high as it was based on a well-conducted study of good quality.

- 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 2023b
  - Ethyl acetate was not sensitizing in a guinea pig maximization test (OECD 406, non-GLP). Female Dunkin-Hartley guinea pigs (20 treated and 10 control) were intradermally induced with 10% ethyl acetate (99.9% purity) and epidermally induced with 100% ethyl acetate. Two weeks after induction, animals were epidermally challenged with 100% ethyl acetate

[27] Conversion from ppm to mg/L (assuming normal temperature and pressure): (ppm * MW) / 24,450 = mg/L
$\frac{(350\ ppm)(88.1052)}{24,450} = 1.26$ mg/L.

for 24 hours under occlusive conditions. Zero animals had a positive skin reaction to ethyl acetate (Klimisch 1, reliable without restriction).

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

Ethyl acetate was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential, according to ECHA's guideline (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and it is not GHS classified (CPA 2018b). Confidence in the score was low as the ECHA guidance does not include non-immunologic mechanisms of respiratory sensitization, which is primarily based on human data, and no specific data were available for respiratory sensitization on the target substance. Further, there are currently no recognized test protocols for respiratory sensitization, and hence the available data on the hydrolysis product ethanol are not sufficient for a high confidence score.

- 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 2022
  - Ethyl acetate does not contain any structural alerts for respiratory sensitization (Appendix J).
- ECHA 2023b
  - *Surrogate: Ethanol (CAS #64-17-5):* A respiratory sensitization study was performed to evaluate the potential respiratory sensitization of ethanol (GLP status and guideline not specified). Brown Norway rats (8/group) received ethanol (95% purity) via a subcutaneous induction phase and via inhalation at 3,000 ppm 6 hours per day for 22 days. The challenge dose was administered as chicken egg ovalbumin (OVA) in solution with aluminum hydroxide and saline via inhalation on study day 14. Bronchiolar lavage was performed at 6, 24, 36, 48, and 72 hours after the challenge. White blood cells were counted, and plasma concentrations of seven cytokines relevant to asthma inflammation (MCP-1, IL-1B, IL-4, IL-6, IL-10, INF-G, and TNF-a) were measured. No increase in any of these endpoints was observed, and the study authors determined that ethanol was not a respiratory sensitizer (Klimisch 2, reliable with restrictions).
  - *Surrogate: Ethanol (CAS #64-17-5):* Male Hartley guinea pigs were administered inhalation exposures to ethanol aerosol (purity not specified) in 0.9% saline at 31, 52.5, 125, or 250 mM. Ethanol exposure did not elicit broncho-restriction. No further details were provided. This study is reported in the REACH dossier with a Klimisch score of 4 (not assignable).
  - *Surrogate: Ethanol (CAS #64-17-5):* A study of six healthy volunteers (4 women, 2 men, ages 28-45 years) was performed by exposure to 0.25% aerosolized ethanol in saline for an unspecified amount of time. Coughing was reported at the beginning of the exposure period and 3 volunteers reported chest tightness at the end of the exposure. Exposure to ethanol decreased the maximum expiratory flow rate for the 4-hour period following the exposure, with an 8-37% statistically significant reduction for the first 90 minutes after the exposure. No significant treatment-related effects were detected on the one second forced expiratory volume. No further details were provided. This study is reported in the REACH dossier with a Klimisch score of 4 (not assignable).
- 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). In a high quality repeated inhalation sensitization study in rats for the surrogate ethanol, there was no evidence of respiratory inflammation. In an animal study with low reliability for ethanol, no evidence of broncho-restriction was detected in guinea pigs. In another study with a low reliability rating on ethanol, human volunteers reported chest tightness and exhibited a decreased maximum expiratory flow rate following inhalation exposure to ethanol. The relevance of surrogate data for this endpoint is questionable as metabolism is likely limited at the site of contact (i.e., lung). Nevertheless, according to the ECHA guidance, chemicals that are not dermal sensitizers are not classifiable as respiratory sensitizers (ECHA 2017). As ethyl acetate was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by ethyl acetate, and as ethyl acetate does not contain any structural alerts for respiratory sensitization (OECD 2022), ethyl acetate is not expected to be a respiratory sensitizer.

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

Ethyl acetate was assigned a score of Low for skin irritation/corrosivity based on three studies providing no-to-mild irritation which is below the criteria for GHS classifications. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score was high as it was based on well-conducted studies of good quality.

- 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 2023b
  - Rabbits were administered 0.01 mL ethyl acetate (purity not specified) to clipped skin for 24 hours under open conditions (pre-guideline, pre-GLP). The overall irritation score was 1 based on a lack of observed skin irritation. No additional study details were provided (Klimisch 3, not reliable due to lack of occlusion of the solvent).
  - A semi-permeable membrane containing a solution of 96.5% ethyl acetate was placed on shaved skin of New Zealand White rabbits for 24 hours (similar to OECD 404, GLP not specified). Animals were observed for an additional 72 hours after treatment. Treatment caused dermal irritation with a mean erythema score of 1.33 and a mean edema score of 0.4 (Klimisch 2, reliable with restrictions. The study was similar to OECD 404, however the test substance was not in direct contact with the animal skin, but exposure duration was longer than usual).
  - Unchanged (no vehicle/undiluted) ethyl acetate (0.5 mL, 99.5% purity) was applied to the skin of New Zealand White rabbits under semiocclusive conditions for 4 hours (according to "Classification of Corrosive Hazards", Federal Reg vol 37, 57 (1972), and equivalent or similar to US Code of Federal Regulations 1500.41 (2009), non-GLP). Animals were observed for an additional 72 hours after treatment. The overall irritation score was 0 at all time points; therefore, treatment was not irritating to rabbit skin (Klimisch 2, reliable with restrictions due to limited report details).
- Based on the weight of evidence, a score of Low was assigned. The application of ethyl acetate to rabbit skin was not irritating to mildly irritating. However, the mean erythema score of 1.33 did not warrant classification as a dermal irritant per GHS Criteria (1.5 – 2.3).

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

Ethyl acetate was assigned a score of High for eye irritation/corrosivity based on its presence on authoritative and screening lists. Although experimental data suggested that it was at most slightly

irritating to the eyes in animals, ToxServices conservatively relied on the authoritative lists to assign the score for this endpoint. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when it is associated with H319 (CPA 2018b). The confidence in the score was high as it was based on an authoritative list with support from screening lists.

- Authoritative and Screening Lists
  - *Authoritative:* EU - GHS (H Statement) – H319: Causes serious eye irritation.
  - *Screening:* Korea - GHS - Serious eye damage/irritation - Category 2 [H319 - Causes serious eye irritation].
  - *Screening:* Australia - GHS - H319 - Causes serious eye irritation.
  - *Screening:* Malaysia - GHS - H319 - Causes serious eye irritation.
  - *Screening:* New Zealand - GHS - 6.4A - Irritating to the eye (Cat. 2A).
  - *Screening:* Japan - GHS - Serious eye damage / eye irritation - Category 2B.
- ECHA 2023b (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
  - Ethyl acetate was mildly irritating in an OECD Guideline 405 (GLP not specified) acute eye irritation assay with New Zealand White rabbits (n = 4). The rabbit's eye was instilled with 0.1 mL unchanged ethyl acetate (99% purity) and observed for 7 days. The mean (24, 48 and 72 hr time points) cornea opacity score, iris score, conjunctivae score, and chemosis score were 0.41/4, 0.08/2, 1.25/3, and 0.58/4, respectively, with effects fully reversible within 7 days. The overall mean irritation score was 15/110. The authors concluded ethyl acetate was not irritating, and did not warrant a classification under the conditions of the assay (Klimisch 2, reliable with restrictions. Derived from secondary source, however it was subjected to significant peer review).
  - Ethyl acetate was slightly irritating in an acute ocular irritation study similar to OECD Guideline 405 (non-GLP) in New Zealand white rabbits (n = 4-6). The rabbit's eye was instilled with 0.1 mL of 3, 10, 30 or 100% ethyl acetate (>97% purity) and observed for up to 21 days. At 3, 10, 30 and 100%, the Draize overall irritation scores were 2, 3, 5, and 15 (max 110) respectively, and the corneal swelling was 102, 102, 99 and 106%, respectively. Irritation was fully reversible within 14 days. The authors concluded ethyl acetate was only slightly irritating under the conditions of this assay (Klimisch 2, reliable with restrictions. Acceptable, well documented study which meets basic scientific principles and contains sufficient details to be reliable).
- HSDB 2015
  - Ethyl acetate causes mild eye irritation in humans at 400 ppm. Painful conjunctival irritation may occur from splashes in the eye. Repeated or prolonged exposure causes conjunctival irritation and corneal clouding.
- NITE 2009
  - Ethyl acetate is classified to GHS Category 2B by Japan based on a study in rabbits which reported reversible effects on corneal opacity, iritis, conjunctival redness, chemosis and discharge within 7 days after instillation of 0.1 mL test substance in the eyes of 4 rabbits. The modified maximum average score (MMAS) was 15 at 24, 48 and 72 hours after dose administration. Scores for individual effects or individual animals were not reported. *ToxServices noted that this may be the same study as described above. The individual scores reported in that study do not warrant GHS classification.*

Ecotoxicity (Ecotox)

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

Ethyl acetate was assigned a score of Low for acute aquatic toxicity based on L/EC_{50} values in all three trophic levels. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 100 mg/L (CPA 2018b). The confidence in the score was high as it was based on well conducted studies of good quality on all three trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, OECD 2007 (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint).
    - 96h LC_{50} = 230 mg/L (*Pimephales promelas,* fish) (US EPA method E03-05, non-GLP) (Klimisch 2, reliable with restrictions, well-reported, adhering to scientific principles, original report available).
    - 96h LC_{50} > 75.60 mg/L (*P. promelas,* fish) (guideline and GLP not specified) (Klimisch 2, reliable with restrictions. Study is well documented and meets basic scientific principles).
    - 96h LC_{50} = 212.5 mg/L (*Heteropneustes fossilis,* Indian catfish) (Klimisch 2, reliable with restrictions. Study lacks several reporting details, and non-standard species was used).
    - 24h EC_{50} = 3,090 mg/L (*Daphnia magna,* daphnias) (DIN 38412pt 11, non-GLP)) (Klimisch 2, reliable with restrictions due to lack of some study details).
    - 24h EC_{50} = 2,500 mg/L (*D. magna,* daphnias) (DIN 38412pt 11, non-GLP)) (Klimisch 2, reliable with restrictions due to lack of some study details).
    - 48h EC_{50} = 5,600 mg/L (*Scenedesmus subspicatus,* algae) (OECD 201, and GLP) (Klimisch 1, reliable without restriction).
- OECD 2007 (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
    - 96h LC_{50} = 290 mg/L (*P. promelas,* fish)

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

Ethyl acetate was assigned a score of Moderate for chronic aquatic toxicity based on NOEC values in fish and daphnias. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score was high as it was based on well conducted studies of good quality and there are data for all three trophic levels.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b, OECD 2007 (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
    - 32d NOEC < 9.65 mg/L (*P. promelas,* fish) (OECD 201, GLP not specified) (Klimisch 2, reliable with restrictions, well-documented and contains all required information to determine reliability).
    - 21d NOEC = 2.4 mg/L (*D. magna,* daphnias) (OECD 211, GLP not specified) (Klimisch 2, reliable with restrictions, well-documents and meets basic scientific principles).
    - 72h NOEC > 100 mg/L (*S. subspicatus,* algae) (OECD 201, and GLP) (Klimisch 1, reliable without restriction).
- OECD 2007 (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
    - 8d TT (toxicity threshold) = 15 mg/L (*Scenedesmus quadricauda,* algae)
    - 8d TT = 550 mg/L (*Microcystis aeruginosa,* algae)

Environmental Fate (Fate)

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

Ethyl acetate was assigned a score of Very Low for persistence based on its classification as readily biodegradable and meeting the 10-day window in multiple ready biodegradability tests. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when as it is readily biodegradable and meets the 10-day window (CPA 2016c). The confidence in the score was high as it was based on multiple well conducted studies of good quality.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* EC - CEPA DSL – Persistent
        - Based on an EPI predicted hydrolysis half-life in water of 664 days and an EPI predicted ozone reaction half-life of 999 days, although the predicted ultimate degradation half-life is 15 days (CCR 2023). Ethyl acetate has an experimental atmospheric oxidation half-life of 6.68 days.
- ECHA 2023b (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
    - Ethyl acetate was readily biodegradable in a modified BOD test (GLP not specified), in which aerobic, domestic, non-adapted sewage was exposed to 3, 7, or 10 mg/L of the test substance for 20 days. The test substance degraded 68% after 5 days and 79% after 20 days (Klimisch 2, reliable with restrictions, well-reported with sufficient details).
    - Ethyl acetate was readily biodegradable in a test similar to the OECD 301B CO_2 Production Test, in which aerobic, secondary effluent from an activated sludge plant was exposed to 1-2 mL of the test substance for 28 days. The test substance degraded 75% after 4 days, 91% after 8 days, and 93.9% after 28 days (Klimisch 2, reliable with restrictions, well-documented and meets basic scientific principles).
    - In a non-guideline, non-GLP continuous flow activated sludge reactor (simulation) test, a mixture simulating industrial wastewater that contains ethyl acetate at 167 mg/L and a total 5-day BOD of 250 – 300 mg/L was added to domestic activated sludge (adaptation unspecified) for 2 – 6 days. Degradation was 91% by TOC removal, 94% by COD, 99.4% by BOD5 on days 2, 4 and 6, and the overall degradation was 99.9% on day 6 (Klimisch 2, reliable with restrictions, well-documented and meets basic scientific principles).
- ECHA 2023b, OECD 2007 (Only reliable studies with Klimisch scores of 1 (reliable without restrictions) or 2 (reliable with restrictions) were included for this endpoint.)
    - Ethyl acetate was readily biodegradable in a BOD test, in which aerobic, filtered settled raw wastewater was exposed to 10 mg/L of the test substance for 20 days. The test substance degraded 68% after 5 days and 79% after 20 days (Klimisch 2, reliable with restrictions, well documented and meets basic scientific principles).
    - Ethyl acetate was readily biodegradable in a BOD test, in which an aerobic mixture of artificial salt water and sewage was exposed to 3, 7, or 10 mg/L of the test substance for 20 days. The test substance degraded 47% after 5 days, 54% after 10 days, 55% after 15 days, and 60% after 20 days (Klimisch 2, reliable with restrictions, well-reported with sufficient details).
    - Ethyl acetate was readily biodegradable in a test similar to OECD Guideline 301C (GLP not specified), Modified MITI test, in which aerobic, domestic, activated sludge (adaption not specified) was exposed to 100 mg/L of the test substance for 14 days. The test substance degraded 43% after 5 days (Klimisch 2, reliable with restrictions, reasonably well

documented and meets basic scientific principles but some details are not reported).

- OECD 2007
    - The Level III Fugacity distribution modeling predicted that ethyl acetate mainly partitions to water (47.6%) and soil (35.1%), and less to air (17.2%) and sediment (<0.1%), with the assumption that equal amounts are released to air, water and soil.
- U.S. EPA 2017
    - The BIOWIN model of EPI Suite predicts that ethyl acetate is readily biodegradable. The Level III Fugacity Model (MCI Method) indicates that 43.8% partitions to soil with a half-life of 30 days, 41.2% partitions to water with a half-life of 15 days, and 15% partitions to the air with a half-life of 7 days (Appendix K).
- Based on the weight of evidence, a score of Very Low was assigned. Although ethyl acetate was listed on the Environment Canada Domestic Substances List as Persistent due to its estimated half-life in water and air, ethyl acetate was readily biodegradable and met the 10-day window in multiple ready-biodegradability tests. Level III Fugacity modeling performed by EPI Suite™ as well as by the Organization for Economic Cooperation and Development (OECD) predict ethyl acetate will mainly partition to water and soil. It is ToxServices' internal policy to assign the hazard score for persistence based on the dominant environmental compartment(s) (ToxServices 2016). Therefore, ToxServices assigned a Very Low score for this endpoint as it met the 10-day window in a ready biodegradation test and it is predicted to mainly partition to soil and water.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL

Ethyl acetate was assigned a score of Very Low for bioaccumulation based on a measured BCF of 30 and a measured log K_{ow} of 0.68. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF is less than 100 and the log K_{ow} is less than 4 (CPA 2018b). The confidence in the score was high as it was based on measured data of good quality.

- 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 2023b
    - Log K_{ow} = 0.68 (measured).
    - Ethyl acetate has a measured BCF of 30 in *Leuciscus idus melanotus* (ide fish) (guideline and GLP not specified) (>98% purity) (Klimisch 2, reliable with restrictions due to lack of reported details).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): L

Ethyl acetate was assigned a score of Low for reactivity based on measured data indicating it is not explosive, with support from its HMIS and NFPA ratings. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not explosive, and there are no data to suggest they are reactive otherwise (CPA 2018b). The confidence in the score was high as it was based on measured data of good quality.

- 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 2007
    - Not explosive (ASTM E537).
- HSDB 2015

  - Ethyl acetate has a reactivity/physical hazard score of 0 from NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water (e.g. helium)").
- Screening procedures for explosivity were used here to estimate the reactivity property of ethyl acetate. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, ethyl acetate is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (Appendix L).
  - Based on the structure of its components or moieties, ethyl acetate 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. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of ethyl acetate has 2 oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.

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

Ethyl acetate was assigned a score of High for flammability based on measured data and its presence on authoritative and screening lists. GreenScreen® criteria classify chemicals as a High hazard for flammability when it is present on EU H-Statement: H225 Highly flammable liquid and vapor, and a GHS Category 2 classification is warranted (CPA 2018b). The confidence in the score was high as it was based on authoritative lists and measured data of good quality.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS (H-Statement) – H225: Highly flammable liquid and vapor.
  - *Authoritative:* Québec CSST - WHMIS 1988 Class B2 - Flammable liquids.
  - *Screening:* Australia - GHS - H225 - Highly flammable liquid and vapour.
  - *Screening:* Japan - GHS - Flammable liquids - Category 2.
  - *Screening:* Korea - GHS - Flammable liquids - Category 2 [H225 - Highly flammable liquid and vapour].
  - *Screening:* Malaysia - GHS - H225 - Highly flammable liquid and vapour.
  - *Screening:* New Zealand - GHS - 3.1B - Flammable Liquids: high hazard.
- ECHA 2023b
  - Ethyl acetate is highly flammable with explosive limits of 2.2 to 11.5%.
  - Ethyl acetate has a boiling point of 77.1°C.
  - Ethyl acetate had a flash point of -4°C in a closed cup test.
- Based on GHS Guidance (UN 2021), when a liquid has a flash point of < 23°C and a boiling point > 35°C, a Category 2 classification is warranted.

Use of New Approach Methodologies (NAMs)[28] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, and persistence, and *in vitro* assays for genotoxicity and endocrine activity. NAMs are non-animal alternatives 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 2020). 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 2020):

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

As shown in Table 5, Type I (input data) uncertainties in ethyl acetate's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Ethyl acetate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to evaluate ethyl acetate's carcinogenic potential, the non-transparency of VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in silico* prediction and *in vitro* testing of endocrine receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of ethyl acetate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: Insufficient experimental data are available. **Endocrine activity:** No *in vivo* data are available on circulating hormones on the target substance. **Respiratory sensitization**: No experimental data are available on the target substance, and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). Two VEGA models' predictions were based on measured data on the target chemical, which ToxServices could not identify. One VEGA model with high confidence was based on chemicals with additional structural alerts for carcinogenicity, reducing its reliability. OncoLogic could not evaluate the structure of the compound.

[28] 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).

	Genotoxicity: The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[29]. The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[30]. The *in vitro* SCE assay (as defined in OECD 479, a guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[31]. **Endocrine activity:** ToxCast models don't define applicability domain. The *in vivo* relevance of *in silico* modeling and *in vitro* testing of receptor binding is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **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	Y	*In silico* modeling: Toxtree/Danish QSAR/ VEGA/ OncoLogic
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* chromosome aberration assay/*in vitro* chromatid exchange assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays; *In silico* modeling: ToxCast / Danish QSAR/ VEGA
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	

[29] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[30] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[31] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301B Biodegradation tests
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 Ethyl Acetate (CAS #141-78-6)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
						S	R *	S	R *	*	*								
C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
L	L	L	L	DG	L	M	M	M	L	L	*L*	L	H	L	M	vL	vL	L	H

Table 2: Chemical Details

Inorganic Chemical?	Chemical Name	CAS#
No	Ethyl acetate	141-78-6

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
Ethyl acetate	2

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

Table 6

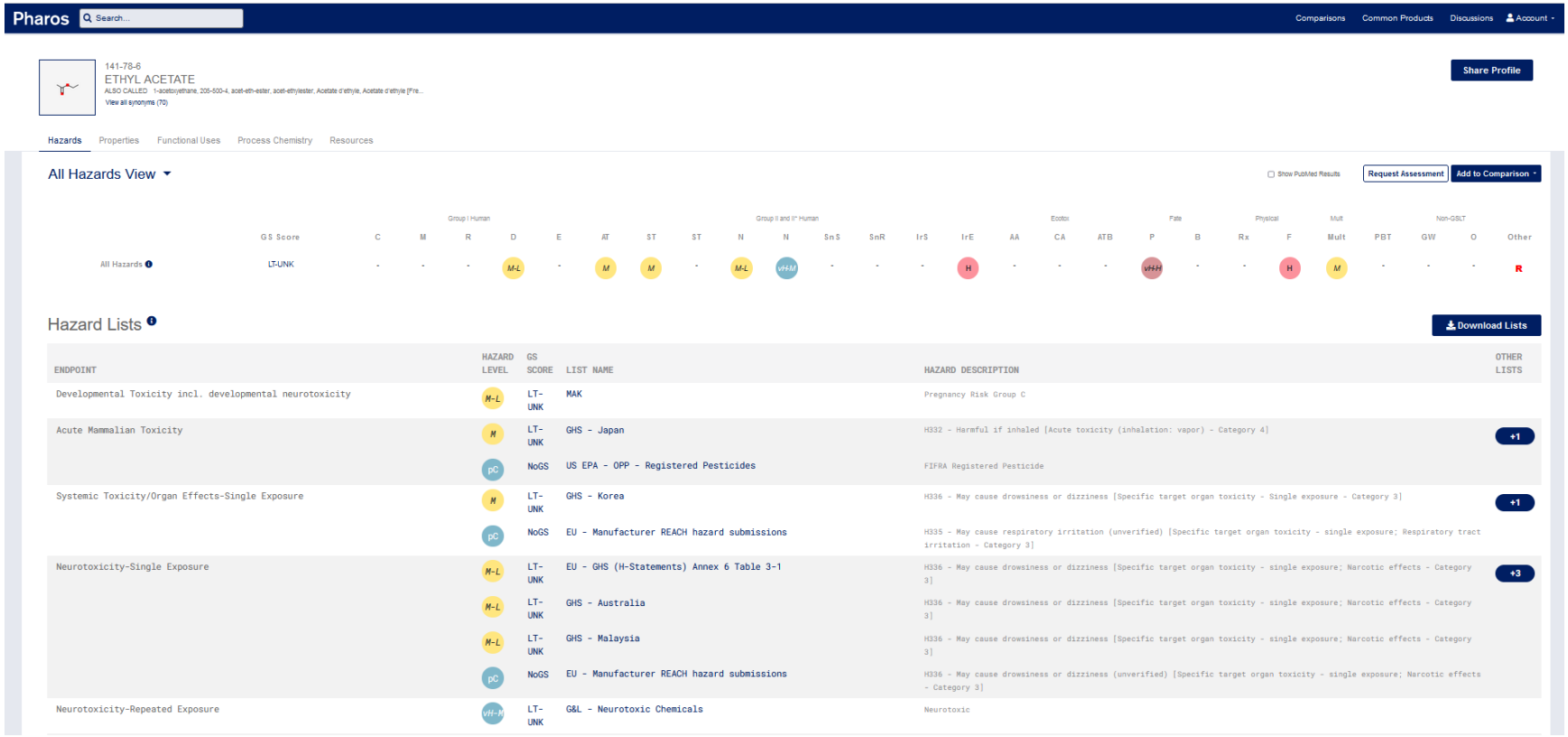
Chemical Name	Final GreenScreen® Benchmark Score
Ethyl acetate	2

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 Ethyl Acetate (CAS #141-78-6)



Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+6
	H	LT-UNK	GHS - Korea	H319 - Causes serious eye irritation [Serious eye damage/irritation - Category 2]	
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - Malaysia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	
	M	LT-UNK	GHS - Japan	H319 - Causes serious eye irritation [Serious eye damage / eye irritation - Category 2B]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	
Flammability	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	+8
	H	LT-UNK	GHS - Australia	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Japan	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Korea	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - Malaysia	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	
	vH-M	LT-UNK	Québec CSST - WHMIS 1988	Class B2 - Flammable liquids	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H225 - Highly flammable liquid and vapour (unverified) [Flammable liquids - Category 2]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H226 - Flammable liquid and vapour (unverified) [Flammable liquids - Category 3]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	
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]	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 1]	
Systemic Toxicity/Organ Effects [Repeated Exposure] and/or Neurotoxicity [Repeated Exposure]	M	LT-UNK	GHS - New Zealand	Specific target organ toxicity - repeated exposure category 2	

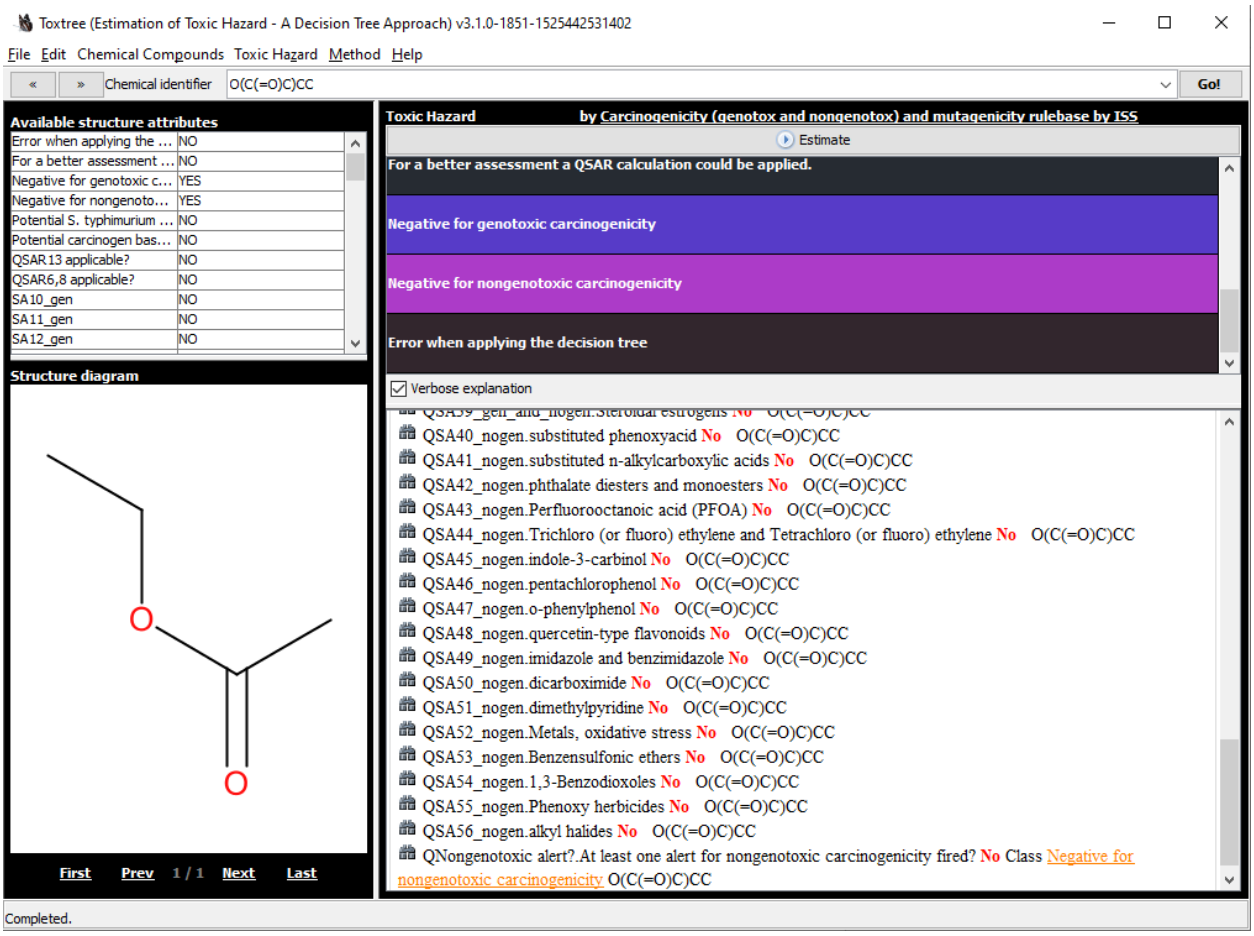
Restricted Substance Lists (9)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- Food Contact Chemicals of Concern (FCCoCL): Food Contact Chemicals of Concern List (FCCoCL)
- Food Contact Chemicals of Concern (FCCoCL): Food Contact Chemicals of Concern List (FCCoCL) - TIER 2
- FSAP Food Packaging Product Stewardship Considerations: FSAP Food Packaging Product Stewardship Considerations
- GSPI - Six Classes of Problematic Chemicals: Some Solvents
- MA Toxics Use Reduction Act (TURA) listed substances: Reportable Chemicals
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

Positive Lists (4)

- Cosmetic Ingredient Review (CIR): Safe as Used
- GB 9685 National Food Safety Standard (2016): GB 9685 National Food Safety Standard (2016)
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients
- TCO Certified potential candidate list (tentative - awaiting assessment): TCO Certified potential candidate list (tentative - awaiting assessment)

APPENDIX D: Toxtree Carcinogenicity Modeling Output for Ethyl Acetate (CAS #141-78-6)



APPENDIX E: Danish (Q)SAR Database Carcinogenicity Modeling for Ethyl Acetate (CAS #141-78-6)

Carcinogenicity

	E Ultra	Leadscope
FDA RCA Cancer Male Rat	NEG_IN	INC_OUT
FDA RCA Cancer Female Rat	NEG_IN	NEG_IN
FDA RCA Cancer Rat	NEG_IN	INC_OUT
FDA RCA Cancer Male Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Female Mouse	NEG_IN	NEG_IN
FDA RCA Cancer Mouse	NEG_IN	NEG_OUT
FDA RCA Cancer Rodent	NEG_IN	INC_OUT

Commercial models from CASE Ultra and Leadscope
FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Not classified

OECD QSAR Toolbox v.4.2 profilers
Profiler predictions are supporting information to be used together with the relevant QSAR predictions

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	NEG_IN	NEG_IN	NEG_IN

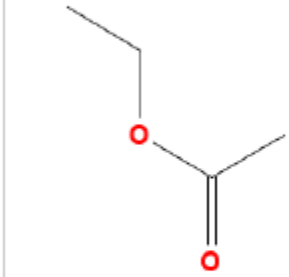
DTU-developed models

APPENDIX F: VEGA Carcinogenicity Modeling Output for Ethyl Acetate (CAS #141-78-6)

VEGA Carcinogenicity model (CAESAR) 2.1.9 page 1

1. Prediction Summary

Prediction for compound Molecule 0

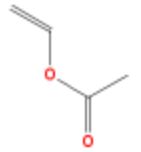


Prediction: Reliability:

Prediction is Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.769
P(NON-Carcinogen): 0.231
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

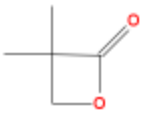
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-05-4
Dataset id: 794 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

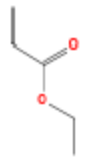
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #2

CAS: 1955-45-9
Dataset id: 663 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.888

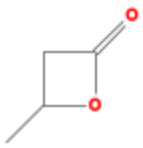
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 140-88-5
Dataset id: 302 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

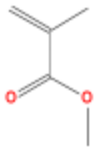
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 3068-88-0
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.85

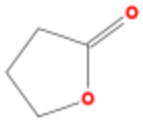
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 80-62-6
Dataset id: 452 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.837

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 96-48-0
Dataset id: 120 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.829

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.944
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.891
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = 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.

Model class assignment reliability
Pos/Non-Pos difference = 0.537
Explanation: model class assignment is well defined.

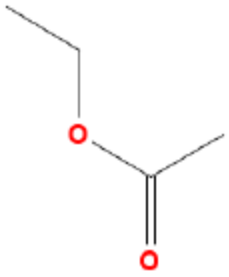
Neural map neurons concordance
Neurons concordance = 1
Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

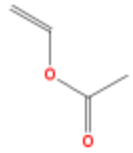


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

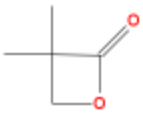
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-05-4
Dataset id: 499 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

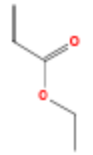


Compound #2

CAS: 1955-45-9
Dataset id: 219 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.888

Experimental value: Carcinogen
Predicted value: Carcinogen

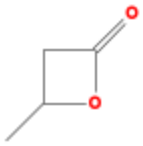
Alerts (not found in the target): SA6 Propiolactones and propiosultones



Compound #3

CAS: 140-88-5
Dataset id: 55 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

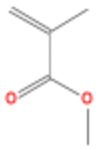


Compound #4

CAS: 3068-88-0
Dataset id: 15 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.85

Experimental value: Carcinogen
Predicted value: Carcinogen

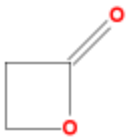
Alerts (not found in the target): SA6 Propiolactones and propiosultones



Compound #5

CAS: 80-62-6
Dataset id: 272 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.837

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



Compound #6

CAS: 57-57-8
Dataset id: 22 (Training set)
SMILES: O=C1OCC1
Similarity: 0.826

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA6 Propiolactones and propiosultones

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.891 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.498 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

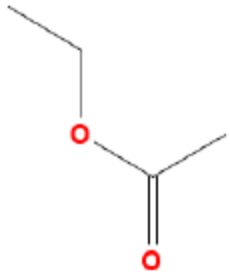
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

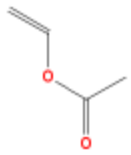


Prediction: Reliability:

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

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

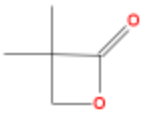
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 792 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

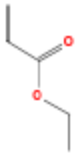


Compound #2

CAS: N.A.
Dataset id: 673 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.888

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 114



Compound #3

CAS: N.A.
Dataset id: 302 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

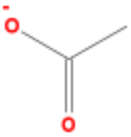
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #4

CAS: N.A.
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.85

Experimental value: Carcinogen
Predicted value: Carcinogen

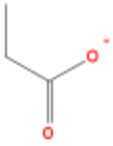
Alerts (not found in the target): Carcinogenity alert no. 114



Compound #5

CAS: N.A.
Dataset id: 1046 (Training set)
SMILES: O=C([O-])C
Similarity: 0.841

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: N.A.
Dataset id: 1122 (Training set)
SMILES: O=C([O-])CC
Similarity: 0.841

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Similar molecules with known experimental value
Similarity index = 0.882
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.336
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

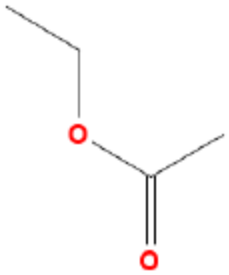
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

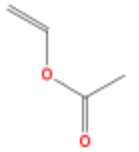


Prediction: Reliability:

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

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

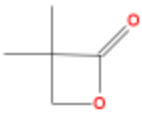
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 108-05-4
Dataset id: 412 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

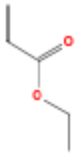


Compound #2

CAS: 1955-45-9
Dataset id: 178 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.888

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 29



Compound #3

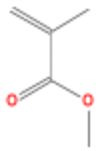
CAS: 140-88-5
Dataset id: 46 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #4

CAS: 3068-88-0
Dataset id: 11 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.85

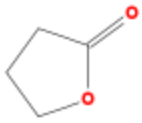
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 80-62-6
Dataset id: 222 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.837

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



Compound #6

CAS: 96-48-0
Dataset id: 931 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.829

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.882 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.336 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

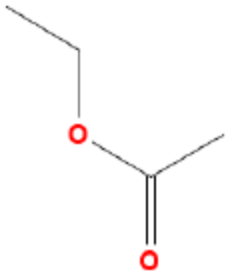
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

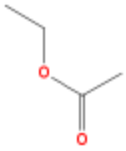


EXPERIMENTAL DATA

Experimental value is NON-Carcinogen. Model prediction is NON-Carcinogen (good reliability).

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: NON-Carcinogen
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

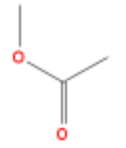
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-78-6
Dataset id: 501 (Test set)
SMILES: O=C(OCC)C
Similarity: 1

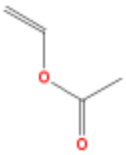
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 79-20-9
Dataset id: 578 (Training set)
SMILES: O=C(OC)C
Similarity: 0.941

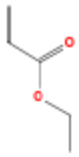
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 108-05-4
Dataset id: 740 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

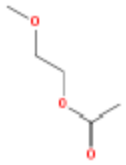
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 140-88-5
Dataset id: 142 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

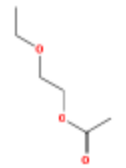
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 576 (Training set)
SMILES: O=C(OCCOC)C
Similarity: 0.865

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



Compound #6

CAS: 111-15-9
Dataset id: 499 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.864

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

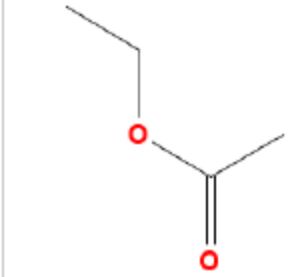
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

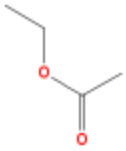


EXPERIMENTAL DATA

Experimental value is NON-Carcinogen. Model prediction is NON-Carcinogen (good reliability).

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: NON-Carcinogen
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

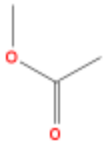
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-78-6
Dataset id: 473 (Training set)
SMILES: O=C(OCC)C
Similarity: 1

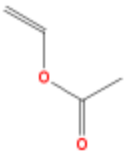
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 79-20-9
Dataset id: 557 (Training set)
SMILES: O=C(OC)C
Similarity: 0.941

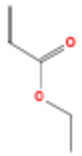
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 108-05-4
Dataset id: 745 (Test set)
SMILES: O=C(OC=C)C
Similarity: 0.895

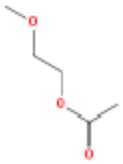
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 140-88-5
Dataset id: 474 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

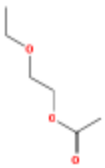
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 555 (Test set)
SMILES: O=C(OCCOC)C
Similarity: 0.865

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



Compound #6

CAS: 111-15-9
Dataset id: 471 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.864

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

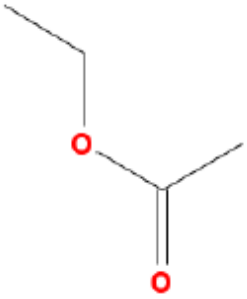
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

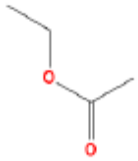


EXPERIMENTAL DATA

Experimental value is NON-Carcinogen. Model prediction is NON-Carcinogen (good reliability).

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: NON-Carcinogen
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

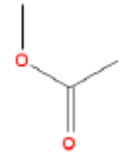
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-78-6
Dataset id: 501 (Test set)
SMILES: O=C(OCC)C
Similarity: 1

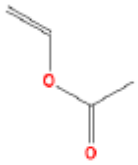
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 79-20-9
Dataset id: 578 (Training set)
SMILES: O=C(OC)C
Similarity: 0.941

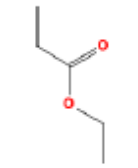
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 108-05-4
Dataset id: 740 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.895

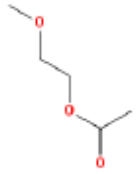
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 140-88-5
Dataset id: 142 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

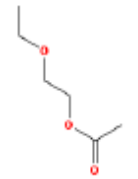
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 576 (Training set)
SMILES: O=C(OCCOC)C
Similarity: 0.865

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



Compound #6

CAS: 111-15-9
Dataset id: 499 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.864

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

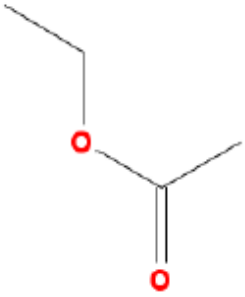
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

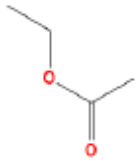


EXPERIMENTAL DATA

Experimental value is NON-Carcinogen. Model prediction is NON-Carcinogen (good reliability).

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: NON-Carcinogen
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

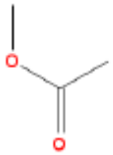
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-78-6
Dataset id: 473 (Training set)
SMILES: O=C(OCC)C
Similarity: 1

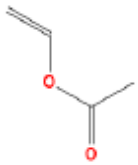
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 79-20-9
Dataset id: 557 (Training set)
SMILES: O=C(OC)C
Similarity: 0.941

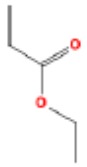
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 108-05-4
Dataset id: 745 (Test set)
SMILES: O=C(OC=C)C
Similarity: 0.895

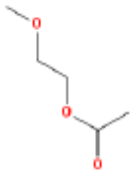
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 140-88-5
Dataset id: 474 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.866

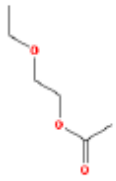
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 110-49-6
Dataset id: 555 (Test set)
SMILES: O=C(OCCOC)C
Similarity: 0.865

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



Compound #6

CAS: 111-15-9
Dataset id: 471 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.864

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

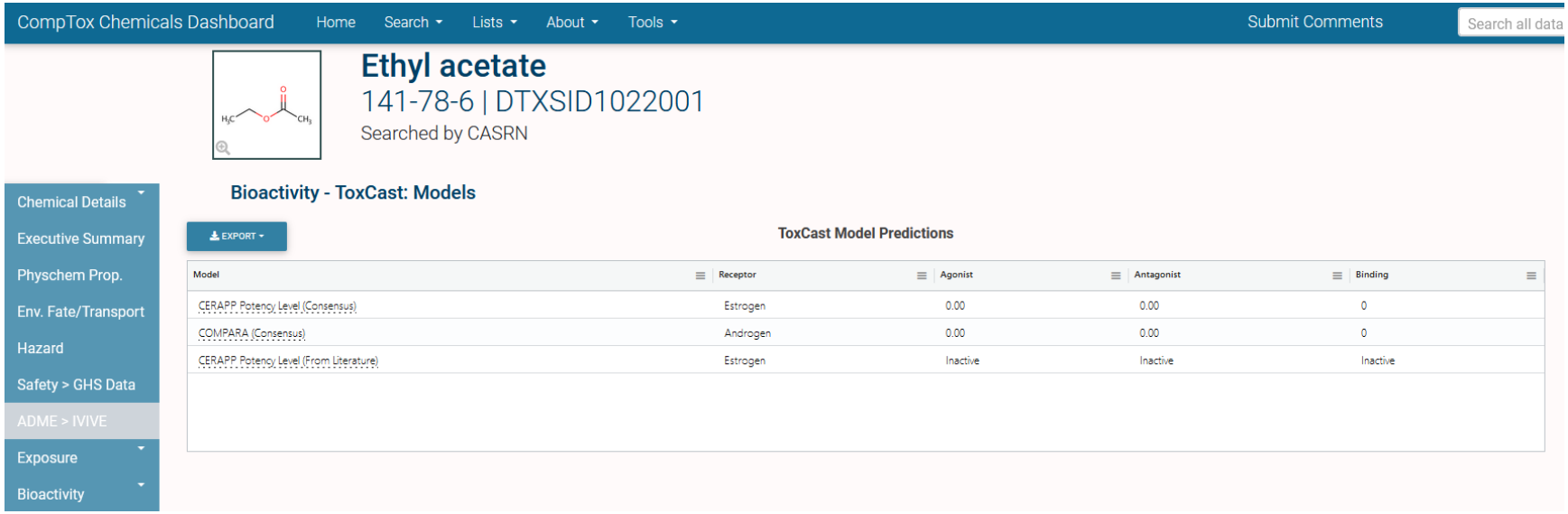
Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

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 G: ToxCast Endocrine Activity Modeling Output for Ethyl Acetate (CAS #141-78-6)



APPENDIX H: Danish (Q)SAR Endocrine and Molecular Endpoints Results for Ethyl Acetate (CAS #141-78-6)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	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	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
mg/L			14093.71	1420.121	57.87957
µM			159955.8	16117.59	656.9013
Positive for $IC_{50} \leq 10$ µM					
Positive for $IC_{50} \leq 100$ µM					
Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
mg/L			2851.185	22.61597	238.4653
µM			32359.38	256.6788	2706.45
Positive for $IC_{50} \leq 10$ µM					
Positive for $IC_{50} \leq 100$ µM					
Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	POS_OUT	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW	NEG	N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	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*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)	NEG	N/A	N/A	NEG_IN	N/A

DTU-developed models

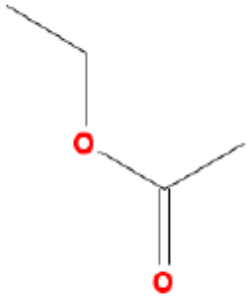
Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, non cyclic structure
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	Non binder, non cyclic structure
rtER Expert System - USEPA, alerts 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 I: VEGA Endocrine Activity Modeling Results for Ethyl Acetate (CAS #141-78-6)

1. Prediction Summary

Prediction for compound Molecule 0

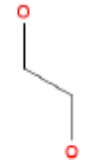


Prediction: Reliability:

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

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

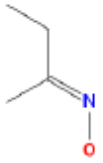
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 107-21-1
Dataset id: 22 (Training set)
SMILES: OCCO
Similarity: 0.776

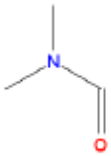
Experimental value: Inactive
Predicted value: Inactive



Compound #2

CAS: 96-29-7
Dataset id: 7 (Training set)
SMILES: ON=C(C)CC
Similarity: 0.724

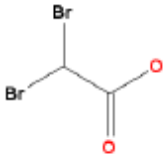
Experimental value: Inactive
Predicted value: Inactive



Compound #3

CAS: 68-12-2
Dataset id: 23 (Test set)
SMILES: O=CN(C)C
Similarity: 0.707

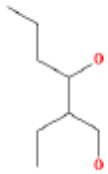
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: 631-64-1
Dataset id: 8 (Training set)
SMILES: O=C(O)C(Br)Br
Similarity: 0.686

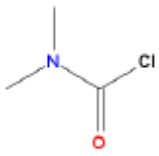
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 94-96-2
Dataset id: 17 (Training set)
SMILES: OCC(CC)C(O)CCC
Similarity: 0.68

Experimental value: Inactive
Predicted value: Inactive



Compound #6

CAS: 79-44-7
Dataset id: 25 (Training set)
SMILES: O=C(N(C)C)Cl
Similarity: 0.677

Experimental value: Inactive
Predicted value: Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

✓	**Global AD Index** AD index = 0.865 Explanation: the predicted compound is into the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.748 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✓	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✓	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✓	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

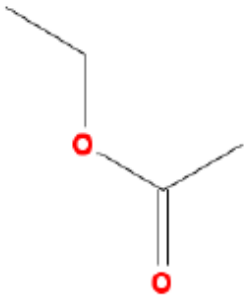
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

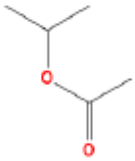
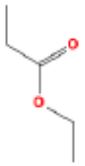
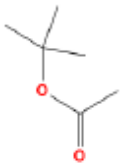
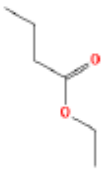


Prediction: Reliability:

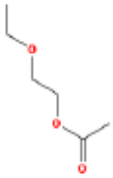
Prediction is Possible NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: -
Predicted ER-mediated effect: Possible NON-active
No. alerts for activity: 0
No. alerts for possible activity: 0
No. alerts for non-activity: 0
No. alerts for possible non-activity: 2
Structural alerts: ER possible non-activity alert no. 1; ER possible non-activity alert no. 9
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

	Compound #1 CAS: N.A. Dataset id: 813 (Training set) SMILES: O=COC(C)C Similarity: 0.961 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 9
	Compound #2 CAS: N.A. Dataset id: 431 (Training set) SMILES: O=C(OC(C)C)C Similarity: 0.945 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9
	Compound #3 CAS: N.A. Dataset id: 394 (Training set) SMILES: O=C(OCC)CC Similarity: 0.933 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9
	Compound #4 CAS: N.A. Dataset id: 770 (Training set) SMILES: O=C(OC(C)(C)C)C Similarity: 0.916 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9
	Compound #5 CAS: N.A. Dataset id: 396 (Training set) SMILES: O=C(OCC)CCC Similarity: 0.88 Experimental value: NON-active Predicted value: Possible NON-active Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9 Alerts (not found in the target): ER possible non-activity alert no. 2

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



Compound #6

CAS: N.A.
Dataset id: 477 (Training set)
SMILES: O=C(OCCOCC)C
Similarity: 0.864

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

Alerts (not found in the target): ER possible non-activity alert no. 3

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.972
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.946
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

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

Symbols explanation:

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

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

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

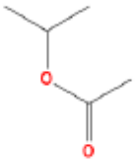
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 1 of 2:

Fragment found: ER possible non-activity alert no. 1

Fragment related to possible non-activity for ER-mediated effect, defined by the SMARTS: CCOCC

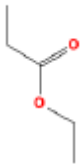
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 431 (Training set)
SMILES: O=C(OC(C)C)C
Similarity: 0.945

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

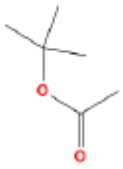
Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9



CAS: N.A.
Dataset id: 394 (Training set)
SMILES: O=C(OCC)CC
Similarity: 0.933

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9



CAS: N.A.
Dataset id: 770 (Training set)
SMILES: O=C(OC(C)(C)C)C
Similarity: 0.916

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 2 of 2:

Fragment found: ER possible non-activity alert no. 9

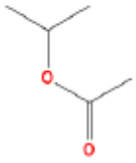
Fragment related to possible non-activity for ER-mediated effect, defined by the SMARTS: C(=O)

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

CAS: N.A.
Dataset id: 813 (Training set)
SMILES: O=COC(C)C
Similarity: 0.961

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

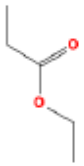
Alerts (found also in the target): ER possible non-activity alert no. 9



CAS: N.A.
Dataset id: 431 (Training set)
SMILES: O=C(OC(C)C)C
Similarity: 0.945

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9



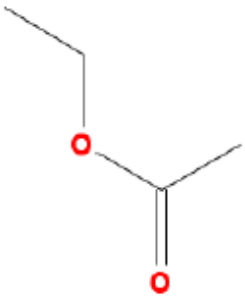
CAS: N.A.
Dataset id: 394 (Training set)
SMILES: O=C(OCC)CC
Similarity: 0.933

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

Alerts (found also in the target): ER possible non-activity alert no. 1; ER possible non-activity alert no. 9

1. Prediction Summary

Prediction for compound Molecule 0

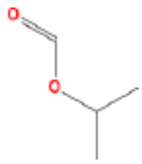


Prediction: Reliability:

Prediction is NON-active, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

Compound: Molecule 0
Compound SMILES: O=C(OCC)C
Experimental value: -
Predicted AR binding activity: NON-active
No. alerts for binding activity: 0
No. alerts for non-binding activity: 0
Structural alerts: -
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

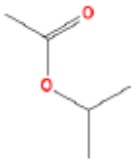
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 625-55-8
Dataset id: 951 (Training set)
SMILES: CC(C)OC=O
Similarity: 0.961

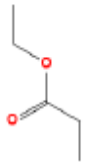
Experimental value: NON-active
Predicted value: NON-active



Compound #2

CAS: 108-21-4
Dataset id: 826 (Training set)
SMILES: CC(C)OC(C)=O
Similarity: 0.945

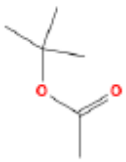
Experimental value: NON-active
Predicted value: NON-active



Compound #3

CAS: 105-37-3
Dataset id: 1212 (Training set)
SMILES: CCC(=O)OCC
Similarity: 0.933

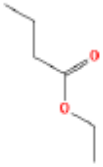
Experimental value: NON-active
Predicted value: NON-active



Compound #4

CAS: 540-88-5
Dataset id: 586 (Training set)
SMILES: CC(=O)OC(C)(C)C
Similarity: 0.916

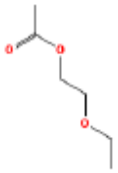
Experimental value: NON-active
Predicted value: NON-active



Compound #5

CAS: 105-54-4
Dataset id: 1213 (Training set)
SMILES: CCOC(=O)CCC
Similarity: 0.88

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



Compound #6

CAS: 111-15-9
Dataset id: 553 (Training set)
SMILES: CCOCCOC(C)=O
Similarity: 0.864

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

Alerts (not found in the target): ER alert no. 18, inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.976
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.953
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

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

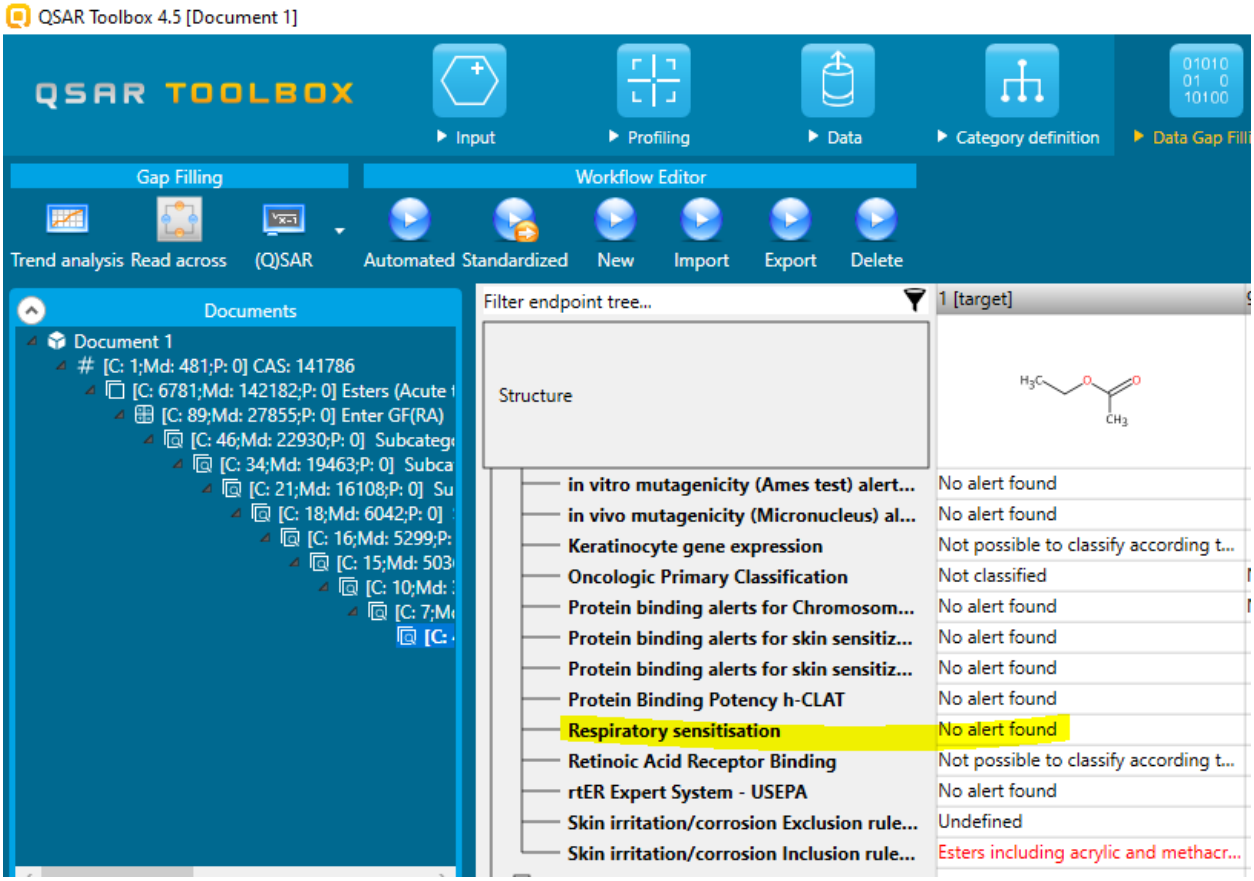
Symbols explanation:

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

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

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

APPENDIX J: OECD Toolbox for Respiratory Sensitization Results for Ethyl Acetate (CAS #141-78-6)



APPENDIX K: EPI Suite™ Modeling Results for Ethyl Acetate (CAS #141-78-6)

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

CAS Number: 141-78-6
SMILES : O=C(OCC)C
CHEM : Acetic acid ethyl ester
MOL FOR: C4 H8 O2
MOL WT : 88.11
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 0.68
Boiling Point (deg C) : 77.10
Melting Point (deg C) : -83.60
Vapor Pressure (mm Hg) : 93.2
Water Solubility (mg/L): 80000
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.86
Log Kow (Exper. database match) = 0.73
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 77.91 (Adapted Stein & Brown method)
Melting Pt (deg C): -82.08 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 98.3 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.31E+004 (Mean VP of Antoine & Grain methods)
MP (exp database): -83.6 deg C
BP (exp database): 77.1 deg C
VP (exp database): 9.32E+01 mm Hg (1.24E+004 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 5.112e+004
log Kow used: 0.68 (user entered)
melt pt used: -83.60 deg C
Water Sol (Exper. database match) = 8e+004 mg/L (25 deg C)
Exper. Ref: BANERJEE,S (1984)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 38942 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 2.33E-004 atm-m3/mole (2.36E+001 Pa-m3/mole)
Group Method: 1.58E-004 atm-m3/mole (1.60E+001 Pa-m3/mole)

Exper Database: 1.34E-04 atm-m3/mole (1.36E+001 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: 1.351E-004 atm-m3/mole (1.369E+001 Pa-m3/mole)
VP: 93.2 mm Hg (source: User-Entered)
WS: 8E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 0.68 (user entered)
Log Kaw used: -2.261 (exp database)
Log Koa (KOAWIN v1.10 estimate): 2.941
Log Koa (experimental database): 2.700

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.8798
Biowin2 (Non-Linear Model) : 0.9971
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1447 (weeks)
Biowin4 (Primary Survey Model) : 3.9496 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7527
Biowin6 (MITI Non-Linear Model): 0.9188
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.8748
Ready Biodegradability Prediction: YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.24E+004 Pa (93.2 mm Hg)
Log Koa (Exp database): 2.700
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.41E-010
Octanol/air (Koa) model: 1.23E-010
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 8.72E-009
Mackay model : 1.93E-008
Octanol/air (Koa) model: 9.84E-009

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 1.7038 E-12 cm3/molecule-sec
Half-Life = 6.278 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 75.331 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

1.4E-008 (Junge-Pankow, Mackay avg)
9.84E-009 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 5.583 L/kg (MCI method)
Log Koc: 0.747 (MCI method)
Koc : 17.2 L/kg (Kow method)
Log Koc: 1.236 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 1.208E-001 L/mol-sec
Kb Half-Life at pH 8: 66.387 days
Kb Half-Life at pH 7: 1.818 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.8001 days (HL = 0.01584 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.036 (BCF = 1.086)
Log BAF Arnot-Gobas method (upper trophic) = 0.036 (BAF = 1.086)
log Kow used: 0.68 (user entered)

Volatilization from Water:
Henry LC: 0.000134 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 5.059 hours
Half-Life from Model Lake : 133.9 hours (5.579 days)

Removal In Wastewater Treatment:
Total removal: 8.07 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.68 percent
Total to Air: 6.30 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air 15	**152**	**1000**
Water 41.2	**360**	**1000**
Soil 43.8	**720**	**1000**
Sediment 0.085	**3.24e+003**	**0**

Persistence Time: 263 hr

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

Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air 15	152	1000
Water 41.2	360	1000

water (41.1)
biota (9.85e-006)
suspended sediment (0.000345)
Soil 43.8 720 1000
Sediment 0.085 3.24e+003 0
Persistence Time: 263 hr

Level III Fugacity Model: (EQC Default)
Mass Amount Half-Life Emissions
(percent) (hr) (kg/hr)
Air 16.2 152 1000
Water 44 360 1000
water (44)
biota (1.05e-005)
suspended sediment (0.00013)
Soil 39.7 720 1000
Sediment 0.0842 3.24e+003 0
Persistence Time: 249 hr

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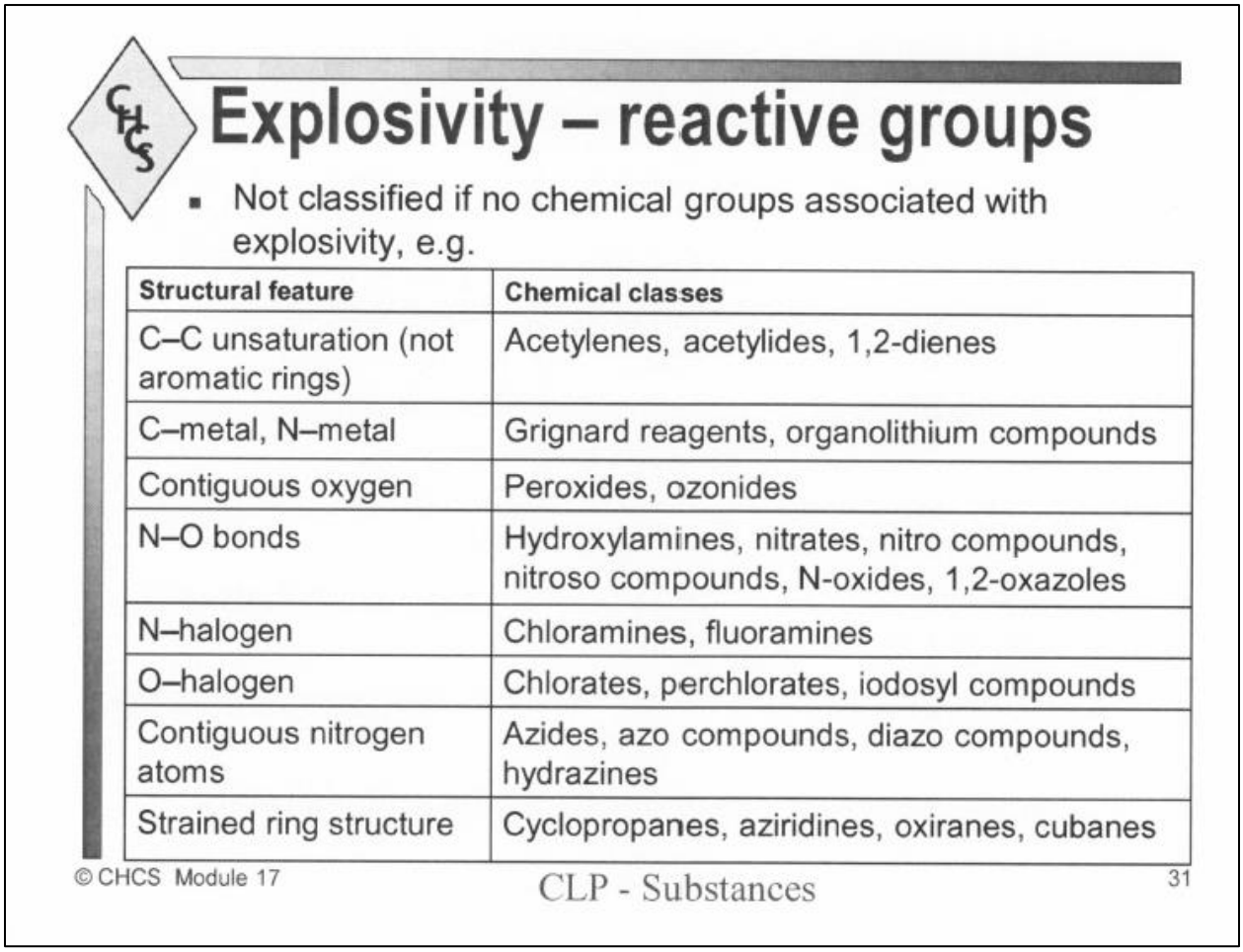
APPENDIX L: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



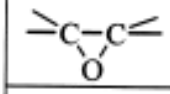
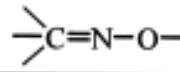
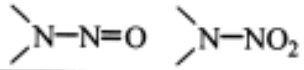
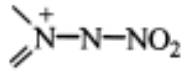
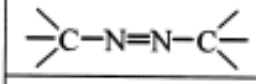
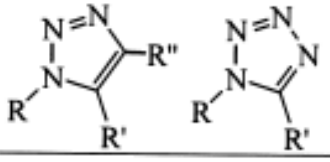
Explosivity – reactive groups

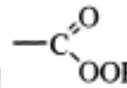
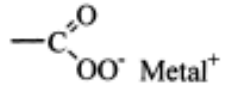
- Not classified if no chemical groups associated with explosivity, e.g.

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

Explosivity – Full List

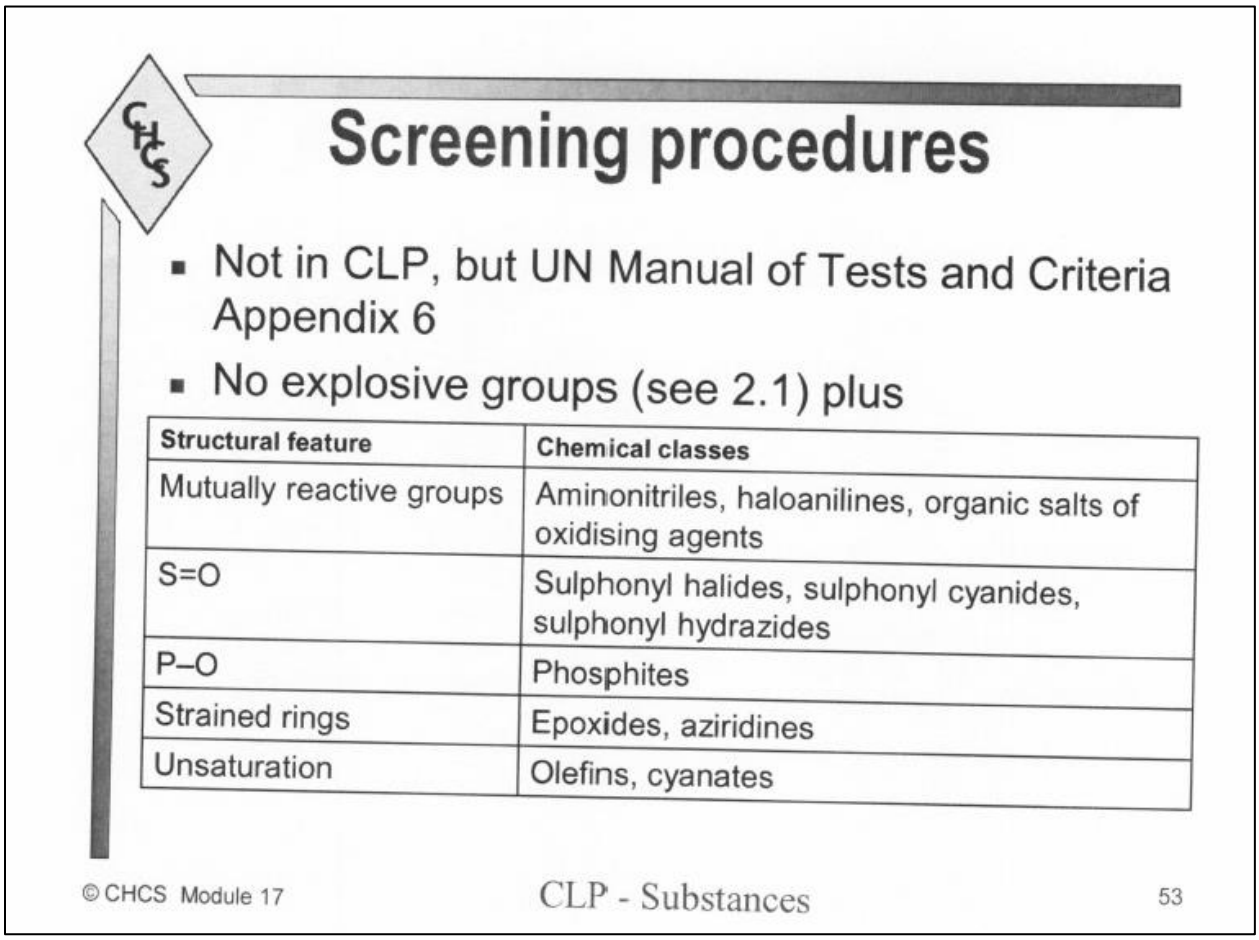
Table R.7.1-28 Chemical groups associated with explosive properties

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
$^{-}O-C-N_2^{+}$	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 M: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for ethyl acetate. The GreenScreen® Benchmark Score for ethyl acetate has not changed over time. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017, and version 1.4 updates in 2019 and in this 2023 report.

Table 6: Change in GreenScreen® Benchmark™ for Ethyl Acetate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 21, 2014	BM-2	v. 1.2	New GreenScreen® assessment.
February 7, 2017	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template.
May 10, 2019	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
September 23, 2019	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
January 25, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template. The score for carcinogenicity is changed from **Moderate** (High confidence) to *Low* (low confidence) due to re-evaluation of the weight of evidence; the score for endocrine activity is changed from **Moderate** to Data Gap due to re-evaluation of the weight of evidence.

Licensed GreenScreen® Profilers

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