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BUTYL ACETATE

(CAS #123-86-4)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: April 3, 2023

Expiration Date: April 3, 2023

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GreenScreen® Executive Summary for Butyl Acetate (CAS #123-86-4)

Butyl acetate, also known as butyl ethanoate or 1-acetoxybutane, is an organic carboxylic acid ester. It exists as a colorless, volatile, and flammable liquid at room temperature and has a sweet smell of banana or apple. Butyl acetate is very soluble in water.

Butyl acetate is predominately used as a solvent in the production of lacquers, coatings, artificial leathers, photographic films, plastics, food packaging, nail polish, home repair products, cleaning agents, and thermosets. When used as a solvent or fragrance ingredient in cosmetics/personal care products in the EU, it does not have restrictions under EC Regulation No. 1223/2009. The United States Food and Drug Administration (U.S. FDA) has approved butyl acetate for direct addition to food as a synthetic flavoring substance as well as multiple indirect food additive uses in food packaging applications.

Butyl acetate has a relatively complete dataset, although limited data were identified for a few endpoints. ToxServices selected its hydrolysis products n-butanol (CAS #71-36-3) and acetic acid (CAS #64-19-7), and its isomer isobutyl acetate (CAS #110-19-0) as surrogates where necessary. ToxServices also performed modeling when possible and necessary. Nevertheless, insufficient data were identified to evaluate endocrine activity.

In terms of human health hazards, butyl acetate has moderate concerns for single dose systemic toxicity based on respiratory irritation, and for single dose neurotoxicity based on transient narcotic effects.

In terms of environmental hazards, butyl acetate has moderate concerns for acute aquatic toxicity based on L/EC_{50} values of 18 mg/L in fish and 44 mg/L in daphnia, and for chronic aquatic toxicity based on a modeled chronic aquatic toxicity value of 1.48 mg/L in fish. It meets the 10-day window in an OECD Guideline 301 D ready biodegradability test indicating that it degrades rapidly in the environment. It is not expected to bioaccumulate based on its hydrophilicity and high degradability.

Butyl acetate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement"). This score is based on the following hazard score:

- Benchmark 3b
  - Moderate Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
- Benchmark 3c
  - Moderate Group II Human Health Hazard (single dose systemic toxicity-STs, single dose neurotoxicity-Ns)
- Benchmark 3d
  - Moderate flammability-F

Data gaps (DG) exist for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), butyl acetate meets requirements for a GreenScreen Benchmark™ Score of 3 despite the hazard data gap. In a worst-case scenario, if butyl 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 butyl acetate has 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 a version 1.4 update in 2020 and 2021. In the present report, ToxServices altered the developmental

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toxicity-D score from moderate to low based on a consideration of effects only identified at maternally-toxic doses, which altered the Benchmark Score from a BM-2 to a BM-3.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation, and *in vitro* assays for mutagenicity and endocrine activity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 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 butyl acetate's NAMs dataset include no or lack of adequate experimental or human data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and chronic aquatic toxicity. Butyl acetate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the lack of applicability domains for ToxCast models for endocrine activity and OECD Toolbox for respiratory sensitization, limited confidence in VEGA predictions due to low ADIs and concordance indices, the limitation of OECD Toolbox in not accounting for non-immunologic mechanisms of respiratory sensitization, and the questionable reliability of chronic aquatic toxicity predictions by ECOSAR. Some of butyl 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 Butyl 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*	**L**	**M**	**L**	*L*	*L*	*L*	**L**	**M**	*M*	**vL**	**vL**	*L*	**M**

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.

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GreenScreen® Chemical Assessment for Butyl Acetate (CAS #123-86-4)

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

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Expiration Date: April 3, 2028[2]
Chemical Name: Butyl Acetate
CAS Number: 123-86-4

[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).

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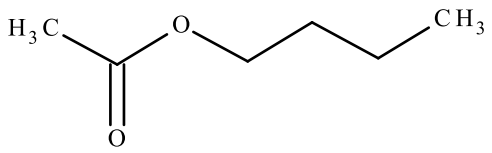
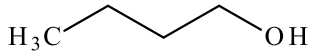
Chemical Structure(s):

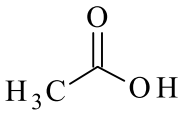


Also called: Acetic acid, butyl ester; n-Butyl acetate; 1-Butyl acetate; Acetic acid n-butyl ester; Butyl ethanoate; EINECS 204-658-1; n-Butyl ethanoate; Butyl acetate, n-; n-Butyl acetate [UN1123] (PubChem 2023)

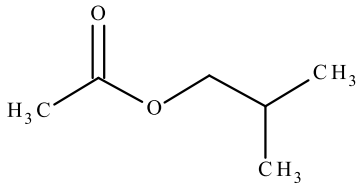
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited data were identified for chronic aquatic toxicity and carcinogenicity for butyl acetate. ToxServices used modeled and/or experimental data for the hydrolysis products n-butanol (CAS #71-36-3) and acetic acid (CAS #64-19-7) to support the evaluation of carcinogenicity and/or mutagenicity endpoints, and used experimental data on the isomer isobutyl acetate (CAS #110-19-0) to address the data gap for chronic aquatic toxicity. Butyl acetate and isobutyl acetate share a maximum common substructure (MCS) Tanimoto coefficient of 0.78, indicating a high degree of structural similarity[3]. Isobutyl acetate was also used as a read-across chemical in the REACH registration dossier for butyl acetate (ECHA, CAS #123-86-4, 2023a).



Surrogate: n-Butanol (CAS #71-36-3)



Surrogate: Acetic Acid (CAS #64-19-7)



Surrogate: Isobutyl Acetate (CAS #110-19-0)

ToxServices also considered tert-butyl acetate (CAS #540-88-5) as a possible surrogate, especially for the carcinogenicity endpoint because the California Office of Environmental Health Hazard Assessment (OEHHA) considers tert-butyl acetate to be a carcinogen (Budroe et al. 2004, OEHHA 2018) based on the results of National Toxicology Program carcinogenicity bioassays performed with its metabolite tert-butanol (CAS #75-65-0) (NTP 1995). However, butyl acetate and tert-butyl acetate have a maximum common substructure (MCS) Tanimoto coefficient of 0.600.[3] ToxServices considers a Tanimoto

[3] https://chemminetools.ucr.edu/similarity/

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coefficient of ≥ 0.7 to indicate sufficient chemical structural similarity for surrogates. Therefore, ToxServices did not consider tert-butyl acetate to be sufficiently structurally similar to be used as a surrogate in this assessment of butyl acetate.

Identify Applications/Functional Uses: (HSDB 2018)
1. Solvent
2. Dehydrating agent
3. Synthetic flavoring agent

Known Impurities[4]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Butyl Acetate[5,6 7,8]: Butyl acetate was assigned a **GreenScreen Benchmark™ Score of 3** ("Use but Still Opportunity for Improvement") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 3b
  - Moderate Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
- Benchmark 3c
  - Moderate Group II Human Health Hazard (single dose systemic toxicity-STs, single dose neurotoxicity-Ns)
- Benchmark 3d
  - Moderate flammability-F

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), butyl acetate meets requirements for a GreenScreen Benchmark™ Score of 3 despite the hazard data gaps. In a worst-case scenario, if butyl 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 Butyl 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*	**L**	**M**	**L**	*L*	*L*	*L*	**L**	**M**	*M*	**vL**	**vL**	*L*	**M**

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

[4] Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.
[5] 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.
[6] See Appendix A for a glossary of hazard endpoint acronyms.
[7] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[8] 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.

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after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Butyl acetate has experimentally determined hydrolysis half-lives of 114 and 11 days at pH 8 and 9, respectively (HSDB 2018). No hydrolysis products were identified. Based on the presence of the ester functional group, ToxServices predicts that butanol (CAS #71-36-3) and acetate (CAS #71-50-1)/acetic acid (CAS #64-19-7) will be formed via hydrolysis of the ester group. Butanol is an LT-U chemical, acetate is not listed in Pharos, and acetic acid is listed on the Safer Choice SCIL as an acceptable processing aid and additive (U.S. EPA 2023a). Since butyl acetate is readily biodegradable and meets the 10-day window (see the persistence section below), these hydrolysis products are not relevant to the environmental fate of butyl acetate and do not modify the Benchmark Score for butyl acetate.

Introduction

Butyl acetate, also known as butyl ethanoate or 1-acetoxybutane, is an organic carboxylic acid ester. It exists as a colorless, flammable liquid at room temperature and has a sweet smell of banana or apple. Butyl acetate is predominately used as a solvent in the production of lacquers, coatings, artificial leathers, photographic films, plastics, food packaging, nail polish, home repair products, cleaning agents, and thermosets (PubChem 2023). Butyl acetate is considered a good solvent with low volatility that is prepared through the esterification reaction of butanol and acetic acid with the catalyst sulfuric acid (HSBD 2018). In Europe, butyl acetate does not have any restrictions when used in cosmetics or personal care products as a fragrance or solvent under EC Regulation No. 1223/2009 (EC 2023). The United States Food and Drug Administration (U.S. FDA) has approved butyl acetate as a direct food additive under 21 CFR §172.515 (Synthetic Flavoring Substances), and as an indirect food additive under 21 CFR §175.105 (Adhesives), §175.320 (Resinous and Polymeric Coatings for Polyolefin Films), and §177.1200 (Cellophane) (U.S. FDA 2023).

ToxServices assessed butyl 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 (SCIL)

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).

Butyl 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 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),[9] 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 butyl acetate can be found in Appendix C.

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

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- Butyl acetate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Butyl acetate (UN1123) is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group II.
- Butyl acetate is on the following list[s] 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

Butyl acetate has a harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) classification as reported by the European Chemicals Agency (ECHA) (ECHA 2023b); it is classified as a GHS Category 3 flammable liquid (H226) and a GHS Category 3 specific target organ toxicant following single exposure for narcotic effects (H336).

Table 1: GHS H Statements for Butyl Acetate (CAS #123-86-4) (ECHA 2023b)

H Statement	H Statement Details
H226	Flammable liquid and vapor.
H336	May cause drowsiness or dizziness.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Butyl Acetate (CAS #123-86-4)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respirator with A filter; Wear protective gloves (suitable material butyl-rubber, polyvinylchloride / nitrile rubber); Tightly fitting safety goggles, face shield if there is a reasonable chance for splash to the face; Impervious clothing	ECHA, CAS #123-86-4, 2023a	STEL: 8h: 150 ppm (700 mg/m^3) (recommended) NIOSH REL: 150 ppm (710 mg/m^3) TWA, 200 ppm (950 mg/m^3) STEL OSHA PEL: 150 ppm (710 mg/m^3) TWA	SCOEL 2013 NIOSH 1994, OSHA 2023

NIOSH: National Institute for Occupational Safety and Health; OSHA: Occupational Safety and Health Administration; PEL: Permissible Exposure Limit; REL: Recommended Exposure Limit; STEL: Short-Term Exposure Limit; TWA: Time-weighted Average

Physicochemical Properties of Butyl Acetate

Butyl acetate is a clear, colorless liquid under standard temperature and pressure. It has a high vapor pressure (11.5 mm Hg) indicating that it will exist mostly in the vapor phase. It is soluble in water (8,400 mg/L) but is more soluble in octanol (log $K_{ow} > 0$).

Table 3: Physical and Chemical Properties of Butyl Acetate (CAS #123-86-4)

Property	Value	Reference
Molecular formula	C6-H12-O2	PubChem 2023
SMILES Notation	O(CCCC)C(C)=O	PubChem 2023
Molecular weight	116.159 g/mol	PubChem 2023
Physical state	Liquid	ECHA, CAS #123-86-4, 2023a

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Table 3: Physical and Chemical Properties of Butyl Acetate (CAS #123-86-4)		
Property	**Value**	**Reference**
Appearance	Colorless, clear	ECHA, CAS #123-86-4, 2023a
Melting point	-78°C Less than -90°C (DIN ISO 3016, ASTM D 97)	PubChem 2023 ECHA, CAS #123-86-4, 2023a
Boiling point	126.1°C	PubChem 2023
Vapor pressure	11.5 mm Hg at 25°C 15 hPa (11.25 mm Hg) at 20°C (DIN-EN 13016-2)	PubChem 2023 ECHA, CAS #123-86-4, 2023a
Water solubility	8,400 mg/L at 25°C 5,300 mg/L at 20°C (OECD 105)	PubChem 2023 ECHA, CAS #123-86-4, 2023a
Dissociation constant	Not identified	N/A
Density/specific gravity	0.8812 g/cm^3 at 20°C (DIN 51757, ASTM D 4052)	ECHA, CAS #123-86-4, 2023a
Partition coefficient	Log K_{ow} = 1.78 Log K_{ow} = 2.3 at 25°C (OECD 117)	PubChem 2023 ECHA, CAS #123-86-4, 2023a

Toxicokinetics

- *Absorption:* Data on the toxicokinetic activity of butyl acetate are available for intravenous, inhalational, and dermal exposures. In male Sprague-Dawley rats butyl acetate was readily absorbed following whole body inhalation exposure. The respiratory bioavailability was calculated to be 100% of alveolar ventilation. The maximum blood levels of butyl acetate were reached at about 10 minutes into the exposure period. Similar results were obtained in female Sprague-Dawley rats which were exposed to butyl acetate for 5 hours via tracheal intubation. Absorption of butyl acetate following dermal application is considered to be low based on a permeability constant of n-butyl (1.6 +/- 0.1 g/m^2*h or 1.8 +/- 0.1 cm3/m^2*h) in an *in vitro* human skin assay. Based on the water solubility, molecular mass < 500, and log K_{ow} of -1 to 4, the REACH dossier assumes a default of 100% dermal absorption for butyl acetate (ECHA, CAS #123-86-4, 2023a).

- *Distribution:* Butyl acetate is rapidly distributed throughout the body as seen in an *in vivo* assay with Sprague-Dawley rats which received radioactively labelled butyl acetate intravenously. Radioactively labeled butyl acetate was observed in whole blood and in low concentrations in brain tissues. In both inhalation studies in rats described above, butyl acetate and its metabolite n-butanol were detectable in blood immediately at the start of exposure and maximum concentrations were reached at the 30-minute mark. The concentration of the butyl acetate reached was nearly constant and the butanol metabolite was approximately twice the levels of the butyl acetate concentrations in the blood (ECHA, CAS #123-86-4, 2023a).

- *Metabolism:* Butyl acetate undergoes rapid hydrolysis via esterases to n-butanol and acetic acid. Following hydrolysis, butanol and acetic acid are further metabolized and enter the Krebs cycle. Polar metabolites, presumably Krebs cycle intermediates of butanol and glucuronide and sulfate conjugates of butanol were detected in whole blood (maximum of 12.2 µg equivalents/g at 4.2 min) but were only observed in trace amounts in brain tissue of exposed Sprague-Dawley rats. The

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hydrolysis of butyl acetate in the blood and brain is expected to be 99% complete by 2.7 minutes (ECHA, CAS #123-86-4, 2023a).

- *Excretion:* Butyl acetate is very rapidly eliminated from the blood (biphasic elimination) with a half-life of 0.41 min. The metabolite butanol was undetectable beyond 20 min post dosing. No data were identified indicating detection of butyl acetate or its metabolites in urine, feces, or exhaled air (ECHA, CAS #123-86-4, 2023a).

In summary, butyl acetate is readily and extensively absorbed via oral and inhalation exposures but may have limited absorption following dermal exposures. Butyl acetate distributes throughout the body and is rapidly hydrolyzed via esterase activity to butanol and its sulfate and glucuronide conjugates and acetic acid. Elimination of butyl acetate and its metabolites occurs via entry of the metabolites into the Krebs cycle.

Hazard Classification Summary

<u>Group I Human Health Effects (Group I Human)</u>

Carcinogenicity (C) Score (H, M, or L): *L*
Butyl acetate was assigned a score of Low for carcinogenicity based on the negative modeling results on butyl acetate by VEGA, supported by negative experimental/modeled data on its hydrolysis products acetic acid and n-butanol. 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 is low as it is mainly based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Toxtree 2018
  - Butyl acetate does not have structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D).
- VEGA 2019
  - The CAESAR model predicts butyl acetate is a non-carcinogen with low reliability because the compound is outside of the model's applicability domain (global applicability domain (AD) index = 0.328) (Appendix E).
  - The ISS model predicts butyl acetate is a non-carcinogen with low reliability because the compound is outside of the model's applicability domain (global AD index = 0) (Appendix E).
  - The IRFMN/Antares model predicts butyl acetate is a possible non-carcinogen with good reliability because the compound is inside of the model's applicability domain (global AD index = 0.771) (Appendix E).
  - The IRFMN/ISSCAN-CGX model predicts butyl acetate is a possible non-carcinogen with low reliability because the compound is outside of the model's applicability domain (global AD index = 0.536) (Appendix E).
  - The IRFMN oral classification model predicts butyl acetate is a non-carcinogen with high reliability because the compound is inside of the model's applicability domain (global AD index = 0.938) (Appendix E).
  - The IRFMN inhalation classification model predicts butyl acetate is a non-carcinogen with high reliability because the compound is inside of the model's applicability domain (global

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AD index = 0.938) (Appendix E).
  - In summary, three models have predictions with sufficient reliability (global AD index > 0.70) (Gad 2016), and all three of those models predict that butyl acetate is a non-carcinogen.
- U.S. EPA 2019, 2021
  - Attempts were made to model carcinogenicity; however, butyl acetate does not fit into any of the chemical classes included in the OncoLogic™ modeling program.
- UNEP 2001
  - *Surrogate: n-Butanol (CAS #71-36-3):* There were no reliable data on n-butanol regarding carcinogenicity. However, based on n-butanol's negative mutagenicity and clastogenicity, it presents a very small potential for carcinogenicity.
- U.S. EPA 2019
  - *Surrogate: n-Butanol (CAS #71-36-3):* n-Butanol was modeled as an aliphatic alcohol. According to OncoLogic™, low molecular weight alcohols (especially methanol and ethanol) are of carcinogenic concern because of possible oxidation to reactive aldehydes, especially in individuals deficient in aldehyde dehydrogenase that converts aldehydes to carboxylic acids. Low molecular weight aliphatic alcohols with terminal double bond or Cl/Br/I, α,β-unsaturation, or monosubstitution with Cl/Br/I at α carbon have genotoxic carcinogenicity concerns. n-Butanol has no structures of concern, and therefore the carcinogenicity concern is negligible (Appendix F).
- JECFA 1974
  - *Surrogate: Acetic Acid (CAS #64-19-7):* About 1 g/day of acetic acid has been consumed by humans in vinegar and other items of food and drinks without known adverse effects at these consumption levels.
- U.S. EPA 2019
  - *Surrogate: Acetic Acid (CAS #64-19-7):* Acetic acid is evaluated in OncoLogic™ as an aliphatic carboxylic acid. According to OncoLogic™, low molecular weight aliphatic carboxylic acids (C < 6) with terminal double bond or Cl/Br/I, α,β-unsaturation or monosubstitution with Cl/Br/I at α carbon have cancer concern due to genotoxic carcinogenicity. Additionally, the irritation potential of unsubstituted saturated fatty acids such as pentanoic acid may have marginal cancer concern by the dermal route due to its irritancy (Appendix G). As acetic acid does not have these structural features and is not a concern for irritation as a metabolite of butyl acetate in the body, acetic acid has low cancer concern.
- Based on the weight of evidence, a conservative score of Low was assigned. Butyl acetate does not contain any alerts for genotoxic or nongenotoxic carcinogenicity, but a lack of alerts is not sufficient to assign a Low. Butyl acetate is inside of the applicability domains for three of the VEGA models, and these three models predicted butyl acetate to be a non-carcinogen. No data were available for the hydrolysis product n-butanol, but UNEP determined that it has low cancer concern. Limited data were available for the other hydrolysis product acetic acid, which has a long history of safe use as a food ingredient. OncoLogic™ predictions on both hydrolysis products indicate low cancer concerns. Based on these results and information, ToxServices concluded that butyl acetate is not likely to be carcinogenic.

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

Butyl acetate was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity in several bacterial mutagenicity assays of butyl acetate and for clastogenicity in an *in vitro* chromosomal aberration assay of limited reliability on butyl acetate and a reliable *in vivo*

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micronucleus assay on n-butanol. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both gene mutations and chromosomal aberrations (CPA 2018b). Confidence in the score is high because it is based on reliable data for the target chemical and a strong 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, CAS #123-86-4, 2023a (Note: Several studies were reported in the REACH dossier with a reliability rating of 3 (not reliable) due to methodological deficiencies. Upon review of the studies, ToxServices concluded that the deficiencies were relatively minor, and that they were otherwise well-conducted and appropriate to include as part of the weight of evidence while taking the limitations into consideration. Studies that could not be assessed for reliability (reliability rating of 4) or that were assigned a rating of 3 due to use of an invalidated method were not included as several more reliable studies were available.)
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant bacterial reverse mutation test conducted according to methods similar to OECD Guideline 471. *S. typhimurium* tester strains TA 98, TA 100, TA 1535, TA 1537, TA 1538, and *E. coli* WP_2 *uvr* A were exposed to butyl acetate (99.6% purity) in DMSO at up to 5,000 µg/plate with and without metabolic activation. The positive controls were 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, N-ethyl-N'-nitro-N-nitrosoguanidine, 9-aminoacridine, 4-nitroquinoline-1-oxide, benzo(a)pyrene, and 2-aminoanthracene. There were no increases in revertants, and positive and vehicle controls were reported as valid. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions) as tests were conducted in duplicate instead of triplicate and no historical control data were reported.
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant Ames test conducted according to methods similar to OECD Guideline 471. *Salmonella typhimurium* tester strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 were exposed to butyl acetate (purity not specified) in ethanol at 4.4-8,826 µg/plate with and without metabolic activation. Sodium azide, 2-nitrofluorene, 9-aminoacridine, and 2-anthramine served as positive controls. Treatment was not associated with an increase in the mutation frequency in the presence or absence of metabolic activation, and the vehicle and positive controls were reported as valid. This study was reported in the REACH dossier with a reliability rating of 3 (not reliable), as one bacterial tester strain was not included (*S. typhimurium* TA 102 or *Escherichia coli* WP_2).
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant Ames test conducted according to methods similar to OECD Guideline 471. *S. typhimurium* tester strains TA 97, TA 98, TA 100, TA 1535, and TA 1537 were exposed to butyl acetate (greater than 99% purity) in dimethyl sulfoxide (DMSO) at up to 1,666 µg/plate (TA 98) or 3,333 µg/plate (other strains) without metabolic activation and up to 10,000 µg/plate (all strains) with metabolic activation. Slight cytotoxicity was observed at 3,333 µg/plate without metabolic activation. Sodium azide, 9-aminoacridine, 4-nitro-o-phenylenediamine, and 2-aminoanthracene served as positive controls. There were no increases in revertants at any dose in any strain, and positive and vehicle controls were reported as valid. This study was reported in the REACH dossier with a reliability rating of 3 (not reliable), as one bacterial tester strain was not included (*S. typhimurium* TA 102 or *E. coli* WP_2).
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant Ames test. *S. typhimurium* tester strains TA92, TA 94, TA 98, TA 100, TA 1535, and TA 1537 were exposed to butyl acetate (greater than 99% purity) in DMSO at concentrations up to 10

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mg/plate with and without metabolic activation in a preincubation assay, and there were no increases in revertants. No information regarding use of controls was provided. This study was reported in the REACH dossier with a reliability rating of 3 (not reliable), as one bacterial tester strain was not included (*S. typhimurium* TA 102 or *E. coli* WP_2).

- *In vitro*: Negative results for clastogenicity were obtained in a mammalian chromosome aberration test. Chinese hamster lung cells were exposed to butyl acetate (99% purity) in DMSO at up to 2 mg/mL without metabolic activation. Positive controls were not included in the study design. Treatment was not associated with an increase in the frequency of chromosome aberrations in the absence of metabolic activation. This study was reported in the REACH dossier with a reliability rating of 3 (not reliable), as cells were not tested with metabolic activation, positive control substances were not mentioned, only 100 metaphases/concentration were evaluated, and the maximum concentration tested is insufficient.
- *In vivo: Surrogate: n-Butanol (CAS #71-36-3):* n-Butanol (purity not reported) was negative in a GLP-compliant *in vivo* micronucleus assay that was conducted according to OECD Guideline 474. Male and female NMRI mice (5/sex/dose) were administered a single dose of 500, 1,000, or 2,000 mg/kg via gavage and were sacrificed after 24h (all doses) or 48h (control and high dose). Clinical signs of toxicity were observed at the mid and high doses. There were no increases in micronuclei in the bone marrow at any dose. Positive, negative, and vehicle controls were reported as valid. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).

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

Butyl acetate was assigned a score of Low for reproductive toxicity based on the lack of effects on reproductive parameters in a two-generation rat reproductive toxicity study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and are negative for reproductive toxicity (CPA 2018b). Confidence in the score is high because it is based on a well-conducted study of the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - A GLP-compliant two-generation reproduction toxicity study conducted in 2007 according to the current OECD Guideline 416 from 2001 was performed with Sprague-Dawley rats (30/sex/dose group) administered whole body inhalation exposures of butyl acetate (99.8% purity) vapor at 0, 750, 1,500, or 2,000 ppm (equivalent to 0, 3.56, 7.13, and 9.50 mg/L, respectively[10]) for 6 hours/day, 7 days/week. The parental animals were exposed for at least 70 consecutive days prior to mating. The F0 and F1 females were continuously exposed throughout mating and gestation through gestational day 20. No inhalation exposures were administered on gestational day 21 through lactation day 4, but oral gavage doses of 0, 1,125, 2,250, or 3,000 mg/kg/day were administered to the parental females on lactational days 1-4. Inhalation exposures were continued on lactation day 5 through the day prior to sacrifice. Inhalation exposures of the F1 generation began on post-natal day 22. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, estrous cyclicity, sperm parameters, and reproductive indices. The offspring were evaluated for viability indices, number and sex, stillbirths, live births, postnatal

[10] The equivalent concentration in mg/L was determined using the formula mg/L = (ppm x molecular weight)/24,450. The molecular weight of butyl acetate is 116.159 g/mol.

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mortality, presence of gross anomalies, body weights, and physical or behavioral abnormalities. No treatment-related effects were observed on the reproduction endpoints including estrous cycles, mating and fertility indices, number of days between pairing and coitus, spermatogenic endpoints and gestation length in the treated groups of the F0 or F1 generations. Treatment-related effects on the offspring of treated dams included decreased pup body weights in the mid and high concentration groups and delayed attainment of post-weaning developmental landmarks in the mid and high concentration groups, which were considered to be secondary to lower body weights. The survival of the F1 and F2 pups was not affected by treatment. The study authors identified a fertility NOAEC of 2,000 mg/kg/day based on the lack of treatment-related effects on reproductive parameters. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L
Butyl acetate was assigned a score of Low for developmental toxicity based on the lack of data supporting a specific developmental toxic effect by butyl acetate following in utero exposure to rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). Confidence in the score is high as it is based on measured data and supported by an authoritative opinion for the hydrolysis product 1-butanol.

- Authoritative and Screening Lists
  - *Authoritative:* MAK - Pregnancy Risk Group C.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - A GLP-compliant two-generation reproduction toxicity study conducted according to OECD Guideline 416 was performed as previously described with Sprague-Dawley rats (30/sex/dose group) administered whole body inhalation exposures of butyl acetate (99.8% purity) vapor at 0, 750, 1,500, or 2,000 ppm (equivalent to 0, 3.56, 7.13, and 9.50 mg/L, respectively[11]) for 6 hours/day, 7 days/week. The parental animals were exposed for at least 70 consecutive days prior to mating. The F0 and F1 females were continuously exposed throughout mating and gestation through gestational day 20. No inhalation exposures were administered on gestational day 21 through lactation day 4, but oral gavage doses of 0, 1,125, 2,250, or 3,000 mg/kg/day were administered to the parental females on lactational days 1-4. Inhalation exposures were continued on lactation day 5 through the day prior to sacrifice. Inhalation exposures of the F1 generation began on post-natal day 22. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, estrous cyclicity, sperm parameters, and reproductive indices. The offspring were evaluated for viability indices, number and sex, stillbirths, live births, postnatal mortality, presence of gross anomalies, body weights, and physical or behavioral abnormalities. Treatment in the mid and high concentration groups decreased maternal body weight gains during the premating period, gestation days 14-20, and gestation days 0-10 and decreased body weights for these same groups during the lactation period. Decreased body weight gains correlated with decreased maternal food consumption during the affected time periods. Treatment-related effects on the offspring of treated dams included decreased pup body weights in the mid and high concentration groups and delayed attainment of post-weaning developmental landmarks in the mid and high concentration groups, which were

[11] The equivalent concentration in mg/L was determined using the formula mg/L = (ppm x molecular weight)/24,450. The molecular weight of butyl acetate is 116.159 g/mol.

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considered to be secondary to lower body weights. The survival of the F1and F2 pups was not affected by treatment. The study authors identified a developmental toxicity NOAEC of 750 ppm based on decreases to pup body weights measured in the mid and high concentration groups. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

- A GLP-compliant prenatal developmental toxicity study conducted according to OECD Guideline 414 was performed with female Sprague-Dawley rats (37-43/concentration group) administered whole body inhalation exposures of butyl acetate (99.1% purity) vapor at 1,500 ppm (equivalent to 7.23 mg/L) for 7 hours/day. Four different groups were included in this study: the controls were administered filtered air (group 1), one treatment group was exposed from gestational day (GD) 7-16 (group 2), another group was exposed from GD 1-16 (group 3), and the last group was exposed for 5 days/week for 3 weeks prior to mating and then from GD 1-16 (group 4). All exposures were for 7 hours/day. The females were evaluated for clinical signs of toxicity, body weight, food consumption, and ovarian and uterine content. The fetuses were evaluated for external, visceral, skeletal, and head malformations. Food consumption was decreased during the first week in females exposed prior to gestation. At sacrifice, extra-gestational weights and liver weights decreased in exposed rats. Relative lung and kidney weights were increased in treated rats. Reproductive performance was not affected by treatment with butyl acetate. The body weights and crown-rump lengths of male and female fetuses were lower in the treatment groups relative to controls. The duration of exposure and period of gestation in which the treatment was administered did not affect the developmental outcomes. Reductions in placental weight were measured with treatment. Major malformations consisting of multiple facial defects, eye defects, diaphragmatic hernias, and generalized brain dysmorphology were observed in 2 fetuses in group 2, one fetus in group 3, and 3 fetuses in group 4. The generalized brain dysmorphology consisted of massive distortion of the external and internal architecture of the brain, inequalities in size of the olfactory lobes, and abnormalities in shape and size of the cerebral hemispheres. Hemorrhages were apparent around the exterior brain surfaces. The incidence of rib dysmorphology was increased in fetuses in groups treated during gestation. The incidence of reduced pelvic ossification was also measured in fetuses of groups 2 and 3. The study authors identified a maternal toxicity and developmental toxicity LOAEC of 7.23 mg/L, the only concentration tested, based on the changes to food consumption and body weight in the dams and reduced fetal size and increased frequency of malformations with treatment. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- In a second prenatal developmental toxicity study in Sprague-Dawley rats that was conducted in a manner similar to OECD Guideline 414, dams (19-21/dose) were exposed to 0, 500, 1,000, 2,000, or 3,000 ppm butyl acetate ($\geq$ 99.0% purity) vapor (equivalent to 0, 2.38, 4.75, 9.50, and 14.25 mg/L, respectively) via whole body inhalation for 6 hours/day on GD 6-20 and were sacrificed on GD 21. Dams were evaluated for clinical signs of toxicity, body weight and food consumption, and ovaries uterine content. Fetuses were evaluated for external, skeletal, and soft tissue malformations. Maternal weight gain was significantly reduced at 2,000 and 3,000 ppm, and food consumption was significantly decreased at 1,000 ppm and above. Fetal weights were slightly reduced at 2,000 and 3,000 ppm (by 3% and 12-13%, respectively; statistically significant at the high dose). Malformation was only observed in single fetuses in these dose groups. Authors reported a NOAEC and LOAEC of 2.38 and 4.75 mg/L, respectively, for maternal toxicity, and a NOAEC of 14.25 mg/L for developmental toxicity, as effects on fetal weight were measured only in the presence of

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maternal toxicity. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
    - A GLP-compliant prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414 (additional exposure during pre-gestation period) was performed with female New Zealand White rabbits (21-25/dose group) administered whole body inhalation exposures of butyl acetate (99.1% purity) vapor at 0 or 1,500 ppm (equivalent to 7.23 mg/L). Three groups of animals were exposed in the following manner: the control was provided filtered air, one treatment group received treatment on GD 7-19, and the second treatment group received treatment on GD 1-19. The animals were sacrificed and necropsied on GD 30. The dams were evaluated for clinical signs of toxicity, body weight, food consumption, and ovarian and uterine content. The fetuses were evaluated for the incidence of external, visceral, skeletal, and head malformations. No treatment-related effects were measured on body weight or reproductive performance for the dams and no evidence of developmental toxicity was observed in the fetuses. The study authors identified a maternal toxicity and developmental toxicity NOAEC of 7.23 mg/L, the only concentration tested, based on the lack of treatment-related effects observed. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- In summary, butyl acetate treatment reduced pup body weights in a two-generation reproduction toxicity study in rats at concentrations also reducing maternal body weights, induced developmental and maternal toxicity in a prenatal developmental toxicity test in rats at the only concentration tested (7.23 mg/L), and decreased fetal weights and maternal body weight gains and food consumption at 9.50 and 14.25 mg/L in a second prenatal developmental toxicity test in rats. In contrast, butyl acetate treatment did not produce evidence of developmental toxicity in a prenatal developmental toxicity test in rabbits exposed to 7.23 mg/L. Based on the observation that butyl acetate was not developmentally toxic to rabbits and only produced adverse developmental effects in rats at concentrations that also induced maternal toxicity, ToxServices considers it likely that butyl acetate produced the developmental toxicity via non-specific mechanisms secondary to maternal toxicity. This is in agreement with ECHA (2018)'s conclusion that the hydrolysis product 1-butanol is not a direct-acting developmental toxicant. Butyl acetate data were used as supportive evidence in ECHA (2018)'s evaluation. Therefore, ToxServices concludes that butyl acetate is not a specific developmental toxicant and is not classified for developmental toxicity under GHS criteria (UN 2021).

Endocrine Activity (E) Score (H, M, or L): DG
Butyl acetate was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint. Although there were negative results in *in vitro* mechanistic assays for four pathways (estrogen, androgen, thyroid, and steroidogenesis) and lack of adverse effects on parameters related to these pathways in developmental/reproductive and repeated dose toxicity studies following inhalation exposures, no mechanistic *in vivo* assays for the three receptors (estrogen, androgen, and thyroid) were identified. Thus, data are insufficient to assign a score of Low for this endpoint.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
    - Butyl acetate was active in 0/8 estrogen receptor (ER) agonism and antagonism assays [gene symbols: ESR1 – estrogen receptor α (6 assays); ESR2 – estrogen receptor β (2 assays)], 0/7 androgen receptor (AR) assays (gene symbol: AR), 0/2 steroidogenesis assays (aromatase inhibition), and 0/7 thyroid receptor assays (gene symbols: TRHR – thyrotropin releasing

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hormone receptor (2 assays); THRA – thyroid hormone receptor α and THRB – thyroid hormone receptor β (2 assays); TSHR – thyroid stimulating hormone receptor (3 assays)]) performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (note: only Tox21 data were considered) (Appendix H).
    - Butyl 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 I).
- VEGA 2021
    - Butyl acetate was predicted to be inactive in the Estrogen Receptor Relative Binding Affinity model (IRFMN) with strong reliability (Global AD Index = 0.865) (see Appendix J).
    - Butyl 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 = 0.98) (see Appendix J).
    - Butyl 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 = 0.983) (see Appendix J).
- DTU 2020
    - Butyl acetate, its predicted metabolites from *in vivo* rat metabolism simulator, and predicted metabolites from the rat liver S9 metabolism simulator, contain no structural alerts for estrogen receptor binding (Appendix K).
    - Butyl acetate was predicted to be negative and in domain for the model batteries for estrogen receptor α-binding with full and balanced training sets (comprised of negative and in domain results by Case Ultra, Leadscope and SciQSAR), and by the Leadscope model for estrogen receptor activation, CERAPP data (*in vitro*) (Appendix K).
    - Butyl acetate was predicted to be negative and in domain for the model battery for androgen receptor inhibition (human *in vitro*) (comprised of negative and in domain results by Case Ultra, Leadscope and SciQSAR), and by the Leadscope model for androgen receptor binding, CoMPARA data (*in vitro*), androgen receptor inhibition, CoMPARA data (*in vitro*), and androgen receptor activation, CoMPARA data (*in vitro*) (Appendix K).
    - Butyl acetate was predicted to be negative and in domain for TPO inhibition QSAR1 (Rat *in vitro*) and QSAR2 (Rat *in vitro*) (Appendix K).
- ECHA, CAS #123-86-4, 2023a
    - *Inhalation*: A GLP-compliant repeated exposure toxicity test conducted according to EPA OTS 798.2450 was performed with Sprague-Dawley rats (15/sex/concentration group) administered whole-body inhalation exposures of butyl acetate (at least 99.9% purity) vapor at 0, 500, 1,500, or 3,000 ppm (equivalent to 0, 2.4, 7.2, and 14.4 mg/L, respectively) for 6 hours/day, 5 days/week for 13 weeks. The equivalent concentrations for a 7-day/week exposure frequency were 0, 357, 1,071, and 2,142 mg/L, respectively. Organ weights and histopathological examination was performed on endocrine related organs such as pituitary gland, thymus, thyroid gland, parathyroid gland, ovaries, vagina, uterus, fallopian tubes, adrenals, prostate, testes, epididymides, and seminal vesicles. Mean relative testes weight was increased for mid and high concentration males and mean relative adrenal gland weight was increased for mid concentration females and high concentration males and females. No gross pathological lesions in endocrine related organs were observed in any treatment animals. The study authors identified a NOAEC of 2.4 mg/L based on epithelial necrosis

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observed at 7.2, and 14.4 mg/L. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

- *Inhalation*: In a previously described GLP-compliant two-generation reproductive toxicity study conducted in 2007 according to the current OECD Guideline 416, Sprague-Dawley rats (30/sex/dose group) were administered whole body inhalation exposures of butyl acetate (99.8% purity) vapor at 0, 750, 1,500, or 2,000 ppm (equivalent to 0, 3.56, 7.13, and 9.50 mg/L, respectively[12]) for 6 hours/day, 7 days/week. The parental animals were exposed for at least 70 consecutive days prior to mating. The F0 and F1 females were continuously exposed throughout mating and gestation through gestational day 20. No inhalation exposures were administered on gestational day 21 through lactation day 4, but gavage doses of 0, 1,125, 2,250, or 3,000 mg/kg/day were administered to the parental females on lactational days 1-4. Inhalation exposures were continued on lactation day 5 through the day prior to sacrifice. Inhalation exposures of the F1 generation began on post-natal day 22. The parental animals were evaluated for endocrine related parameters including estrous cyclicity, sperm parameters (count, motility, and morphology), and histopathology of adrenals, prostate, coagulating lands, seminal vesicles, liver, testis, epididymis, thyroid, uterus, oviducts, cervix, ovaries, vagina, oviducts, and pituitary. The offspring were evaluated for endocrine related parameters including preputial separation and other (unspecified) measures of sextual maturation. No treatment-related effects were observed on the reproduction endpoints including estrous cycles, mating and fertility indices, number of days between pairing and coitus, spermatogenic endpoints and gestation length in the treated groups of the F0 or F1 generations. The study authors identified a fertility NOAEC of 2,000 mg/kg/day based on the lack of treatment-related effects on reproductive parameters. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

Table 4: Endocrine Activity Summary Table

Endocrine pathways		***In silico* mechanistic data**	***In vitro* mechanistic data**	***In vivo* effects**
Estrogen	Agonism	Negative by ToxCast, VEGA, Danish (Q)SAR	Negative in EDSP assays	No effects on estrous cyclicity and sperm parameters (number and motility) and histopathology of testes, epididymides, prostate, coagulating lands, seminal vesicles, coagulating glands, pituitary, adrenal, pituitary, ovaries, oviduct, uterus, cervix, fallopian tubes, and vagina in repeated and/or reproductive toxicity studies.
	Antagonism	Negative by ToxCast, VEGA, Danish (Q)SAR	Negative in EDSP assays	
Androgen	Agonism	Negative by ToxCast, VEGA	Negative in EDSP assays	
	Antagonism	Negative by ToxCast, VEGA, Danish (Q)SAR	Negative in EDSP assays	
Steroidogenesis	Activity	No models available	Negative in EDSP assays	

[12] The equivalent concentration in mg/L was determined using the formula mg/L = (ppm x molecular weight)/24,450. The molecular weight of butyl acetate is 116.159 g/mol.

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Table 4: Endocrine Activity Summary Table				
Endocrine pathways		***In silico* mechanistic data**	***In vitro* mechanistic data**	***In vivo* effects**
Thyroid	Activity	Negative for TPO inhibition	Negative in EDSP assays	No histopathological effects on thyroid, liver, and parathyroid in reproductive and repeated dose toxicity studies.

- As summarized in Table 4, above, butyl acetate was reported to be inactive in several *in vitro* mechanistic assays for androgen receptor activity (binding, inhibition, and activation), estrogen receptor activation, thyroperoxidase (TPO) inhibition and steroidogenesis. Additional modeling indicated that butyl acetate was negative for the agonism and antagonism of estrogen and androgen receptors. One inhalational repeat dose toxicity study identified an increase in testes weight and adrenal gland weight; however, no corresponding gross pathological or histopathological lesions in endocrine related organs were observed in treated animals. A two-generation reproductive toxicity study did not report any adverse effects on endocrine related parameters (weight of thyroid, histopathology of thyroid, adrenals, prostate, testes, epididymides, seminal vesicles, and ovaries) following inhalation exposure. According to the EFSA Guidance for the identification of endocrine disruptors, these parameters cover the estrogen, androgen, thyroid, and steroidogenesis (EATS) modalities/pathways (EFSA 2018). However, no mechanistic *in vivo* assays for the three receptors (estrogen, androgen, and thyroid) were identified, and *in silico* predictions along with a lack of endocrine related organ effects in two *in vivo* inhalational studies is not sufficient to assign a score of Low for this endpoint. Therefore, due to insufficient data identified for this endpoint, a Data Gap was assigned.

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*

Butyl acetate was assigned a score of Low based on oral and dermal LD_{50} values greater than 10,000 mg/kg, and the weight of evidence on multiple acute inhalation toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when acute oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation LC_{50} values are > 20 mg/L for vapors (CPA 2018b). Confidence in the score was reduced as results of acute inhalation studies were mixed.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* New Zealand - GHS Category 4 acute inhalation toxicant.
    - Based on inhalation LC_{50}s of 1.36 - 2.38 mg/L in rats (CCID 2023).
- ECHA, CAS #123-86-4, 2023a
  - *Oral*: LD_{50} (Sprague-Dawley rat) = 10,760 mg/kg for females and 12,789 mg/kg for males (non-GLP-compliant, OECD Guideline 423) (reliability rating of 2, reliable with restrictions).
  - *Dermal*: LD_{50} (New Zealand White rabbit) > 14,112 mg/kg (non-GLP-compliant, OECD Guideline 402) (reliability rating of 2, reliable with restrictions).

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  - *Inhalation*: 4-hour nose/head only vapor LC_{50} (Wistar rat) > 21 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction).
  - *Inhalation:* 4-hour nose/head only aerosol LC_{50} (Wistar rat) > 23.4 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction).
  - *Inhalation*: 4-hour head only vapor LC_{50} (Wistar rat) > 4.9 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction).
  - *Inhalation*: 4-hour whole body vapor LC_{50} (Sprague Dawley rat) = 1.802 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction). The LC_{50} of 1.802 mg/L was only observed when the study authors used an atomizer to generate the vapor, but no deaths occurred at up to 30.6 mg/L when repeated using a heated evaporator to generate the vapor. Therefore, the reliability of this LC_{50} value is reduced.
  - *Inhalation:* 4-hour head only aerosol (vaporized completely at lower concentrations) LC_{50} (Wistar rat) = 0.74 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction).
  - *Inhalation:* 4-hour nose/head only LC_{50} (Wistar rat) > 21.1 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 1, reliable without restriction).
  - *Inhalation*: 4-hour whole body aerosol LC_{50} (Sprague Dawley rat) > 44.9 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 2, reliable with restrictions).
  - *Inhalation*: 4-hour whole body aerosol LC_{50} (Sprague Dawley rat) = 5.3 mg/L (GLP-compliant, OECD Guideline 403) (reliability rating of 2, reliable with restrictions). When repeated, no mortalities occurred using the target substance, even when tested at higher concentrations; therefore, the reliability of this LC_{50} value is reduced.
- ECHA, CAS #110-19-0, 2023a
  - *Inhalation:* 6-hour whole body vapor LC_{50} (Sprague Dawley rat) > 30 mg/L (GLP-compliant, EPA OTS 798.6050/EPA OTS 798.6200) (reliability rating of 2, reliable with restriction). Although this study was completed on the target substance, it was not included in the REACH dossier for butyl acetate.
- ECHA, CAS #71-36-3, 2023a
  - *Inhalation: Surrogate: n-Butanol (CAS #71-36-3):* 4-hour whole body vapor LC_{50} (Sprague Dawley rat) > 17.76 mg/L (non GLP-compliant, OECD Guideline 403) (reliability rating of 2, reliable with restriction).
  - *Inhalation: Surrogate: n-Butanol (CAS #71-36-3):* 7-hour whole body vapor LC_{50} (Sprague Dawley rat) > 21.48 mg/L (non GLP-compliant) (reliability rating of 2, reliable with restriction).
  - *Inhalation: Surrogate: n-Butanol (CAS #71-36-3):* 4-hour whole body vapor LC_{50} (Sprague Dawley rat) > 24 mg/L (non GLP-compliant, OECD Guideline 403) (reliability rating of 2, reliable with restriction).
- ECHA, CAS #64-19-7, 2023a
  - *Inhalation: Surrogate: Acetic acid (CAS #64-19-7):* 4-hour whole body vapor LC_{50} (Sprague Dawley rat) = 11.4 mg/L (non GLP-compliant, OECD Guideline 403) (reliability rating of 2, reliable with restriction).
- EC 2008
  - *Inhalation: Surrogate: Acetic acid (CAS #64-19-7):* LC_{50} = 14.0 mg/L after a 1 hour exposure in mice (no other study details were provided, non GLP-compliant).
  - *Inhalation: Surrogate: Acetic acid (CAS #64-19-7):* 4-hour LC_{50} = 40.0 mg/L (no other study details were provided, non GLP-compliant).
- SCOEL 2017

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  - The available published LC_{50} values for butyl acetate are "highly inconsistent." The reported values vary between 773 mg/m^3 to 43,478 mg/m^3 (equivalent to 0.773-43.478 mg/L). In some inhalational studies, the animals were exposed to vapor and in others, aerosolized butyl acetate. The LC_{50} values for studies conducted with aerosol were "not reproducible" and may have produced excess lethality resulting from oral uptake of aerosolized particles (from animals licking fur). All studies conducted according to OECD Guideline 403 had LC_{50} values of > 4,000 ppm [equivalent to > 19,000 mg/m^3 and > 19 mg/L using a conversion factor of 1 ppm = 4.75 mg/m^3 (NIOSH 2019)] in rats.
- UNEP 2009
  - Butyl acetate exhibits low acute toxicity across oral, dermal, and inhalational routes. Oral LD_{50} values range from 3,200 mg/kg in rabbits to 14,130 mg/kg in rats. Dermal LD_{50} values range from > 5,000 mg/kg to 17,600 mg/kg in rabbits. Inhalational LC_{50} values for vapor exposures were > 8,000 ppm (equivalent to 38,320 mg/m^3 or 38.3 mg/L) in well-controlled studies. Nose-only studies using atomizers to generate a mixture of aerosols and vapors resulted in inconsistencies and nonreplicable data with deaths below 8,000 ppm in some studies.
- Health Council of the Netherlands 2001
  - The acute inhalational LC_{50} values in rats show that exposures to nearly saturated atmospheres generated by evaporation did not result in mortality. The data from aerosols generated by atomizers are "highly inconsistent" ranging from 740 mg/m^3 (160 ppm or 0.74 mg/L) to above 42,930 mg/m^3 (> 9,312 ppm or > 42.9 mg/L). Across six follow-up studies conducted to replicate the data, to differentiate between vapors and aerosols, and to investigate the role of small particles/humidity, the LC_{50} values were statistically significantly different within and between the laboratories. Therefore, the validity of the studies reporting low LC_{50} values is reduced.
- WHO 2005
  - Data on the acute inhalational toxicity of butyl acetate are "highly inconsistent." LC_{50} values range from 740 to 45,000 mg/m^3 (0.74 mg/L to 45 mg/L) with an unknown explanation for the inconsistencies. The results of a well-designed study indicate that butyl acetate has low inhalational toxicity following a 4-hour exposure where no deaths occurred up to approximately 45,000 mg/m^3 (45 mg/L). In addition, butyl acetate has low oral and dermal acute toxicity; therefore, the weight of evidence suggests low overall acute toxicity.
- Several of the acute inhalation toxicity studies have LC_{50} values of greater than 20 mg/L while one has an LC_{50} of 0.74 mg/L. Three of the acute inhalation toxicity studies in Wistar rats were performed with nose and head-only inhalation exposures while the one with the LC_{50} of 0.74 mg/L was performed with head-only inhalation exposures. It is not clear why the LC_{50} values reported by different GLP-compliant studies in the same species are so variable, with values corresponding to scores ranging from Low to Very High. Authors of the REACH dossier acknowledged the variation in reported values. They noted that the lowest LC_{50} of 0.74 mg/L was reported from a study that did not report the purity of the test item and the exposure concentrations were not analytically verified. Therefore, Union Carbide Corporation and BASF conducted further studies to confirm the finding. However, these efforts produced inconsistent results as well, and there did not appear to be any difference between whole-body and head-only exposure. In addition, after taking into considering concentrations tolerated in repeated dose toxicity studies (2.4-14.4 mg/L in an EPA 789.2450 study), the authors of the REACH dossier determined the LC_{50} values between 0.74 and 5.3 mg/L to be outliers and did not classify butyl acetate for acute inhalation toxicity under GHS (ECHA, CAS #123-86-4, 2023a). Further review of the hydrolysis products, n-butanol and acetic acid, resulted in insufficient evidence to resolve the inconsistencies. Concordant with the conclusions of the REACH

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dossier authors, additional reviews conducted by authoritative bodies including SCOEL, UNEP, Health Council of the Netherlands, and WHO, all discussed the inconsistencies identified in the acute inhalational toxicity data and conclude that the most reliable studies indicate low toxicity overall. Therefore, ToxServices concludes that butyl acetate is not likely to be acutely toxic via the oral, dermal, and inhalation exposure routes.

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

Butyl acetate was assigned a score of Moderate for systemic toxicity (single dose) based on respiratory irritation observed in inhalation studies that classified it to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation (CPA 2018b). Confidence in the score was reduced due to inconsistencies among inhalation studies.

- 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 (respiratory tract irritation) (NITE 2014).
- ECHA, CAS #123-86-4, 2023a
  - *Oral*: In the oral acute toxicity study that identified LD_{50} values of 10,760-12,789 in rats, sluggishness and prostration were observed at all doses. No treatment-related effects were measured on body weight. At necropsy, no dose-related effects were observed in those animals that survived to the scheduled sacrifice but those that died during the course of the observation period exhibited gas-filled stomachs that were tan to red and livers that were pale tan in color on the ventral surface. The lowest dose tested in this study was 9,966 mg/kg. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
  - *Dermal*: In the acute dermal toxicity study that identified an LD_{50} of greater than 14, 112 mg/kg in rabbits, the clinical signs of toxicity were limited to one case each of diarrhea, emaciation, ecchymosis, erythema, edema, necrosis, fissuring, desquamation, scabs, ulceration, and/or alopecia in males and females. Body weights of females were slightly decreased during the observation period. In males and females, the lungs were a light pink to dark red color at necropsy. The only dose tested was 14,112 mg/kg. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
  - *Inhalation*: In the acute inhalation toxicity study that identified an LC_{50} of greater than 21 mg/L, accelerated respiration, reddish nasal discharge, salivation, and an absence of a pain reflex was observed during the exposure period. Following the exposure, nasal edges with reddish crusts (positive for blood) and accelerated respiration were observed up to day 4 when no abnormalities were observed for the remainder of the observation period. No gross pathological findings were observed with treatment. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
  - *Inhalation*: In the acute inhalation toxicity study that identified an LC_{50} of greater than 23.4 mg/L, trembling of the head, salivation, nasal discharge, reduced pain reflex, and aqueous discharge of the eyes were observed during the exposure at 23.4 mg/L. After the exposure, slightly accelerated respiration and nasal edges positive for blood were observed at 23.4 mg/L. No clinical signs of toxicity were observed at 1.97 mg/L during the exposure, but accelerated respiration was observed following the exposure. No gross pathological findings of note were observed at 1.97 mg/L. Focal atelectasis in all lobes of the lung were observed

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in 1/5 males and 2/5 females at 23.4 mg/L. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
  - *Inhalation*: In the acute inhalation toxicity study that identified an LC_{50} of 0.74 mg/L, lethargy hyperpnea, ataxia, and tremors were observed. Bloody noses and/or mouths and hyperemic lungs were observed in animals of all treatment groups following macroscopic examination. Vesicular emphysema of the lungs was observed in all animals. Dose levels tested were 0.8, 2.2 and 5.2 mg/L (analytical; vaporized completely at lower concentrations). This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
  - *Inhalation*: In the acute inhalation toxicity study that identified an LC_{50} of greater than 21.1 mg/L, no abnormalities were observed during the exposure or following the exposure. No pathological findings of note were observed at necropsy. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- The doses for the oral and dermal acute toxicity studies are well above the guidance values of 2,000 mg/kg for those exposure routes. Three of the four acute inhalation toxicity studies presented above have LC_{50} values of greater than 20 mg/L while the fourth has an LC_{50} of 0.74 mg/L. In the study that reported the lowest LC_{50}, vesicular emphysema of the lung was detected in all animals even at the lowest concentration of 0.8 mg/L, and this effect may be regarded as more than transient in nature. However, as previously discussed, this study is of questionable reliability. Therefore, ToxServices did not score this endpoint based on that study. In other inhalation studies, no significant systemic toxicity was detected at concentrations of 20 mg/L or less, but reversible signs of respiratory irritation were noted. These effects warrant classification to GHS Category 3 for specific target organ toxicity following single exposures due to respiratory irritation.

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

Butyl acetate was assigned a score of Low for systemic toxicity (repeated dose) based on an inhalation NOAEC of 2.4 mg/L in a subchronic toxicity study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when vapor NOAECs are greater than 1.0 mg/L (CPA 2018b). Confidence in the score was high because it was based on a well-conducted study on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - *Inhalation*: A GLP-compliant repeated exposure toxicity test conducted according to EPA OTS 798.2450 was performed with Sprague-Dawley rats (15/sex/concentration group) administered whole-body inhalation exposures of butyl acetate (at least 99.9% purity) vapor at 0, 500, 1,500, or 3,000 ppm (equivalent to 0, 2.4, 7.2, and 14.4 mg/L, respectively) for 6 hours/day, 5 days/week for 13 weeks. The equivalent concentrations for a 7-day/week exposure frequency were 0, 357, 1,071, and 2,142 mg/L, respectively. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, gross pathology, and histopathology. Decreased activity was observed in the mid and high concentration groups. High dose animals also exhibited decreased alertness and slower response to stimuli. Body weights and food consumption were significantly reduced in the mid and high concentration groups. No significant treatment-related effects were measured on hematology or clinical chemistry parameters. Mean absolute liver and spleen weights were significantly decreased in mid and high concentration males and females and

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decreased mean absolute kidney weights were measured in mid concentration females and high concentration males and females. Relative spleen weights were decreased for high concentration males. Mean relative testes weight was increased for mid and high concentration males and mean relative lung weight was increased for high concentration males. Mean relative adrenal gland weight was increased for mid concentration females and high concentration males and females. No gross pathological lesions were observed in males with treatment. Two high concentration females exhibited minimal hemorrhage of the glandular stomach and white discoloration in the non-glandular stomach. All high concentration males and females and 4/10 males and 6/10 females in the mid concentration group exhibited necrosis of the olfactory epithelium that was mild for the mid concentration group and mild to moderate for the high concentration group. The study authors identified a NOAEC of 2.4 mg/L based on epithelial necrosis observed at 7.2, and 14.4 mg/L. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

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

Butyl acetate was assigned a score of Moderate for neurotoxicity (single dose) based on data indicating a transient narcotic effect. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when the available data indicate that GHS Category 3 classification is warranted (CPA 2018b). Confidence in the score was high because it is based on reliable experimental data and an authoritative list H336, which translates to a score of Low to Moderate.

- Authoritative and Screening Lists
  - *Authoritative:* EU - GHS (H-Statements) - H336 - May cause drowsiness or dizziness.
  - *Screening:* Japan - GHS - Specific target organs/systemic toxicity following single exposure - Category 3 (central nervous system) (NITE 2014).
  - *Screening:* Malaysia - GHS - H336 - May cause drowsiness or dizziness.
  - *Screening:* Australia - GHS - H336 - May cause drowsiness or dizziness.
- ECHA, CAS #123-86-4, 2023a
  - A GLP-compliant neurotoxicity screening battery conducted according to EPA OTS 798.6050 and EPA OTS 798.6200 was performed with Sprague-Dawley rats (10/sex/concentration group) administered single inhalation exposures of butyl acetate (99.9% purity) vapor at 0, 7.53, 15.43, or 30.21 mg/L for males and 0, 7.48, 15.08, or 30.41 mg/L for females for 6 hours. The animals were evaluated for clinical signs of toxicity, body weight, motor activity, gross pathology, and histopathology, and were assessed in a functional observational battery (FOB). During the exposure, males and females in the low and mid concentration groups exhibited minimal to minor hypoactivity and males and females in the high concentration group exhibited minor to moderate hypoactivity. A decrease in the mean total motor activity and total number of ambulations was measured in the mid and high concentration males and females 30 minutes after the exposure but not on days 1, 7, or 14. On day 0, the hair coat appeared slightly unkempt in the high concentration males and females. No gross lesions were observed at necropsy. The study authors identified a NOAEC of 7.53 mg/L based on the transient decrease in motor activity observed in the mid and high concentration groups. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- Based on the weight of evidence, a score of Moderate was assigned. The GHS Hazard Statement H336 corresponds to a Moderate to High score, and the GHS Category 3 classification in Japan, Australia and Malaysia corresponds to a Moderate. ToxServices considers Category 3 classification to be appropriate and assigned a Moderate score for this endpoint.

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Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Butyl acetate was assigned a score of Low for neurotoxicity (repeated dose) based on a NOEC of 2.41 mg/L in a neurotoxicity screening battery in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when no evidence of neurotoxicity is observed below the guidance value of 1.0 mg/L vapor (CPA 2018b). Confidence in the score was high because it was based on a well conducted study on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - A GLP-compliant neurotoxicity screening battery conducted according to EPA OTS 798.6050 was performed with Sprague-Dawley rats (20-25 males/concentration, 10-15 females/concentration) administered inhalation exposures of butyl acetate (at least 99.9% purity) vapor at 0, 500, 1,500, or 3,000 ppm (equivalent to 0, 2.41, 7.23, and 14.46 mg/L, respectively) for 6 hours/day, 5 days/week for 13 weeks. The animals were evaluated for clinical signs of toxicity, body weight, motor activity, gross pathology, and neuropathology, and were assessed in a functional observation battery (FOB). Reduced activity levels in the mid and high concentrations were observed during the exposures but there was no evidence of a cumulative effect on the magnitude of activity reduction as the study progressed. No evidence of neurotoxicity was observed in the FOB and no treatment-related effects were detected on gross pathology or neuropathology. The study authors identified a NOAEC of 2.41 mg/L based on the decreased activity observed in the mid and high concentration groups during the exposures. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *L*
Butyl acetate was assigned a score of Low for skin sensitization based on negative experimental results supported by modeling. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and are negative, and the chemical is not present on authoritative or screening lists (CPA 2018b). Confidence in the score was reduced due to the low reliability of the available experimental studies and partial reliance on modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a (Three skin sensitization studies are available in the REACH Dossier but they all have been assigned Klimisch scores of 3 ("not reliable") based on insufficient documentation. Therefore, ToxServices did not consider these studies alone to be sufficient to assign the hazard classification but summarized them and included them in the weight of evidence.)
  - A Buehler test conducted in a manner similar to OECD Guideline 406 was performed with male and female Hartley guinea pigs (10/dose group, sex distribution not specified) induced via topical applications of an unspecified amount of butyl acetate (at least 98% purity) under occlusive dressing for an unspecified duration. No information on the challenge dose was provided other than it was applied topically under occlusive dressing. No positive reactions were observed following challenge with butyl acetate.
  - A mouse ear swelling test (MEST) was performed with female CF-1 mice (10-15/dose group, 5-10 in control group) induced with 100 µL 100% butyl acetate (at least 98% purity) applied to the skin without covering (durations of exposures not specified). The challenge

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dose was applied 7 days later with 20 µL of 50% butyl acetate in 70% ethanol without covering. The ear thickness was evaluated at 24 and 48 hours. No positive reactions were observed following challenge with butyl acetate.
    - A guinea pig maximization test conducted in a manner similar to OECD Guideline 406 was performed with Hartley guinea pigs (15/dose group, 6 in control group, sex not specified) induced with intradermal injections of 50% butyl acetate (at least 98% purity) in ethanol on day 0 and topical applications of 100% butyl acetate under occlusive dressing for 48 hours on day 7. The challenge dose was applied on day 21 as a topical application of 100% butyl acetate under occlusive dressing for 24 hours. The dermal reactions were scored 24 hours after the challenge and the animals were re-challenged on day 28. No positive reactions were observed following challenge with butyl acetate.
- Payne and Walsh 1994
    - Butyl acetate is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh (1994) (see Appendix L).
- OECD 2022
    - Butyl acetate is predicted to not be a skin sensitizer using the OECD Toolbox model using the read-across methodology (see Appendix M).
- Toxtree 2018
    - Butyl acetate is predicted to not be a skin sensitizer using the Toxtree model using decision tree methodology. This chemical has not been identified as a substrate for any of the 5 electrophilic mechanisms known to produce a skin sensitization reaction (see Appendix N).
- VEGA 2021
    - Butyl acetate is predicted to be a skin sensitizer using the VEGA CAESAR 2.1.6 model with high confidence, based on a global AD index of 0.908, indicating that the prediction is reliable (see Appendix O).
    - Butyl acetate is predicted to be a skin non-sensitizer using the VEGA IRFMN/JRC 1.0.0 model with moderate confidence, based on a global AD index of 0.786, indicating that the prediction is reliable (see Appendix O).
- LabMol 2020
    - Butyl acetate is predicted to be a sensitizer in the DPRA and h-CLAT prediction models (see Appendix P).
    - Butyl acetate is predicted to be a non-sensitizer in the KeratinoSens, LLNA, and HRIPT/HMT prediction models (see Appendix P).
    - The overall Bayesian Outcome predicts that butyl acetate is a non-sensitizer with high confidence (see Appendix P).
- As Klimisch scores of 3 were assigned to the skin sensitization studies, ToxServices performed modeling to determine the potential of butyl acetate to be a skin sensitizer. Four of the five models, OECD QSAR toolbox, structural alerts, VEGA IRFMN/JRC model and Toxtree, predicted that butyl acetate is not a skin sensitizer. The fourth model, VEGA CAESAR, predicted that butyl acetate is a skin sensitizer with high confidence; however, ToxServices noted that the read-across chemicals used in the prediction were not structurally-similar acetates. The three experimental studies available were given Klimisch score of 3 due to insufficient documentation rather than method deficiencies. Therefore, ToxServices did not discount their negative results but used them as supporting evidence for a lack of sensitization potential. Considering the weight of evidence, ToxServices concluded that butyl acetate has a low potential to be a skin sensitizer.

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Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Butyl acetate was assigned a score of Low for respiratory sensitization based on a lack of skin sensitization potential, based on ECHA's guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available, and they are not classified under GHS (CPA 2018b). Confidence in the score was low as this evaluation did not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2022
  - Butyl acetate does not contain any structural alerts for respiratory sensitization (see Appendix Q).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As butyl 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 butyl acetate, and as butyl acetate does not contain any structural alerts for respiratory sensitization (OECD 2022), butyl acetate is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
Butyl acetate was assigned a score of Low for skin irritation/corrosivity based on negative results in a reliable *in vivo* dermal irritation test. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when negative data and no GHS classification are available (CPA 2018b). The confidence in the score was low due to the presence of positive studies with limited documentation.

- 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, CAS #123-86-4, 2023a
  - A non-GLP-compliant dermal irritation test conducted as a Draize test was performed with New Zealand White rabbits (6 animals total, sex not specified) administered topical applications of 0.5 mL butyl acetate to intact or abraded skin under occlusive dressing for 24 hours. An observation period of 72 hours followed the exposure period. One animal administered butyl acetate to abraded skin exhibited barely perceptible erythema at 24 hours and another with application to intact skin exhibited barely perceptible erythema at 72 hours. No erythema was observed in the other animals and no edema was observed in any of the animals following treatment. The study authors concluded that butyl acetate was not irritating to skin under the tested conditions. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
- OECD 2008 (no Klimisch scores assigned in the source document for the studies summarized below)
  - A non-GLP-compliant dermal irritation test was conducted with 5 rabbits (unspecified sex and species) exposed to 0.01 mL of butyl acetate undiluted (purity unreported) to clipped

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skin for 24 hours under open conditions. The mean overall irritation score was 3. Moderate irritation was observed.
  - A non-GLP-compliant dermal irritation test was conducted with 4 male rabbits (unspecified species) exposed to doses of 1.25, 5, or 10 mL/kg (purity unreported) to clipped skin for 24 hours under occlusive conditions. Signs of irritation, including erythema, scabs, and extensive desquamation were observed. No additional study details were provided.
  - A non-GLP-compliant dermal irritation test was conducted with 6 rabbits (unspecified sex and species) exposed to a 0.5 mL dose (purity unreported) to clipped skin for 24 hours under occlusive conditions. No signs of irritation were observed.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): L
Butyl acetate was assigned a score of Low for eye irritation/corrosivity based on results in an ocular irritation study in rabbits demonstrating that it did not meet criteria for classification under GHS. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and indicate that the chemical does not warrant GHS classification, and the chemical is not present on authoritative or screening lists (CPA 2018b). Confidence in the score was high because it was based on experimental data from a well-conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* New Zealand - GHS Category 2 eye irritant.
  - *Screening:* Japan - GHS - Serious eye damage / eye irritation - Category 2B.
- ECHA, CAS #123-86-4, 2023a
  - A GLP-compliant ocular irritation test conducted according to OECD Guideline 405 was performed with New Zealand white rabbits (4 total, sex not specified) administered ocular instillations of 0.1 mL undiluted butyl acetate (99% purity) without washing. The animals were observed for up to 14 days. The eyes were evaluated at 24, 48, and 72 hours after instillation. The mean corneal score was 0.165/4 (individual scores of 0,0.33, 0, and 0.33), the mean iris score was 0/2, the mean conjunctival score was 1/3 (all individual scores were 1), and the mean chemosis score was 0.2475/4 (individual scores of 0, 0.33, 0.33, and 0.33). The study authors concluded that butyl acetate was not irritating to the eyes under the tested conditions. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
    - ToxServices did not classify butyl acetate as an ocular irritant according to GHS guidelines. GHS criteria (UN 2021) classify chemicals as ocular irritants if they produce corneal opacity scores of ≥ 1, iritis scores of ≥ 1, conjunctival redness scores of ≥ 2, and/or chemosis scores of ≥ 2 in at least 2 of 3 animals tested at 24, 48, and 72 hours after instillation.
- ECB 2000
  - Eleven eye irritation studies including 10 rabbit studies and 1 human study were found. Most of the studies were not GLP-compliant or did not identify GLP status. The results vary from not irritating to highly irritating. The two studies that reported it as highly irritating were conducted decades ago and the results were interpreted as being not irritating according to the EC classification criteria. Only one rabbit study was GLP compliant. However, only limited results were reported. When applied at 0.1 mL (concentration not specified), there were no corneal injury in 6 eyes, iritis in 4 eyes and minor to moderate conjunctival irritation in 6 eyes, which were reversible in 48 hours. When applied at 0.005 mL, there were no corneal injury in 6 eyes, iritis in 2 eyes, and minor to moderate conjunctival irritation in 6

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eyes which were reversible in 48 hours. The study results were interpreted as not irritating by the authors of the IUCLID dataset.

- Based on the weight of evidence, a score of Low was assigned. Although Japan and New Zealand classified butyl acetate as highly irritating, the limited data provided from these sources did not support the classifications. The classification in Japan was based on maximum scores of 0 for the cornea and iris and 1 for conjunctival redness and chemosis, and the classification in New Zealand was based on a report of irritation in the IUCLID dataset. ToxServices' evaluation of the REACH dossier data and IUCLID data suggest that butyl acetate is not likely to be an eye irritant according to GHS criteria.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): M
Butyl acetate was assigned a score of Moderate for acute aquatic toxicity based on L/EC_{50} values of 18 mg/L in fish and 44 mg/L in daphnia. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity values are between 10 and 100 mg/L (CPA 2018b). Confidence in the score was high because it was based on reliable experimental data for three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Japan - GHS - Hazardous to the aquatic environment (acute) - Category 3.
    - Based on a 96-hour LC_{50} of 18 mg/L in fathead minnow (*Pimephales promelas*) (NITE 2014).
- ECHA, CAS #123-86-4, 2023a (only key studies were described below)
  - 96-hour LC_{50} (*P. promelas*, fathead minnow) = 18 mg/L (OECD Guideline 203) (reliability rating of 2, reliable with restrictions).
  - 48-hour mobility EC_{50} (*Daphnia* species) = 44 mg/L (non-GLP-compliant) (reliability rating of 2, reliable with restrictions).
  - *Surrogate: Isobutyl acetate (CAS #110-19-0)*: 72-hour EC_{50} (*Pseudokirchneriella subcapitata*, green algae) = 246 mg/L (biomass), 397 mg/L (growth rate) (both measured) (GLP-compliant, OECD Guideline 201) (reliability rating of 2, reliable with restrictions).
- OECD 2008 (only reliable studies that were not previously summarized and have reliability scores of 1 or 2 were included below)
  - 96-hour LC_{50} (*Lepomis macrochirus,* bluegill) = 100 mg/L
  - 96-hour LC_{50} (*Leuciscus idus*, ide) = 62 mg/L
  - 96-hour LC_{50} (*Menidia beryllina*, inland silverside) = 185 mg/L
  - 48-hour EC_{50} (*A. salina*, aquatic invertebrate) = 32 mg/L

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
Butyl acetate was assigned a score of Moderate for chronic aquatic toxicity based on a modeled ChV of 1.48 mg/L in fish. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when the most conservative chronic aquatic toxicity values are ≥ 1 mg/L and less than 10 mg/L (CPA 2018b). Confidence in the score was reduced as it was based on modeled data.

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

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- ECHA, CAS #123-86-4, 2023a
  - *Surrogate: Isobutyl acetate (CAS #110-19-0)*: 21-day reproduction NOEC (*D. magna*) = 23 mg/L (non-GLP-compliant, OECD Guideline 211) (reliability rating of 2, reliable with restrictions).
  - *Surrogate: Isobutyl acetate (CAS #110-19-0)*: 72-hour NOEC (*P. subcapitata*, green algae) = 105 mg/L (biomass), 196 mg/L (growth rate) (both measured) (GLP-compliant, OECD Guideline 201) (reliability rating of 2, reliable with restrictions).
- U.S. EPA 2017a
  - Butyl acetate is designated to the esters and neutral organics ECOSAR chemical classes (see Appendix R). The most conservative predicted chronic values (ChV) are 1.48 mg/L in fish, 28.83 mg/L in daphnia, and 4.29 mg/L in green algae.
- Based on the weight of evidence, a score of Moderate was assigned. Chronic aquatic toxicity data are available for algae and daphnia (for a surrogate). The NOEC values for the surrogate isobutyl acetate are > 10 mg/L, indicating a low order of toxicity. However, acute aquatic toxicity data indicate that fish are more sensitive than both algae and daphnia. In addition, modeling predicts a ChV of 1.48 mg/L for fish, which corresponds to a Moderate score for this endpoint.

Environmental Fate (Fate)

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

Butyl acetate was assigned a score of Very Low for persistence based on meeting the 10-day window in a ready biodegradability test. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when the chemical meets the 10-day window for chemicals partitioning primarily to soil (CPA 2018b). Confidence in the score was high because it was based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC - CEPA DSL – Persistent.
    - Based on a measured hydrolysis half-life of 1,131.5 days and a predicted ozone reaction half-life of 999 days (OECD 2023).
- ECHA, CAS #123-86-4, 2023a
  - A ready biodegradability test conducted according to OECD Guideline 301 D (Closed Bottle test) was performed with a course-filtered mixture of domestic treatment plant effluents and rich soil microorganisms or commercial Polyseed® BOD seed exposed to butyl acetate (purity not specified) at 0.1-10 mg/L for 28 days. The level of degradation was 80% after 5 days, 83% after 15 days, and 83% after 28 days. Butyl acetate was considered to be readily biodegradable in this test and it met the 10-day biodegradation window. This study was reported in the REACH dossier with a reliability rating of 2 (reliable with restrictions).
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that butyl acetate is expected to be readily biodegradable (see Appendix S). Fugacity modeling (MCI method) predicts 50.9% will partition to soil with a half-life of 416 hours (17 days), 35.8% will partition to water with a half-life of 208 hours (8.7 days), and 13.3% will partition to air with a half-life of 52.4 hours (2.2 days).
- Based on the weight of evidence, a score of Very Low was assigned. While butyl acetate is classified as persistent in the Canadian DSL based on a measured hydrolysis half-life and predicted ozone reaction half-life, EPI Suite™ predicts butyl acetate to mainly partition to soil and water, experimental data from a reliable study demonstrate that butyl acetate is readily biodegradable, and this result is supported by modeling.

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Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Butyl acetate was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 2.3. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when measured log K_{ow} values are no greater than 4 (CPA 2018b). Confidence in the score was high because it was based on experimental partition coefficient data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - Butyl acetate had a measured log K_{ow} value of 2.3 at 25°C in a GLP-compliant OECD 117 test. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- U.S. EPA 2017b
  - BCFBAF predicted a BCF of 15.29 based on a measured log K_{ow} of 2.3 using the regression-based method. Taking metabolism into consideration, the Arnot-Gobas model predicted a BCF of 9.548 for the upper trophic level (see Appendix S).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Butyl acetate was assigned a score of Low for reactivity based on safety data sheets stating that it is not reactive and, on a structure indicating that it is not an organic peroxide, does not contain reactive groups associated with self-reactive substances, is not an organometallic substance that may produce flammable gases on contact with water, and does not contain alerts for explosivity. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2018b). Confidence in the score was reduced due to the lack of experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #123-86-4, 2023a
  - Butyl acetate does not contain structural groups associated with explosive properties.
- ThermoFisher Scientific 2021
  - A material safety data sheet for butyl acetate states that it has an instability rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water").
- UN 2021
  - Based on examination of the structure, ToxServices determined that butyl acetate is not an organic peroxide, does not contain reactive groups associated with self-reactive substances, and is not an organometallic substance that may produce flammable gases on contact with water (Appendix T).
  - Based on examination of the structure, ToxServices determined that butyl acetate does not have any alerts for explosivity (Appendix T).

Flammability (F) Score (vH, H, M, or L): M
Butyl acetate was assigned a score of Moderate for flammability based on a flash point of 27°C and presence on an authoritative list. GreenScreen® criteria classify chemicals as a Moderate hazard for

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flammability when experimental data indicate that the chemical warrants GHS Category 3 classification and the chemical is associated with H226 (CPA 2018b). Confidence in the score was high because it was based on experimental data and an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:* EU – GHS (H-Statements) – H226 – Flammable liquid and vapour.
  - *Screening:* Québec CSST – WHMIS 1988 – Class B2 – Flammable liquids.
  - *Other:* New Zealand – GHS Category 2 flammable liquid.
    - Based on a flash point of 22°C in a closed cup test and a boiling point of 124°C (CCID 2023).
  - *Other:* Japan – GHS – Flammable liquids – Category 2.
    - Based on a flash point of 22°C in a closed cup test and a boiling point of 126°C (NITE 2014).
  - *Other:* Malaysia – GHS – H226 – Flammable liquid and vapour.
  - *Other:* Australia – GHS – H226 – Flammable liquid and vapour.
- ECHA, CAS #123-86-4, 2023a
  - Butyl acetate has a flash point of 27°C at 1,013 hPa in a GLP-compliant EU Method A.9 closed cup test. This study was reported in the REACH dossier with a reliability rating of 1 (reliable without restriction).
- ToxServices classified butyl acetate as a GHS Category 3 flammable liquid based on the flash point of 27°C. GHS Category 3 flammable liquids have flash points of ≥ 23°C and ≤ 60°C (UN 2021).

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Use of New Approach Methodologies (NAMs)[13] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation, and *in vitro* assays for mutagenicity and endocrine activity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 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 butyl acetate's NAMs dataset include no or lack of adequate experimental or human data for carcinogenicity, endocrine activity, skin sensitization, respiratory sensitization, and chronic aquatic toxicity. Butyl acetate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism, their focusing on one or only a few types of genotoxicity events, the lack of applicability domains for ToxCast models for endocrine activity and OECD Toolbox for respiratory sensitization, limited confidence in VEGA predictions due to low ADIs and concordance indices, the limitation of OECD Toolbox in not accounting for non-immunologic mechanisms of respiratory sensitization, and the questionable reliability of chronic aquatic toxicity predictions by ECOSAR. Some of butyl 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**: No *in vivo* experimental data are available. **Endocrine activity:** No *in vivo* experimental data are available. **Skin sensitization**: No high quality experimental data are available on the target substance. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Chronic aquatic toxicity:** No experimental data are available for two trophic levels. Some data are available on the isobutyl acetate surrogate.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (Sas), and no applicability domain can be defined (Toxtree 2018). Three models in VEGA produced non-reliable (i.e., Global AD index

[13] 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).

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	<0.7) predictions, and the read-across chemicals used in these models (CAESAR, ISS, and IRFMN/ISSCAN-CGX) have additional functional groups than the target compound, limiting the confidence of the prediction from these models. **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[14]. The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[15]. **Endocrine activity:** ToxCast models don't define applicability domain; the *in vivo* relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Skin sensitization:** The *in silico* and *in vitro* assays evaluating key events in the skin sensitization adverse outcome pathway (AOP) don't typically include metabolism or abiotic transformation to address chemicals that are pro-haptens or pre-haptens, respectively. Further, each test has their applicable domain such as limitations in test substance solubility or log $K_{ow.}$[16] **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. **Chronic aquatic toxicity**: The reliability of predicted chronic aquatic toxicity is questionable as the predicted acute values are more conservative than the measured acute values.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/ OncoLogic™
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/ *in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays,

[14] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[15] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
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		In silico modeling: VEGA/Danish QSAR/ToxCast
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	Y	*In silico* modeling: VEGA/Payne and Walsh (1994) structural alerts/Toxtree/OECD Toolbox/LabMol
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD Guideline 301D Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

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APPENDIX B: Results of Automated GreenScreen® Score Calculation for Butyl Acetate (CAS #123-86-4)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Butyl acetate	123-86-4	*L*	L	L	L	DG	*L*	*M*	L	M	L	*L*	*L*	*L*	L	M	*M*	vL	vL	*L*	M

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	No
3	No	Yes	Yes	Yes			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Butyl acetate	3

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Butyl acetate	3

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												
3	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		3
4												

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APPENDIX C: Pharos Output for Butyl Acetate (CAS #123-86-4)

Pharos | Search... | Comparisons | Common Products | Discussions | Account

123-86-4
BUTYL ACETATE
ALSO CALLED: 1-acetoxybutane, 1-Butanol, acetate, 1-Butyl acetate, 1-Butylacetate, 204-658-1, BJZ, Acetate de but...
View all synonyms (50)

Share Profile

Hazards | Properties | Functional Uses | Process Chemistry | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

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

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GS SCORE	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Developmental Toxicity incl. developmental neurotoxicity	M-L	LT-UNK	MAK	Pregnancy Risk Group C	
Acute Mammalian Toxicity	M	LT-UNK	GHS - New Zealand	Acute inhalation toxicity category 4	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity – single exposure; Respiratory tract irritation – Category 3]	
Neurotoxicity-Single Exposure	M-L	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H336 - May cause drowsiness or dizziness [Specific target organ toxicity – single exposure; Narcotic effects – Category 3]	+3
	M-L	LT-UNK	GHS - Australia	H336 - May cause drowsiness or dizziness [Specific target organ toxicity – single exposure; Narcotic effects – Category 3]	
	M-L	LT-UNK	GHS - Malaysia	H336 - May cause drowsiness or dizziness [Specific target organ toxicity – single exposure; Narcotic effects – Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H336 - May cause drowsiness or dizziness (unverified) [Specific target organ toxicity – single exposure; Narcotic effects – Category 3]	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	+1
	M	LT-UNK	GHS - Japan	H319 - Causes serious eye irritation [Serious eye damage / eye irritation – Category 2B]	

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Acute Aquatic Toxicity	M	LT-UNK	GHS - Japan	H402 - Harmful to aquatic life [Hazardous to the aquatic environment (acute) - Category 3]	
Persistence	vH-H	LT-UNK	EC - CEPA DSL	Persistent	
Flammability	M	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H226 - Flammable liquid and vapour [Flammable liquids - Category 3]	+7
	H	LT-UNK	GHS - Japan	H225 - Highly flammable liquid and vapour [Flammable liquids - Category 2]	
	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	
	M	LT-UNK	GHS - Australia	H226 - Flammable liquid and vapour [Flammable liquids - Category 3]	
	M	LT-UNK	GHS - Malaysia	H226 - Flammable liquid and vapour [Flammable liquids - Category 3]	
	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]	

Restricted Substance Lists (7)

- 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 Accepted Substance List: Benchmark-2 Accepted Substance

Discussions

No discussions have been posted yet.

Ask a question about this chemical in the forums >

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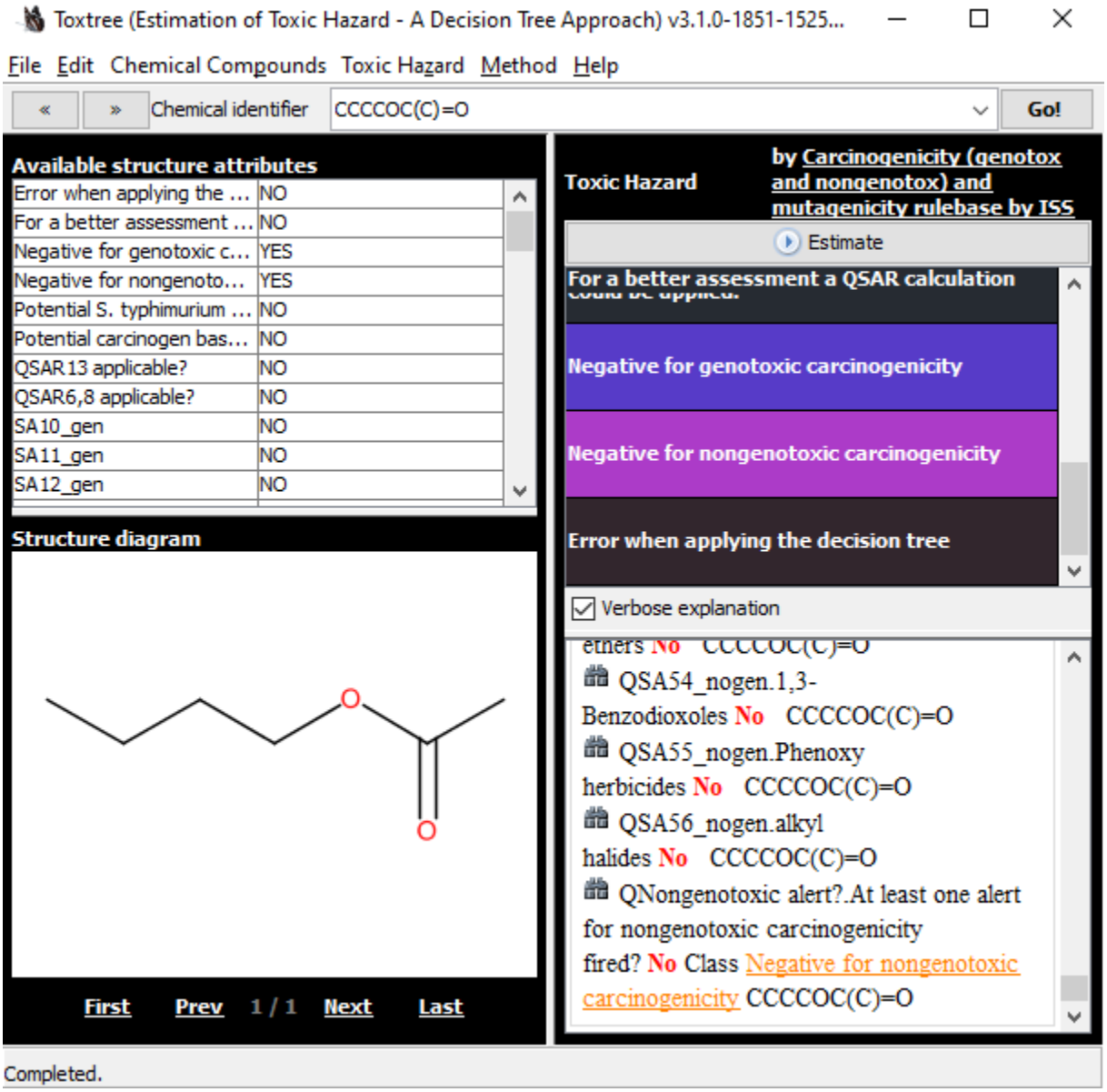
APPENDIX D: Toxtree Carcinogenicity Results for Butyl Acetate (CAS #123-86-4)



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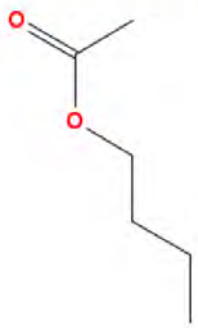
APPENDIX E: VEGA Carcinogenicity Results for Butyl Acetate (CAS #123-86-4)

VEGA Carcinogenicity model (CAESAR) 2.1.9 page 1

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
- predicted substance falls into a neuron that is populated by no compounds of the training set

Compound: Molecule 0
Compound SMILES: O=C(OCCCC)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.248
P(NON-Carcinogen): 0.752
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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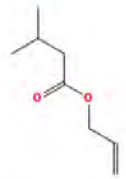
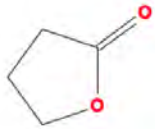
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 2835-39-4
Dataset id: 33 (Test set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.89

Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

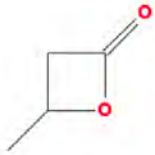
CAS: 96-48-0
Dataset id: 120 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.865

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

Compound #3

CAS: 1955-45-9
Dataset id: 663 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.862

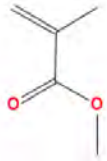
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 3068-88-0
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

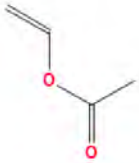
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 80-62-6
Dataset id: 452 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.804

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 108-05-4
Dataset id: 794 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.801

Experimental value: Carcinogen
Predicted value: Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.328
Explanation: the predicted compound is outside the Applicability Domain of the model.

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

Accuracy of prediction for similar molecules
Accuracy index = 0.492
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.492
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

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

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

Model class assignment reliability
Pos/Non-Pos difference = 0.503
Explanation: model class assignment is well defined.

Neural map neurons concordance
Neurons concordance = 0.5
Explanation: predicted substance falls into a neuron that is populated by no compounds of the training set.

Symbols explanation:

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

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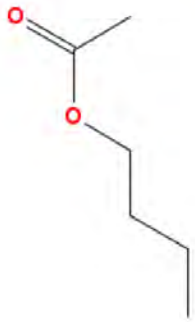
1. Prediction Summary

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(OCCCC)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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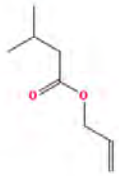
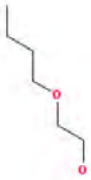
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 2835-39-4
Dataset id: 35 (Training set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.89

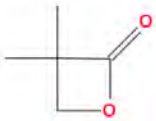
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id: 596 (Training set)
SMILES: OCCOCCCC
Similarity: 0.88

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

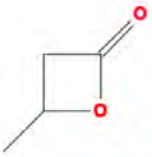


Compound #3

CAS: 1955-45-9
Dataset id: 219 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.862

Experimental value: Carcinogen
Predicted value: Carcinogen

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

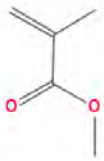


Compound #4

CAS: 3068-88-0
Dataset id: 15 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

Experimental value: Carcinogen
Predicted value: Carcinogen

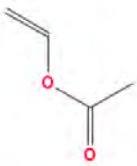
Alerts (not found in the target): SA6 Propiolactones and propiosultones



Compound #5

CAS: 80-62-6
Dataset id: 272 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.804

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



Compound #6

CAS: 108-05-4
Dataset id: 499 (Training set)
SMILES: O=C(OC=C)C
Similarity: 0.801

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

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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 = 0.885
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

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

Symbols explanation:

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

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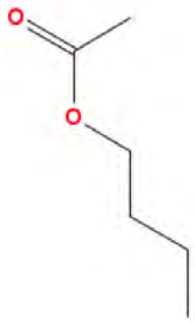
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

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

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

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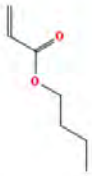
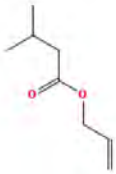
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 1502 (Training set)
SMILES: O=C(OCCCC)C=C
Similarity: 0.902

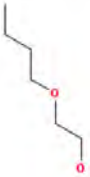
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: N.A.
Dataset id: 33 (Training set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.89

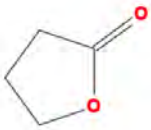
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: N.A.
Dataset id: 1364 (Training set)
SMILES: OCCOCCCC
Similarity: 0.88

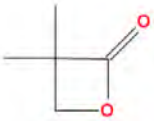
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: N.A.
Dataset id: 120 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.865

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

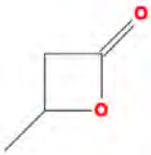


Compound #5

CAS: N.A.
Dataset id: 673 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.862

Experimental value: Carcinogen
Predicted value: Carcinogen

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



Compound #6

CAS: N.A.
Dataset id: 119 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

Experimental value: Carcinogen
Predicted value: Carcinogen

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

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.771
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.89
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.667
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.667
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

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

Symbols explanation:

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

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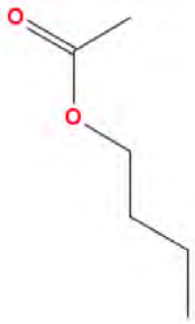
1. Prediction Summary

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(OCCCC)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

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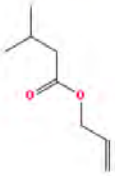
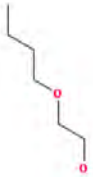
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 2835-39-4
Dataset id: 28 (Training set)
SMILES: O=C(OCC=C)CC(C)C
Similarity: 0.89

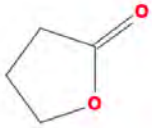
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id: 498 (Training set)
SMILES: OCCOCCCC
Similarity: 0.88

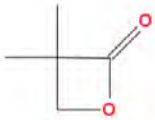
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #3

CAS: 96-48-0
Dataset id: 931 (Training set)
SMILES: O=C1OCCC1
Similarity: 0.865

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

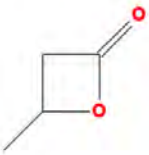


Compound #4

CAS: 1955-45-9
Dataset id: 178 (Training set)
SMILES: O=C1OCC1(C)C
Similarity: 0.862

Experimental value: Carcinogen
Predicted value: Carcinogen

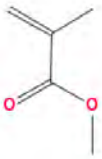
Alerts (not found in the target): Carcinogenity alert no. 29



Compound #5

CAS: 3068-88-0
Dataset id: 11 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #6

CAS: 80-62-6
Dataset id: 222 (Training set)
SMILES: O=C(OC)C(=C)C
Similarity: 0.804

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

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.536
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.878
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.328
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.328
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.

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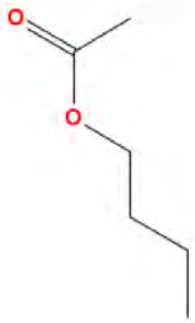
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is NON-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(OCCCC)C
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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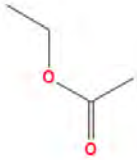
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

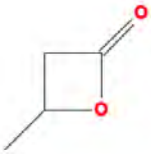
CAS: 141-78-6
Dataset id: 501 (Test set)
SMILES: O=C(OCC)C
Similarity: 0.88

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

Compound #2

CAS: 111-76-2
Dataset id: 509 (Training set)
SMILES: OCCOCCCC
Similarity: 0.88

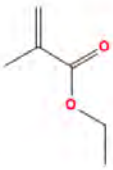
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 3068-88-0
Dataset id: 53 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

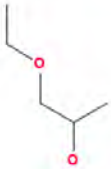
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 97-63-2
Dataset id: 504 (Training set)
SMILES: O=C(OCC)C(=C)C
Similarity: 0.854

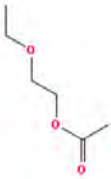
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 1569-02-4
Dataset id: 663 (Training set)
SMILES: OC(C)COCC
Similarity: 0.844

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: 0.831

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

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.938
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.88
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.

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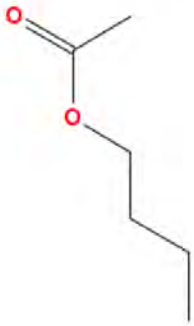
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is NON-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(OCCCC)C
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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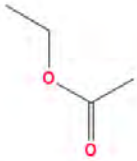
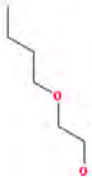
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-78-6
Dataset id: 473 (Training set)
SMILES: O=C(OCC)C
Similarity: 0.88

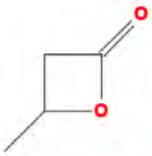
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 111-76-2
Dataset id: 482 (Training set)
SMILES: OCCOCCCC
Similarity: 0.88

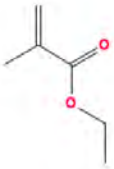
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 3068-88-0
Dataset id: 45 (Training set)
SMILES: O=C1OC(C)C1
Similarity: 0.857

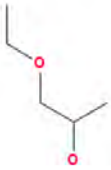
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 97-63-2
Dataset id: 477 (Training set)
SMILES: O=C(OCC)C(=C)C
Similarity: 0.854

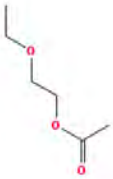
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 1569-02-4
Dataset id: 652 (Training set)
SMILES: OC(C)COCC
Similarity: 0.844

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: 0.831

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

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.938
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.88
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.

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APPENDIX F: OncoLogic™ Modeling Results for the Surrogate n-Butanol (CAS #71-36-3)

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : n-butanol

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Alcohols*

Aliphatic alcohols (R-OH) may be loosely divided into (a) high M.W.alcohols (C > 20), (b) medium size alcohols (C = 6 to 20), and (c) low M.W. alcohols (C < 6). In general, high M.W. aliphatic alcohols have low potential to be significant carcinogens. A number of medium size alcohols (e.g., CF3(CF2)6CH2OH; 2-ethylhexanol) that can be oxidized to metabolically persistent aliphatic carboxylic acids (e.g., perfluorinated fatty acid like perfluoroooctanoic; ω – 1 branched fatty acids like 2-ethylhexanoic acid) are potential nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Low M.W. alcohols, (especially methanol and ethanol) are of carcinogenic concern because of possible oxidation to reactive aldehydes. The concern for carcinogenic risk is especially higher in individuals who are genetically deficient in aldehyde dehydrogenase which detoxifies aldehydes to carboxylic acids. A number of low M.W. tertiary alcohols (e.g., t-butyl, t-amyl) have been shown to induce kidney tumors in male rats by a mechanism (alpha-2-mu nephropathy) not relevant to humans. In addition, low M.W. alcohols with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens.

---

*This is only a brief summary of the structure activity relationships (SAR) knowledge of this class. A more detailed decision logic will be developed in future version of OncoLogic. If the compound of your interest has been tested in any short-term predictive tests, the results of the tests should be entered into OncoLogic's Functional Arm to give an evaluation of carcinogenic potential based on short-term predictive tests.

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APPENDIX G: OncoLogic™ Modeling Results for the Surrogate Acetic Acid (CAS #64-19-7)

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : 64197

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Carboxylic Acids*

Aliphatic carboxylic acids (R-COOH) may be loosely divided into (a) high M.W.fatty acids (C > 20), (b) medium size carboxylic acids (C = 6 to 20), and (c) low M.W. carboxylic acids (C < 6). In general, aliphatic carboxylic acids (especially group (a)) have low potential to be significant carcinogens. However, a number of metabolically persistent aliphatic carboxylic acids (e.g., perflourinated fatty acid like perfluoroooctanoic acid; ω – 1 branched fatty acids like 2-ethylhexanoic acid) have been shown to be nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Among low M.W. carboxyxlic acids, those with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens whereas some unsubstituted saturated fatty acids (e.g., pentanoic acid) may be of marginal concern via dermal route due to their irritancy.

---

*This is only a brief summary of the structure activity relationships (SAR) knowledge of this class. A more detailed decision logic will be developed in future version of OncoLogic. If the compound of your interest has been tested in any short-term predictive tests, the results of the tests should be entered into OncoLogic's Functional Arm to give an evaluation of carcinogenic potential based on short-term predictive tests.

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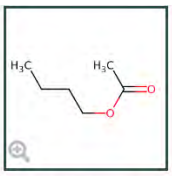
APPENDIX H: CompTox Endocrine Results for Butyl Acetate (CAS #123-86-4)



Butyl acetate

123-86-4 | DTXSID3021982

Searched by CASRN

Bioactivity - TOXCAST Summary

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21			esr1			
TOX21_ERa_LUC_VM7_Ag		NP_000116.2	ESR1 |	-	-	Inactive
TOX21_ERa_LUC_VM7_An		NP_000116.2	ESR1 |	-	-	Inactive
TOX21_ERa_LUC_VM7_An		NP_000116.2	ESR1 |	200 | 29 |...	1181	Inactive
TOX21_ERa_BLA_Agonist_		NP_000116.2	ESR1 |	200 | 29 |...	1181	Inactive
TOX21_ERa_BLA_Antagon		NP_000116.2	ESR1 |	200 | 29 |...	1181	Inactive
TOX21_ERa_LUC_VM7_Ag		NP_000116.2	ESR1 |	200 | 200...	1181	Inactive

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21			esr2			
TOX21_ERb_BLA_Agonist_		NP_001428.1	ESR2 |	-	-	Inactive
TOX21_ERb_BLA_Antagon		NP_001428.1	ESR2 |	-	-	Inactive

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21_AR_			ar			
TOX21_AR_BLA_Agonist_r			AR |	307 | 19 | ...	-	Inactive
TOX21_AR_BLA_Antagoni			AR |	307 | 19 | ...	-	Inactive
TOX21_AR_LUC_MDAKB2_			AR |	307 | 111 |...	-	Inactive
TOX21_AR_LUC_MDAKB2_			AR |	-	-	Inactive
TOX21_AR_LUC_MDAKB2_			AR |	-	-	Inactive
TOX21_AR_LUC_MDAKB2_			AR |	-	-	Inactive
TOX21_AR_LUC_MDAKB2_			AR |	307 | 111 |...	-	Inactive

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Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21_arom						
TOX21_Aromatase_Inhibiti		NP_000094.2	CYP19A1 |	122 | 123 ...	964	Inactive
TOX21_Aromatase_Inhibiti				-	-	Inactive

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21			trhr			
TOX21_TRHR_HEK293_Ag			TRHR |	-	-	Inactive
TOX21_TRHR_HEK293_An			TRHR |	-	-	Inactive

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21			Thr			
TOX21_TR_LUC_GH3_Ago		NP_003241.2 NP_000452.2	THRA | THRB |	-	-	Inactive
TOX21_TR_LUC_GH3_Anta		NP_003241.2 NP_000452.2	THRA | THRB |	-	-	Inactive

Name	Details	SeqAPASS	Gene Symbol	AOP	Event	Hit Call
tox21			TSHR			
TOX21_TSHR_HTRF_Agon			TSHR |	-	-	Inactive
TOX21_TSHR_HTRF_Antag			TSHR |	-	-	Inactive
TOX21_TSHR_HTRF_wt_rat			TSHR |	-	-	Inactive

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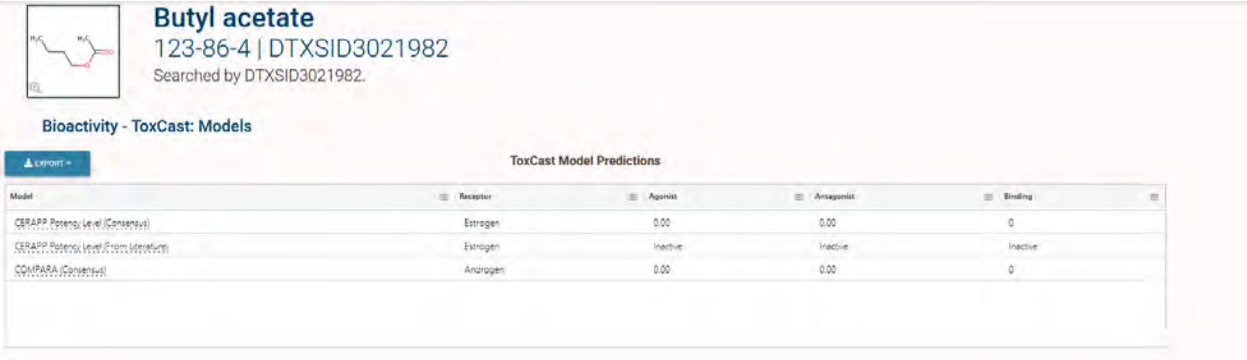
APPENDIX I: ToxCast Model Predictions for Butyl Acetate (CAS #123-86-4)



Butyl acetate
123-86-4 | DTXSID3021982
Searched by DTXSID3021982.

Bioactivity - ToxCast: Models

EXPORT

ToxCast Model Predictions

Model	Receptor	Agonist	Antagonist	Binding
CERAPP Potency Level (Consensus)	Estrogen	0.00	0.00	0
CERAPP Potency Level (From Literature)	Estrogen	Inactive	Inactive	Inactive
COMPARA (Consensus)	Androgen	0.00	0.00	0

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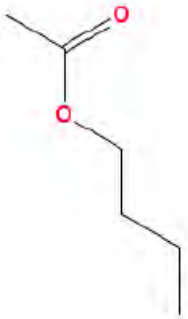
APPENDIX J: VEGA Endocrine Endpoint for Butyl Acetate (CAS #123-86-4)

VEGA Estrogen Receptor Relative Binding Affinity model (IRFMN) page 1

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(OCCCC)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

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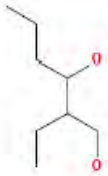
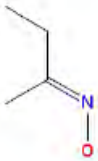
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 94-96-2
Dataset id: 17 (Training set)
SMILES: OCC(CC)C(O)CCC
Similarity: 0.768

Experimental value: Inactive
Predicted value: Inactive



Compound #2

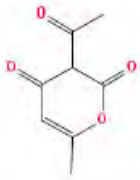
CAS: 96-29-7
Dataset id: 7 (Training set)
SMILES: ON=C(C)CC
Similarity: 0.73

Experimental value: Inactive
Predicted value: Inactive

Compound #3

CAS: 107-21-1
Dataset id: 22 (Training set)
SMILES: OCCO
Similarity: 0.696

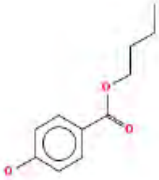
Experimental value: Inactive
Predicted value: Inactive



Compound #4

CAS: 4418-26-2
Dataset id: 873 (Training set)
SMILES: O=C1OC(=CC(=O)C1C(=O)C)C
Similarity: 0.693

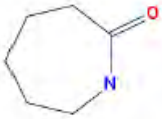
Experimental value: Inactive
Predicted value: Inactive



Compound #5

CAS: 94-26-8
Dataset id: 218 (Training set)
SMILES: O=C(OCCCC)c1ccc(O)cc1
Similarity: 0.689

Experimental value: Active
Predicted value: Active



Compound #6

CAS: 105-60-2
Dataset id: 865 (Training set)
SMILES: O=C1NCCCCC1
Similarity: 0.687

Experimental value: Inactive
Predicted value: Inactive

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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.

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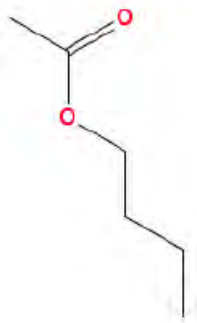
1 Prediction Summary

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(OCCCC)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

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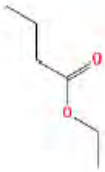
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



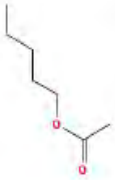
Compound #1

CAS: N.A.
Dataset id: 396 (Training set)
SMILES: O=C(OCC)CCC
Similarity: 0.981

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

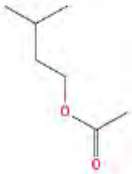


Compound #2

CAS: N.A.
Dataset id: 816 (Training set)
SMILES: O=C(OCCCCC)C
Similarity: 0.954

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

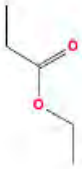


Compound #3

CAS: N.A.
Dataset id: 594 (Training set)
SMILES: O=C(OCCC(C)C)C
Similarity: 0.951

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

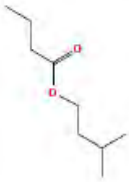


Compound #4

CAS: N.A.
Dataset id: 394 (Training set)
SMILES: O=C(OCC)CC
Similarity: 0.935

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: 405 (Training set)
SMILES: O=C(OCCC(C)C)CCC
Similarity: 0.91

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

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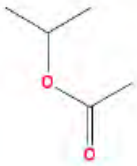
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #6

CAS: N.A.
Dataset id: 431 (Training set)
SMILES: O=C(OC(C)C)C
Similarity: 0.91

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.98
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.961
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.

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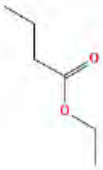
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(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.

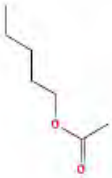


CAS: N.A.
Dataset id: 396 (Training set)
SMILES: O=C(OCC)CCC
Similarity: 0.981

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

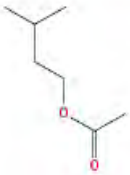
Alerts (not found in the target): ER possible non-activity alert no. 2



CAS: N.A.
Dataset id: 816 (Training set)
SMILES: O=C(OCCCCC)C
Similarity: 0.954

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: 594 (Training set)
SMILES: O=C(OCCC(C)C)C
Similarity: 0.951

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

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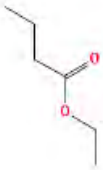
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(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.

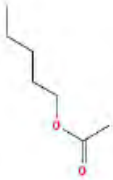


CAS: N.A.
Dataset id: 396 (Training set)
SMILES: O=C(OCC)CCC
Similarity: 0.981

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

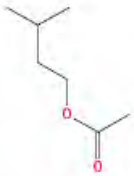
Alerts (not found in the target): ER possible non-activity alert no. 2



CAS: N.A.
Dataset id: 816 (Training set)
SMILES: O=C(OCCCCC)C
Similarity: 0.954

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: 594 (Training set)
SMILES: O=C(OCCC(C)C)C
Similarity: 0.951

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

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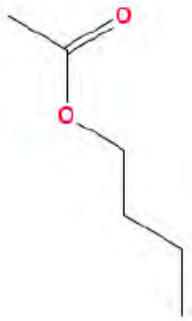
1 Prediction Summary

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(OCCCC)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

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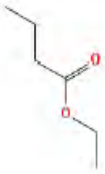
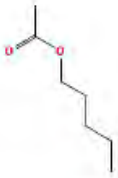
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 105-54-4
Dataset id: 1213 (Training set)
SMILES: CCOC(=O)CCC
Similarity: 0.981

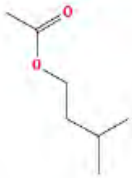
Experimental value: NON-active
Predicted value: NON-active



Compound #2

CAS: 628-63-7
Dataset id: 952 (Training set)
SMILES: CCCCCOC(C)=O
Similarity: 0.954

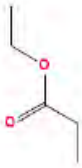
Experimental value: NON-active
Predicted value: NON-active



Compound #3

CAS: 123-92-2
Dataset id: 824 (Training set)
SMILES: CC(C)CCOC(C)=O
Similarity: 0.951

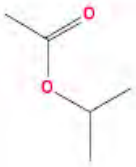
Experimental value: NON-active
Predicted value: NON-active



Compound #4

CAS: 105-37-3
Dataset id: 1212 (Training set)
SMILES: CCC(=O)OCC
Similarity: 0.935

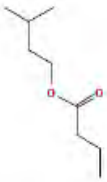
Experimental value: NON-active
Predicted value: NON-active



Compound #5

CAS: 108-21-4
Dataset id: 826 (Training set)
SMILES: CC(C)OC(C)=O
Similarity: 0.91

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



Compound #6

CAS: 106-27-4
Dataset id: 1312 (Training set)
SMILES: CCCC(=O)OCCC(C)C
Similarity: 0.91

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

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.983
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.967
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.

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APPENDIX K: Danish (Q)SAR Endocrine and Molecular Endpoints for Butyl Acetate (CAS #123-86-4)

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_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			18580.47	1606.189	304.8292
- μM			159955.8	13827.38	2624.218
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			3758.866	82.62218	559.1863
- μM			32359.38	711.2791	4813.931
- Positive for IC_{50} ≤ 10 μM					
- Positive for IC_{50} ≤ 100 μM					

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	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
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		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		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*)		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*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		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					

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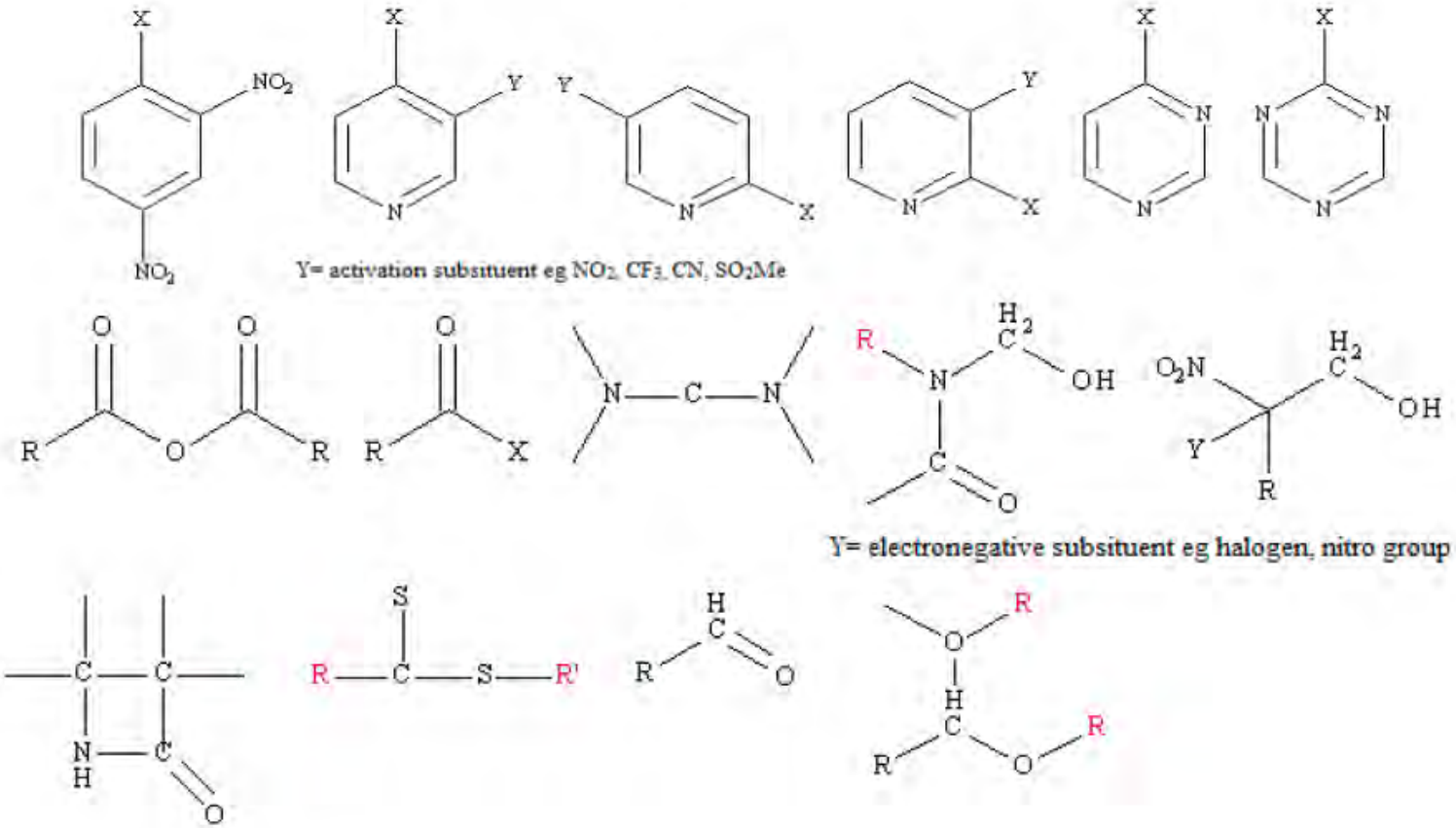
APPENDIX L: Known Structural Alerts for Skin Sensitization

Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Butyl acetate does not possess any known structural alerts.



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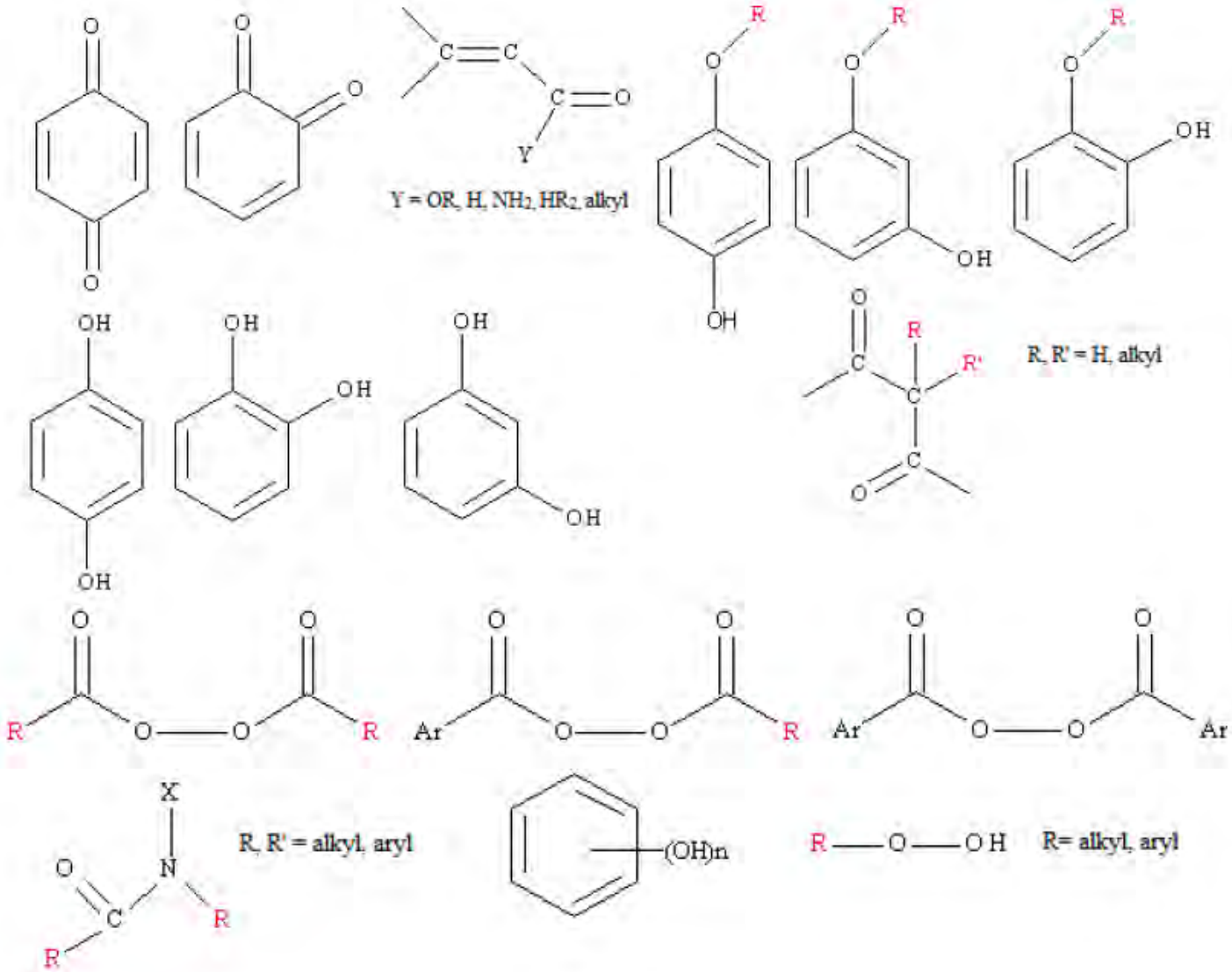

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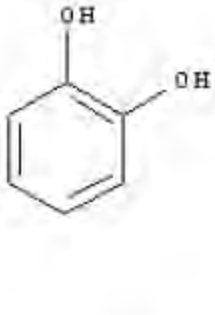
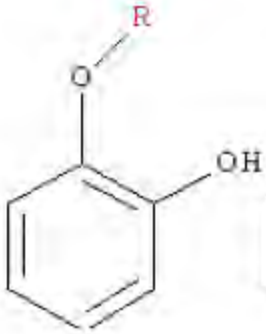
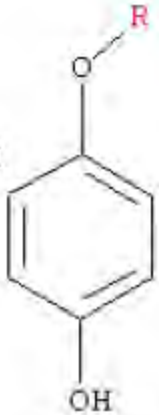
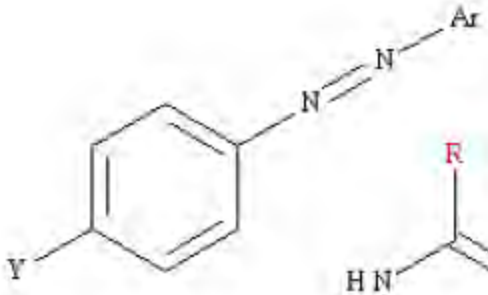
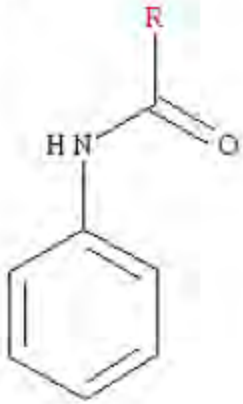
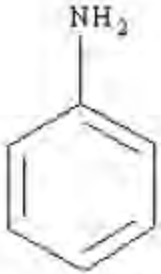


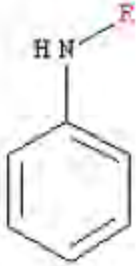


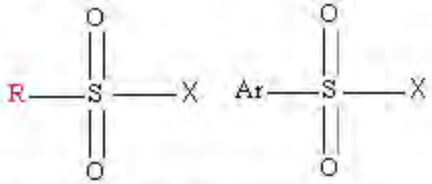




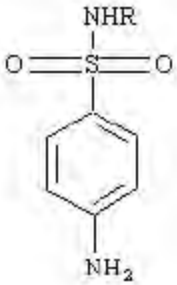


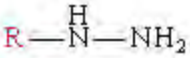




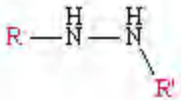


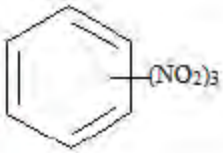
R = H, alkyl, aryl, heterocyclic group

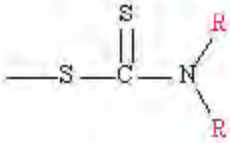




R = alkyl, aryl







R = $(CH_2)_nNR'R''$; n=2,3
Y=most non-hydrotophilic substituents

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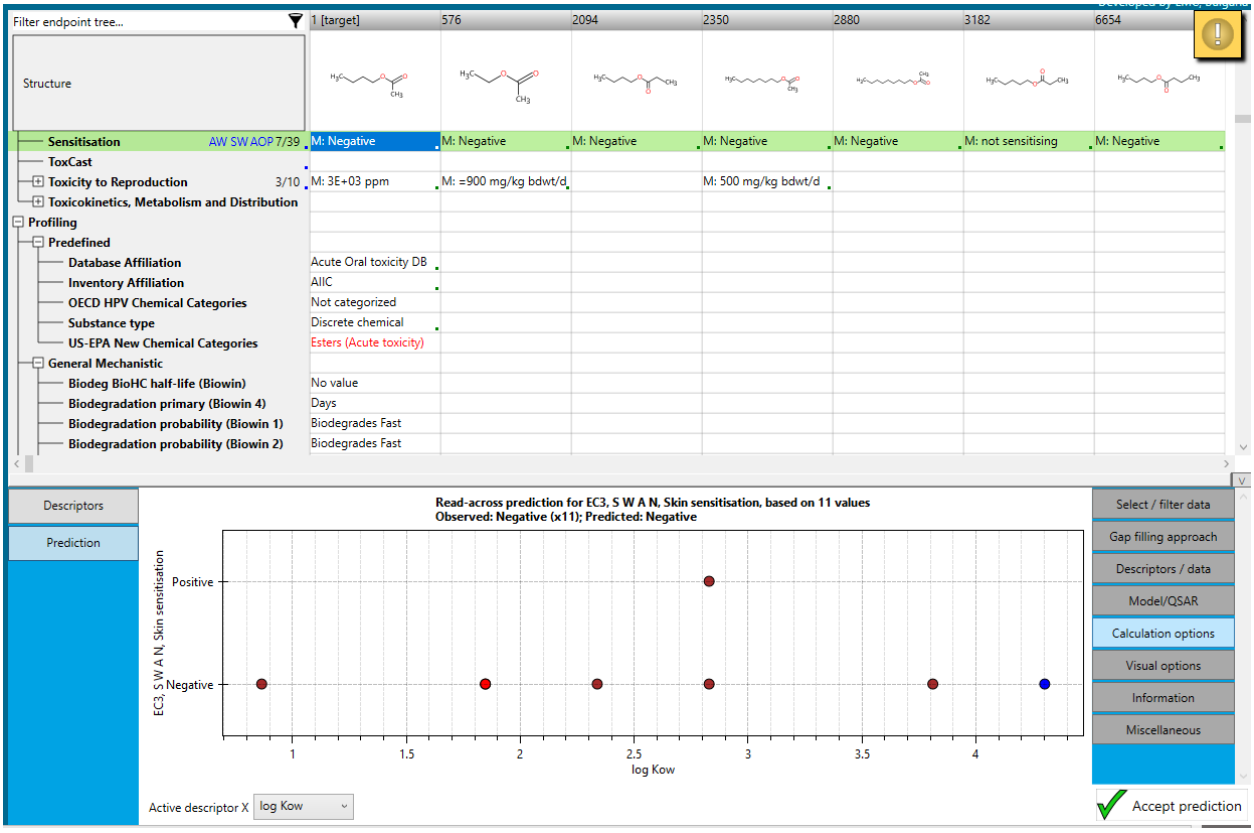
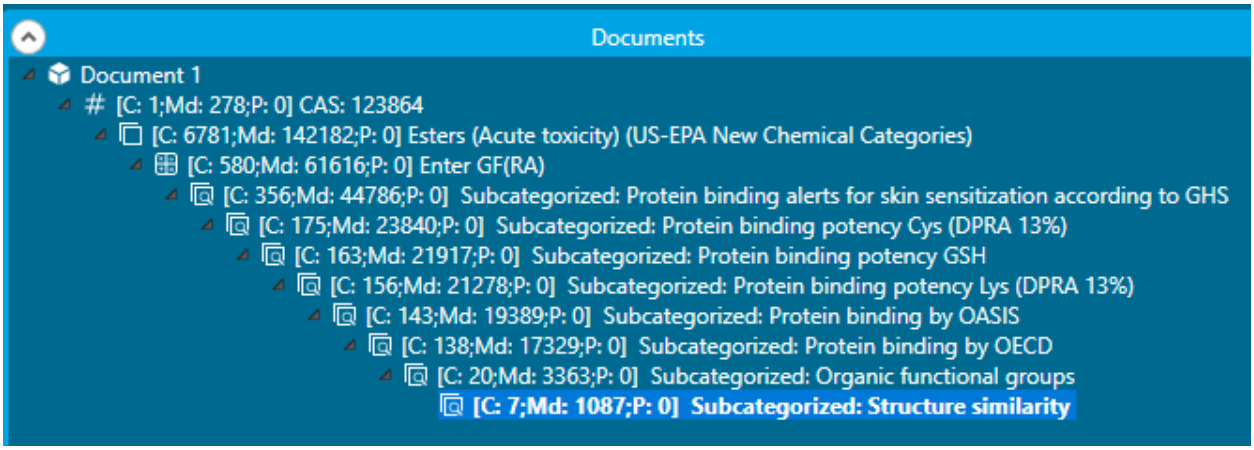
APPENDIX M: OECD Toolbox Skin Sensitization Results for Butyl Acetate (CAS #123-86-4)





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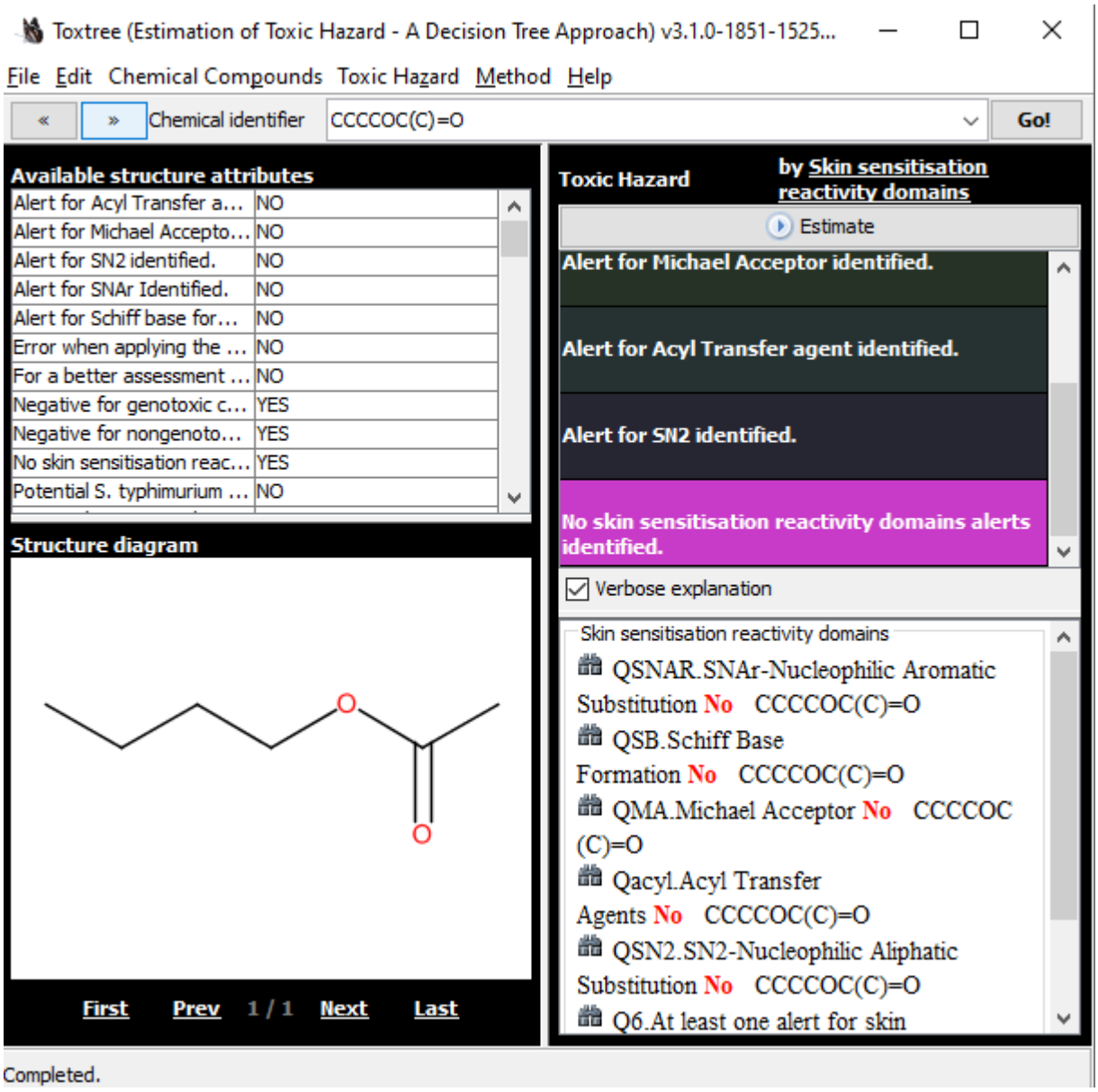
APPENDIX N: Toxtree Skin Sensitization Results for Butyl Acetate (CAS #123-86-4)



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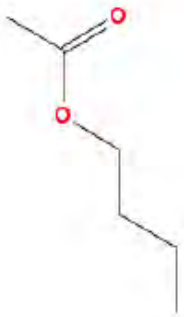
APPENDIX O: VEGA Skin Sensitization Results for Butyl Acetate (CAS #123-86-4)

VEGA Skin Sensitization model (CAESAR) 2.1.6 page 1

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

Prediction is Sensitizer, 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(OCCCC)C
Experimental value: -
Predicted skin sensitization activity: Sensitizer
O(Active): 1
O(Inactive): 0
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 29043-97-8
Dataset id: 81 (Test set)
SMILES: O=C1OC(C)(C)CC1(=C)
Similarity: 0.832

Experimental value: Sensitizer
Predicted value: Sensitizer

Compound #2

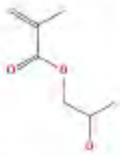
CAS: 2426-08-6
Dataset id: 45 (Training set)
SMILES: O(CCCC)CC1OC1
Similarity: 0.818

Experimental value: Sensitizer
Predicted value: Sensitizer

Compound #3

CAS: 154750-20-6
Dataset id: 32 (Training set)
SMILES: O=C1OC(C)(C)CC1CBr
Similarity: 0.807

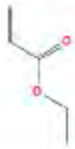
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #4

CAS: 923-26-2
Dataset id: 112 (Test set)
SMILES: O=C(OCC(O)C)C(=C)C
Similarity: 0.805

Experimental value: NON-Sensitizer
Predicted value: Sensitizer



Compound #5

CAS: 140-88-5
Dataset id: 88 (Training set)
SMILES: O=C(OCC)C=C
Similarity: 0.798

Experimental value: Sensitizer
Predicted value: Sensitizer

Compound #6

CAS: 57-57-8
Dataset id: 183 (Training set)
SMILES: O=C1OCC1
Similarity: 0.79

Experimental value: Sensitizer
Predicted value: Sensitizer

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.908
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.825
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.

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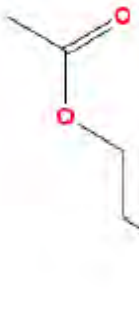
1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(OCCCC)C
Experimental value: -
Predicted skin sensitization activity: NON-Sensitizer
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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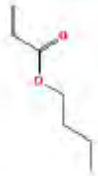
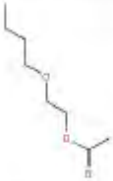
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 141-32-2
Dataset id: 148 (Training set)
SMILES: O=C(OCCCC)C=C
Similarity: 0.902

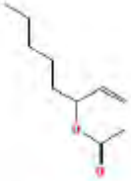
Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #2

CAS: 112-07-2
Dataset id: 244 (Training set)
SMILES: O=C(OCCOCCCC)C
Similarity: 0.867

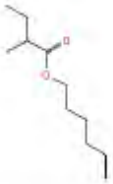
Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



Compound #3

CAS: 198-24-2
Dataset id: 218 (Training set)
SMILES: O=C(OC(C=C)CCCCC)C
Similarity: 0.842

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



Compound #4

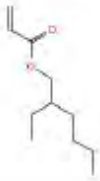
CAS: 10032-15-2
Dataset id: 154 (Training set)
SMILES: O=C(OCCCCCC)C(C)CC
Similarity: 0.841

Experimental value: Sensitizer
Predicted value: NON-Sensitizer

Compound #5

CAS: 29043-97-8
Dataset id: 106 (Training set)
SMILES: O=C1OC(C)(C)CC1(=C)
Similarity: 0.832

Experimental value: Sensitizer
Predicted value: Sensitizer



Compound #6

CAS: 103-11-7
Dataset id: 133 (Training set)
SMILES: O=C(OCC(CC)CCCC)C=C
Similarity: 0.82

Experimental value: Sensitizer
Predicted value: Sensitizer

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.786
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.883
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 0.489
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

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

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

Symbols explanation:

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

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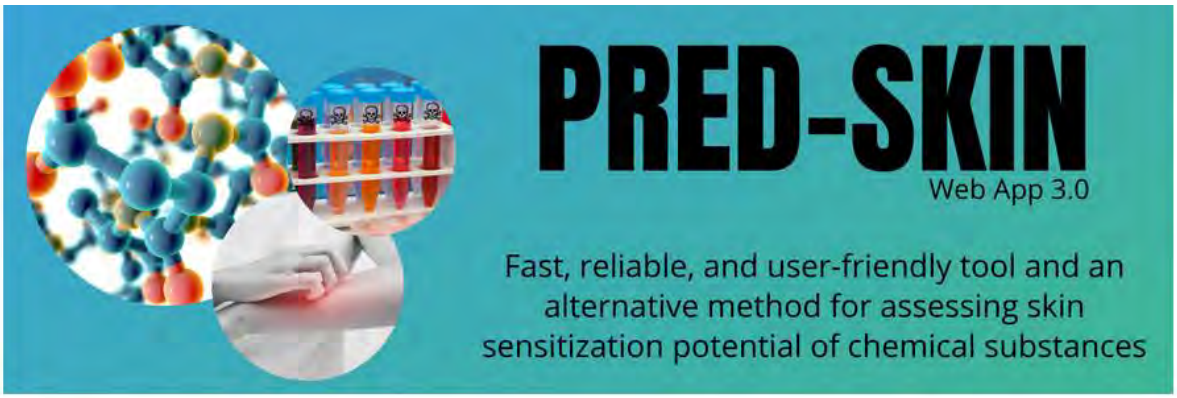
APPENDIX P: LabMol Skin Sensitization Results for Butyl Acetate (CAS #123-86-4)



Chemical Exposure	Molecular initiating event *in chemico*	Cellular response *in vitro*		Tissue / Organ response *in vivo*	Organism response *in vivo*	Pred-Skin 3.0 Outcome *in silico*
•Skin Penetration •Electrophilic substance: directly or via auto-oxidation or metabolism	Covalent interaction with proteins in the skin (OECD442C) Haptenation: covalent modification of epidermal proteins	Keratinocyte responses (OECD442D) • Activation of inflammatory cytokines •Induce cytoprotective genes	Dendritic cells (DCs) (OECD442E) • Induction of inflammatory cytokines •Mobilization of DCs	Proliferation of antigen-specific T cells (OECD429) •Histocompatibility complex representation by DCs •Activation of T cells •Proliferation of activated T cells	Inflammation upon challenge allergen To maximise the use of existing knowledge, we also incorporate historical HRIPT (human repeated insult patch test) and HMT (human maximization test)	The Bayesian model is a consensus model integrating predictions from all the other assays for an integrative qualitative risk assessment (QRA) of skin sensitization based on the weight of evidence (WoE).
•Exposure consideration ? •Physicochemical and Biopharmaceutical properties ? •Skin Penetration ? •Skin Metabolism ?	**Prediction DPRA** Sensitizer (+) (AD, Confiability) (Inside , 86.1%) Probability map	**Prediction KeratinoSens** Non-Sensitizer (-) (AD, Confiability) (Inside, 81.4%) Probability map	**Prediction h-CLAT** Sensitizer (+) (AD, Confiability) (Inside, 57.7%) Probability map	**Prediction LLNA** Non-Sensitizer (-) (AD, Confiability) (Inside, 99.8%) Probability map	**Prediction HRIPT/HMT** Non-Sensitizer (-) (AD, Confiability) (Inside, 87.1%) Probability map	**Bayesian Outcome** Non-sensitizer (-) (Confiability) (High)

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

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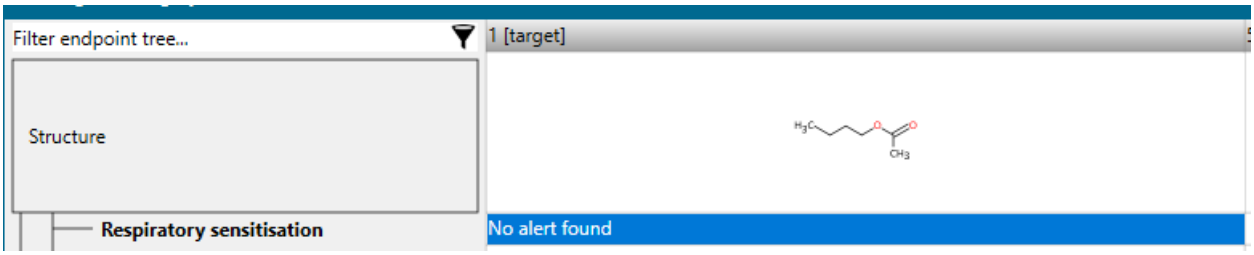
APPENDIX Q: OECD Toolbox Respiratory Sensitization for Butyl Acetate (CAS #123-86-4)



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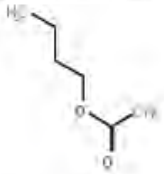
APPENDIX R: ECOSAR Modeling Results for Butyl Acetate (CAS #123-86-4)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
123864	Acetic acid, butyl ester	O=C(OCCCC)C

Structure



Details	
Mol Wt	116.16
Selected LogKow	1.85
Selected Water Solubility (mg/L)	8400
Selected Melting Point (°C)	-78
Estimated LogKow	1.85
Estimated Water Solubility (mg/L)	4836.32
Measured LogKow	1.78
Measured Water Solubility (mg/L)	8400
Measured Melting Point (°C)	-78

Class Results:	

Esters

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	19.09	5	
Daphnid	48h	LC50	40.35	5	
Green Algae	96h	EC50	17.59	6.4	
Fish		ChV	1.48	8	
Daphnid		ChV	28.83	8	
Green Algae		ChV	4.29	8	
Fish (SW)	96h	LC50	29.32	5	

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Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Mysid	96h	LC50	31.1	5	
Fish (SW)		ChV	4.09	8	
Mysid (SW)		ChV	3130.2	8	
Earthworm	14d	LC50	1697.39	5	

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APPENDIX S: EPI Suite™ Modeling Results for Butyl Acetate (CAS #123-86-4)

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

CAS Number: 123-86-4
SMILES : O=C(OCCCC)C
CHEM : Acetic acid, butyl ester
MOL FOR: C6 H12 O2
MOL WT : 116.16
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log Kow (octanol-water): 2.30
Boiling Point (deg C) : 126.00
Melting Point (deg C) : -78.00
Vapor Pressure (mm Hg) : 11.25
Water Solubility (mg/L): 8400
Henry LC (atm-m3/mole) : 0.000281

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.85
Log Kow (Exper. database match) = 1.78
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 125.79 (Adapted Stein & Brown method)
Melting Pt (deg C): -56.83 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 12 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.6E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): -78 deg C
BP (exp database): 126.1 deg C
VP (exp database): 1.15E+01 mm Hg (1.53E+003 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1532
log Kow used: 2.30 (user entered)
melt pt used: -78.00 deg C
Water Sol (Exper. database match) = 8400 mg/L (25 deg C)
Exper. Ref: YALKOWSKY,SH ET AL. (2010)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 4329.4 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 4.10E-004 atm-m3/mole (4.16E+001 Pa-m3/mole)
Group Method: 3.15E-004 atm-m3/mole (3.19E+001 Pa-m3/mole)

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Exper Database: 2.81E-04 atm-m3/mole (2.85E+001 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: 2.810E-004 atm-m3/mole (2.847E+001 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 2.047E-004 atm-m3/mole (2.074E+001 Pa-m3/mole)
VP: 11.3 mm Hg (source: User-Entered)
WS: 8.4E+003 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.30 (user entered)
Log Kaw used: -1.940 (user entered)
Log Koa (KOAWIN v1.10 estimate): 4.240
Log Koa (experimental database): 3.650

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.9749
Biowin2 (Non-Linear Model) : 0.9993
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.3810 (days-weeks)
Biowin4 (Primary Survey Model) : 4.1782 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7596
Biowin6 (MITI Non-Linear Model): 0.9176
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6090
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): 1.51E+003 Pa (11.3 mm Hg)
Log Koa (Exp database): 3.650
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.99E-009
Octanol/air (Koa) model: 1.1E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 7.19E-008
Mackay model : 1.59E-007
Octanol/air (Koa) model: 8.77E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 4.6094 E-12 cm3/molecule-sec
Half-Life = 2.320 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 27.846 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

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1.16E-007 (Junge-Pankow, Mackay avg)
8.77E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 18.54 L/kg (MCI method)
Log Koc: 1.268 (MCI method)
Koc : 135.4 L/kg (Kow method)
Log Koc: 2.132 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 1.025E-001 L/mol-sec
Kb Half-Life at pH 8: 78.232 days
Kb Half-Life at pH 7: 2.142 years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.185 (BCF = 15.29 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.2917 days (HL = 0.05109 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.980 (BCF = 9.548)
Log BAF Arnot-Gobas method (upper trophic) = 0.980 (BAF = 9.548)
log Kow used: 2.30 (user entered)

Volatilization from Water:
Henry LC: 0.000281 atm-m3/mole (entered by user)
Half-Life from Model River: 3.345 hours
Half-Life from Model Lake : 126.9 hours (5.286 days)

Removal In Wastewater Treatment:
Total removal: 13.92 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 2.32 percent
Total to Air: 11.51 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**13.3**	**52.4**	**1000**
Water	**35.8**	**208**	**1000**
Soil	**50.9**	**416**	**1000**
Sediment	**0.0865**	**1.87e+003**	**0**

Persistence Time: 182 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	13.3	52.4	1000
Water	35.8	208	1000

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water (35.8)
biota (0.000357)
suspended sediment (0.000995)

Soil	50.9	416	1000
Sediment	0.0865	1.87e+003	0

Persistence Time: 182 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	9.18	52.4	1000
Water	27.3	208	1000
water	(27.3)		
biota	(0.000272)		
suspended sediment	(0.00335)		
Soil	63.4	416	1000
Sediment	0.123	1.87e+003	0

Persistence Time: 229 hr

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APPENDIX T: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List

Explosivity – reactive groups

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

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

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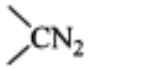
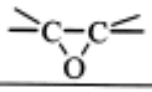
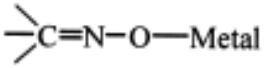
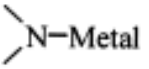
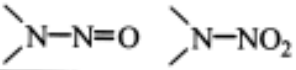
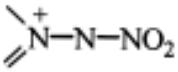
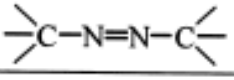
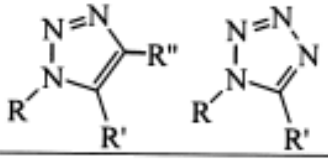
Explosivity – Full List

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

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

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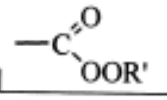
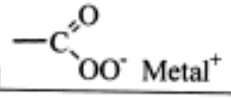
Chemical group	Chemical Class
[1] ROOR',  [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal,  [2]	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O—C–N_2^{+}$	Arenediazonium oxides i.e. 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. NCl_3, $RNCl_2$	N-Halogen Compounds

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

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Self-Reactive Substances

Screening procedures

- Not in CLP, but UN Manual of Tests and Criteria Appendix 6
- No explosive groups (see 2.1) plus

Structural feature	Chemical classes
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising agents
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P–O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

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APPENDIX U: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for butyl acetate. The GreenScreen® Benchmark Score for butyl 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 a version 1.4 update in 2020 and 2021. In the present report, ToxServices altered the developmental toxicity-D score from moderate to low based on a consideration of effects only identified at maternally-toxic doses, which altered the Benchmark Score from 2 to 3.

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

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
November 11, 2014	BM-2	v. 1.2	New screen.
February 14, 2017	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template.
May 4, 2017	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template.
May 9, 2019	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
November 16, 2020	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
January 14, 2021	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
January 2023	BM-3	v. 1.4	BM score altered from 2 to 3 based on revision of developmental toxicity-D score from moderate to low due to identification of effects only at maternally-toxic doses. The GreenScreen® assessment was updated with a v.1.4 template.

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