METHYL ETHYL KETONE

(CAS #78-93-3)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: January 30, 2023

Expiration Date: January 30, 2028

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TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Methyl Ethyl Ketone (CAS #78-93-3)

Methyl ethyl ketone (also known as butyl ketone or butanone) is a colorless, flammable liquid that is used as a solvent, chemical intermediate, and perfuming agent. As a volatile organic compound (VOC), it has an acetone or mint-like smell and is found in lacquers, adhesives, cleaning materials, degreasers, printing inks, paints, wood stains/varnishes, and paint removers. Methyl ethyl ketone is produced via the catalytic oxidation of n-butenes or dehydration of 2-butanol.

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

- Benchmark 2e ("Moderate T (Group I Human)")
    - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2g ("High Flammability or High Reactivity")
    - High flammability-F

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

The GreenScreen® Benchmark Score for methyl ethyl 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 1.4 update in 2019. The BM-2 score was also maintained with a version 1.4 update in this 2023 report.

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

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

As shown in Table 4, Type I (input data) uncertainties in methyl ethyl ketone's NAMs dataset include no or insufficient experimental data for carcinogenicity and for respiratory sensitization, lack of *in vivo* data on circulating hormones for endocrine activity assessments, and lack of established test methods for respiratory sensitization. Methyl ethyl ketone's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, use of non-validated or deleted *in vitro* genotoxicity test methods, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to evaluate methyl ethyl ketone's carcinogenic potential, the inaccuracy/non-transparency of VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in silico* prediction of receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of methyl ethyl ketone'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 Methyl Ethyl Ketone

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

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

GreenScreen® Chemical Assessment for Methyl Ethyl Ketone (CAS #78-93-3)

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

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Date: February 11, 2019

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Organization: ToxServices LLC
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Date: November 28, 2022; January 26, 2023

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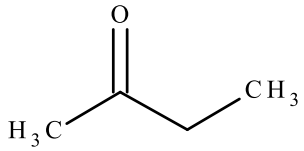
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: December 22, 2022, January 30, 2023

Expiration Date: January 30, 2028[2]

Chemical Name: Methyl Ethyl Ketone

CAS Number: 78-93-3

Chemical Structure(s):



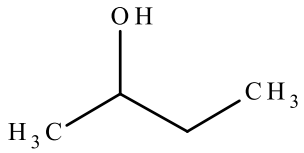
(PubChem 2023)

Also called: 2-Butanone; Butanone; MEK; Methyl ethyl ketone; Methylethyl ketone; 3-Butanone; Acetone, methyl; Ethyl methyl ketone; Ketone, ethyl methyl; Meetco; Methyl acetone; Methylethylketone; Metyl ethyl ketone; Ethyl methyl ketone or methyl ethyl ketone; UN1193; Butan-2-one; Ethylmethylketone; 2-Butanon; Ethylmethyl ketone; Oxobutane; Methylethylketon; Methyl ethylketone; Methylacetone; Methyl-ethyl ketone; Methyl(ethyl) ketone; n-Butanone; 2-Butanal; 2-

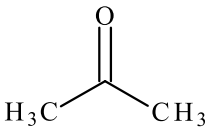
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment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

Oxobutane; Ethyl methylketone; Ethylmathyl ketone; Methyl-ethylketone; Methylethyl-ketone; Butane-2-one; 2 -Butanone; 2- Butanone; Butan-3-one; Methyl etyl ketone; Ethyl-methyl ketone; Methyl ethyl cetone; Methyl-ethyl-ketone; ethyl(methyl) ketone; Ketone, methyl ethyl; UN 1193 (PubChem 2023)

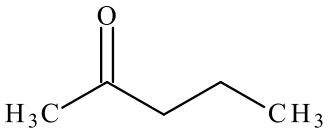
Suitable surrogates or moieties of chemicals used in this assessment (CAS #s):
An incomplete dataset was identified for methyl ethyl ketone. Methyl ethyl ketone is a rapid and direct metabolic product of 2-butanol (CAS #78-92-2), with approximately 96% of an orally administered 2-butanol dose converted to methyl ethyl ketone (U.S. EPA 2003a). Therefore, data for 2-butanol were used to fill data gaps. Additionally, ToxServices identified acetone (CAS #67-64-1) and 2-pentanone (CAS #107-87-9), also known as methyl propyl ketone, as suitable surrogates since they contain alkyl chain lengths differing from methyl ethyl ketone by one carbon.



Surrogate #1: 2-Butanol (CAS #78-92-2)



Surrogate #2: Acetone (CAS #67-64-1)



Surrogate #3: 2-Pentanone (CAS #107-87-9)

Identify Applications/Functional Uses:
1. Perfuming agent (EC 2023)
2. Solvent; chemical intermediate (OECD 2011)
3. Sterilizer for surgical equipment (HSDB 2015)

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

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

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

- Benchmark 2e ("Moderate T (Group I Human)")
  - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2g ("High Flammability or High Reactivity")
  - High flammability-F

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

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As methyl ethyl ketone is readily biodegradable (see the persistence section below) and is not expected to undergo hydrolysis due to the lack of functional groups that hydrolyze under environmental conditions (HSDB 2015), it is not expected to have relevant transformation products.

Introduction

Methyl ethyl ketone (also commonly known as butyl ketone) is a colorless, flammable liquid that is used as a solvent, chemical intermediate, and perfuming agent. As a volatile organic compound (VOC), it has an acetone or mint-like smell and is found in lacquers, adhesives, cleaning materials, degreasers, printing inks, paints, wood stains/varnishes, and paint removers (EC 2023, OECD 2011, HSBD 2015).

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

Methyl ethyl ketone is produced via the catalytic oxidation of n-butenes or dehydration of 2-butanol (HSDB 2015).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2023a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Methyl ethyl ketone is not listed on the U.S. EPA Safer Choice Program's SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 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),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for methyl ethyl ketone can be found in Appendix C.

- Methyl ethyl ketone is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Methyl ethyl ketone is listed on the U.S. DOT list as a Hazard Class 3 chemical (UN1193), Packing Group II.
- Methyl ethyl ketone is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
    - Québec CSST - WHMIS 1988 - Class D2B - Toxic material causing other toxic effects
    - EC - CEPA DSL - Inherently Toxic to Humans (iT human)
    - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters

Hazard Statement and Occupational Control

A harmonized EU classification is available for methyl ethyl ketone (ECHA 2023a); it has been classified as a GHS Category 2 flammable liquid (H225), a GHS Category 2 ocular irritant (H319), and a GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (H336), as summarized in Table 1. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) are presented in Table 2, below.

Table 1: GHS H Statements for Methyl ethyl ketone (CAS #78-93-3) (ECHA 2023a)

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

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

Table 1: GHS H Statements for Methyl ethyl ketone (CAS #78-93-3) (ECHA 2023a)	
H Statement	**H Statement Details**

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Methyl ethyl ketone (CAS #78-93-3)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, safety glasses/goggles, protective clothing, respirator (if necessary)	HSDB 2015	OSHA PEL: 200 ppm (590 mg/m^3) Cal/OSHA PEL (STEL), 8-hr TWA: 200 pm (300 ppm) NIOSH REL (STEL), 8-hr TWA: 200 pm (300 ppm) ACGIH 2018 TLV (STEL), 8-hr TWA: 200 pm (300 ppm) IDLH: 3,000 ppm	OSHA 2020

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

Physicochemical Properties of Methyl Ethyl Ketone

Methyl ethyl ketone is a colorless liquid under standard temperature and pressure. It is significantly volatile from dry surfaces (78-94.5 mm Hg), and is soluble in water (> 10,000 mg/L) but is slightly more soluble in octanol than in water (log K_{ow} = 0.3).

Table 3: Physical and Chemical Properties of Methyl Ethyl Ketone (CAS #78-93-3)

Property	Value	Reference
Molecular formula	C_4H_8O	PubChem 2023
SMILES Notation	C(CC)(C)=O	PubChem 2023
Molecular weight	72.1062 g/mol	PubChem 2023
Physical state	Liquid	ECHA 2023b
Appearance	Colorless	ECHA 2023b
Melting point	-86°C	ECHA 2023b
Boiling point	79.59-79.6°C	ECHA 2023b
Vapor pressure	104 hPa (78 mm Hg) at 20°C 126 hPa (94.5 mm Hg) at 25°C	ECHA 2023b
Water solubility	10,000 mg/L at 20°C 22,000 mg/L (temperature not specified)	ECHA 2023b
Dissociation constant	Not applicable (no ionic structure)	ECHA 2023b
Density/specific gravity	0.805 g/cm^3 at 20°C	ECHA 2023b
Partition coefficient	Log K_{ow} = 0.3 at 40°C (experimental – similar to OECD Guideline 117)	ECHA 2023b

Toxicokinetics

Methyl ethyl ketone is extensively absorbed after inhalation (54%) and oral exposure, and minimally absorbed after dermal exposure (4%). It is predominantly retained in the lung after inhalation exposure, and evenly distributed to other tissues through the blood. Methyl ethyl ketone is mainly metabolized by oxidation by cytochrome P450 enzymes, and excreted rapidly mainly as carbon dioxide and water.

- *Absorption*: As methyl ethyl ketone has a molecular weight of less than 500 g/mol and a log K_{ow} value between 0 and 4, it is expected to be well absorbed by both the oral and inhalational routes. Animal studies report approximately 54% absorption from inhalational exposures, a level that is similar to results identified in human exposure studies. Dermal absorption of methyl ethyl ketone is much lower and was reported to be approximately 4% *in vivo* (ECHA 2023b).
- *Distribution*: The solubility of methyl ethyl ketone in water, blood, and oil are relatively similar. Distribution coefficients of 242 for water/air, 202 for blood/air, and 263 for oil/air indicate that the compound is expected to evenly distribute in the soft tissues. Human exposure studies demonstrate that methyl ethyl ketone is predominately retained in the lung tissue and blood stream following inhalational exposures based on the low concentration measured in exhaled air (ECHA 2023b).
- *Metabolism*: Methyl ethyl ketone is primarily metabolized by cytochrome P450 enzymes in the lungs and liver via oxidation. A small portion of methyl ethyl ketone is reduced to 2-butanol (U.S. EPA 2003a). The main oxidative metabolites of methyl ethyl ketone found in the serum and urine following intraperitoneal dosing in guinea pigs or inhalation exposure in humans were 3-hydroxy-2-butanone (primary), 2,3-butanediol, 4-methyl-2-pentanol, and 4-hydroxy-4-methyl-2-pentanone. The metabolism of 2-butanol and methyl ethyl ketone are similar and minimal qualitative/ quantitative differences between them have been identified (ECHA 2023b). Methyl ethyl ketone concentrations are rapidly converted to the respective oxidated or reduced components (within 16 hours) (U.S. EPA 2003a).
- *Excretion*: In studies involving acute inhalational exposures, urinary excretion of methyl ethyl ketone and metabolites as well as the exhalation of unchanged methyl ethyl ketone account for a very small amount of the total elimination (approximately 0.1-3% of absorbed dose). The remaining absorbed fraction is rapidly transformed to carbon dioxide and water. Methyl ethyl ketone has a reported plasma half-life in humans of 49-96 minutes with a biphasic elimination: $t_{1/2}$ alpha = 30 minutes and $t_{1/2}$ beta = 81 minutes. No methyl ethyl ketone was measured in the blood of human volunteers at 20 hours post exposure (U.S. EPA 2003a, ECHA 2023b).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Methyl ethyl ketone was assigned a score of Low for carcinogenicity based on the lack of carcinogenicity detected in a limited dermal carcinogenicity study for methyl ethyl ketone and higher quality dermal carcinogenicity studies with the surrogate acetone. In addition, modeling with Toxtree, VEGA, and Danish QSAR database support a low carcinogenic concern. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data on the target compound and a strong surrogate and is supported by modeling data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2003a

  - A dermal carcinogenicity study was performed with male C3H mice (10-15/group) administered topical applications of 50 mg of 17%, 25%, or 29%% methyl ethyl ketone solution twice per week for 52 weeks. Treatment with the 25% solution did not produce skin tumors, but a skin tumor was identified in one animal dosed with the 29% solution after 27 weeks and a skin tumor was identified in one animal dosed with the 17% solution after 51 weeks. This study was reported in U.S. EPA (2003a). The U.S. EPA (2003a) authors concluded this study is inadequate to assess methyl ethyl ketone's carcinogenicity as the tested solutions also contained dodecylbenzene and the sulfur-containing compounds benzyl disulfide, 2-phenylbenzothiophene, or decalin, "which are expected to accelerate the rate of skin tumor formation."
- ECHA 2023d
  - *Surrogate: Acetone (CAS #67-64-1):* A dermal carcinogenicity study was performed with female ICR mice (29/treatment group, 249 in untreated group) administered topical applications of 0.1 mL acetone (90% or 100% purity) corresponding to 71 or 79 mg/mouse to shaved dorsal skin three times/week for 424 days/182 total applications (100% acetone) or 365 days/156 total applications (90% acetone). Treatment did not increase tumor incidences above the untreated control incidences. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - *Surrogate: Acetone (CAS #67-64-1):* A series of dermal carcinogenicity studies was performed with Sencar, CF1, C3H/HeJ, ICR/Ha Swiss, and hr/hr Oslo mice (number not specified) administered topical applications of acetone (purity not specified) as a vehicle at 20, 80, or 160 mg one to three times per week for a lifetime. Treatment did not increase the frequency of skin tumors at up to the highest dose tested. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
- Toxtree 2018
  - Methyl ethyl ketone does not have structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D).
- VEGA 2021
  - The CAESAR model predicts methyl ethyl ketone is a non-carcinogen with low reliability because the compound is outside of the model's applicability domain (global applicability domain (AD) index = 0.379) (Appendix E).
  - The ISS model predicts methyl ethyl ketone is a non-carcinogen with moderate reliability because the compound is just outside of the model's applicability domain (global AD index = 0.652) (Appendix E).
  - The IRFMN/Antares model predicts methyl ethyl ketone is a possible non-carcinogen with moderate reliability because the compound is inside of the model's applicability domain (global AD index = 0.759) (Appendix E).
  - The IRFMN/ISSCAN-CGX model predicts methyl ethyl ketone is a possible non-carcinogen with low reliability because the compound is outside of the model's applicability domain (global AD index = 0.552) (Appendix E).
  - The IRFMN oral classification model predicts methyl ethyl ketone is a non-carcinogen with high reliability based on experimental data (global AD index = 1) (Appendix E).
  - The IRFMN inhalation classification model predicts methyl ethyl ketone is a non-carcinogen with high reliability based on experimental data (global AD index = 1) (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 methyl ethyl ketone is a non-carcinogen.

- U.S. EPA 2021
    - ToxServices attempted to evaluate the carcinogenic potential of methyl ethyl ketone using OncoLogic v9.0. However, the class of chemicals methyl ethyl ketone belongs to is not supported by the current version of the software (Appendix F). Additionally, methyl ethyl ketone does not belong to the organic chemical classes included in OncoLogic v8.0 (U.S. EPA 2019). Therefore, ToxServices could not use Oncologic to determine the carcinogenic potential of methyl ethyl ketone.
- DTU 2023
    - Methyl ethyl ketone is inside of the applicability domains of all seven E Ultra FDA RCA carcinogenicity models included in the Danish (Q)SAR Models, and is predicted to be negative for carcinogenicity in male rats, female rats, rats, male mice, female mice, mice, and rodents. Additionally, it is inside of the applicability domains of six of seven Leadscope FDA RCA carcinogenicity models included in the Danish (Q)SAR Models and is predicted to be negative for carcinogenicity in male rats, female rats, rats, male mice, female mice, and mice. Finally, methyl ethyl ketone is inside the applicability domain for the model battery of liver-specific cancer models in mice or rats, with negative in domain predictions from the CASE Ultra and SciQSAR models (Appendix G).

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

Methyl ethyl ketone was assigned a score of Low for mutagenicity/genotoxicity based on negative results obtained for mutagenicity and clastogenicity in a battery of *in vitro* assays and an *in vivo* micronucleus test. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471. *Salmonella typhimurium* strains TA1538, TA1535, TA1537, TA98, and TA100 were exposed to methyl ethyl ketone (purity not specified) in dimethyl sulfoxide (DMSO) at 0.1-32 µL/plate without metabolic activation and 0.05-16 µL/plate with metabolic activation (S9 mix from livers of Aroclor-induced rats). Cytotoxicity was evident as moderately to extremely reduced background bacterial lawn at 32 µL/plate with metabolic activation during the toxicity determination. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive (not specified) controls were reported as valid. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
    - *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471 (positive control did not give anticipated results in the absence of metabolic activation). *S. typhimurium* tester strains TA1535, TA1537, TA1538, TA98, and TA100 were exposed to methyl ethyl ketone (≥ 99.0% purity) in DMSO at 31.25-4,000 µg/plate with and without metabolic activation (S9 mix from livers of Aroclor 1254-induced rats). Treatment did not induce cytotoxicity and did not increase the mutation frequency in the presence or absence

of metabolic activation. The vehicle controls were reported as valid. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

- *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant mammalian cell gene mutation assay conducted in a manner similar to OECD Guideline 476. Mouse lymphoma L5178Y cells were exposed to methyl ethyl ketone (purity not specified) in DMSO at 0.89-21 µL/mL without metabolic activation and 0.67-16 µL/mL with metabolic activation (S9 mix from livers of Aroclor-induced rats). Cytotoxicity was evident at 100 µL/mL during the preliminary toxicity test. Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive (ethyl methanesulfonate, 7,12-dimethylbenz[a]anthracene) controls were reported as valid. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- *In vitro*: Negative results for clastogenicity were obtained in a non-GLP-compliant chromosome aberration test conducted in a manner similar to OECD Guideline 473. Rat liver RL4 cell line cells were exposed to methyl ethyl ketone (≥ 99.0% purity) in distilled water at 0, 250, 500, or 1,000 µg/mL without exogenous metabolic activation (liver cells have innate metabolic activity). Treatment did not induce cytotoxicity and did not increase the frequency of chromosome aberrations in the absence of exogenous metabolic activation. The vehicle and positive (7,12-dimethylbenzanthracene) controls were reported as valid. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions)
- *In vitro*: Negative results for genotoxicity were obtained in a non-GLP-compliant cell transformation assay. BALB/3T3 Clone A31-1 mouse embryo cells were exposed to methyl ethyl ketone (99.91% purity) in Dulbecco's phosphate buffered saline (PBS) at 9-18 µl/mL without metabolic activation and 6-10 µl/mL with metabolic activation (S9 mix from livers of Aroclor 1254-induced male rats). Treatment did not induce cytotoxicity and did not produce evidence of genotoxicity in the presence or absence of metabolic activation. The vehicle and positive [N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), benzo[a]pyrene (B[a]P)] controls were reported as valid. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- *In vitro*: Negative results for genotoxicity were obtained in a non-GLP-compliant DNA damage and repair/unscheduled DNA synthesis (UDS) assay conducted in a manner similar to OECD Guideline 482. Hepatocytes isolated from normal adult male Sprague-Dawley rats were exposed to methyl ethyl ketone (purity not specified) in DMSO at 0.1-5.0 µL/mL without exogenous metabolic activation. Treatment induced cytotoxicity at ≥ 5.0 µL/mL but did not increase the frequency of UDS in the absence of exogenous metabolic activation. The vehicle, untreated negative, and positive (2-acetylaminofluorene) controls were reported as valid. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- *In vitro*: Negative results for mutagenicity were obtained in a non-GLP-compliant fungal gene mutation assay conducted in a manner similar to OECD Guideline 480. *Saccharomyces cerevisiae* cells were exposed to methyl ethyl ketone (≥ 99.0% purity) in DMSO at 0.01-5.0 mg/mL with and without metabolic activation (S9 mix from livers of Aroclor-induced rats). Treatment did not induce cytotoxicity and did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive (4-nitroquinoline-N-oxide, cyclophosphamide) controls were reported as valid. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
- *In vivo*: Negative results for clastogenicity were obtained in a non-GLP-compliant micronucleus test conducted in a manner similar to OECD Guideline 474. CD-1 mice

(5/sex/group) were administered single intraperitoneal injections of methyl ethyl ketone (99.91% purity) in corn oil at 1.96 mL/kg. The animals were subsequently sacrificed and femoral bone marrow samples were isolated and assessed for the presence of micronuclei. Treatment did not increase the frequency of micronuclei. The vehicle and positive (triethylenemelamine) controls were reported as valid. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

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

Methyl ethyl ketone was assigned a score of Low for reproductive toxicity. Treatment of rats with drinking water containing the surrogate 2-butanol reduced the fertility rate and body weight gains at 3% (4,571 mg/kg/day; NOAEL of 3,122 mg/kg/day). Data for the surrogate acetone indicate no adverse effects on male fertility of rats following exposure via drinking water, although one 13-week study identified deficits in sperm parameters at 3,400 mg/kg/day, which exceeded the threshold for systemic toxicity based on effects to the kidneys and hematopoietic system (1,700 mg/kg/day). The surrogate 2-pentanone did not adversely affect reproductive parameters in rats following repeated inhalation exposures in an GLP-compliant, OECD Guideline 421 reproduction / developmental toxicity screening test. Since U.S. EPA (2003a) concluded that the reduced fertility following oral exposure to the surrogate 2-butanol was secondary to reduced body weight gains and the surrogate acetone adversely affected sperm parameters only at a dose that also induced systemic toxicity, ToxServices did not classify methyl ethyl ketone as a reproductive toxicant under GHS. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lacking data for certain endpoints in the two-generation study with the surrogate 2-butanol, lack of female fertility data for the surrogate acetone, and that the data for surrogate 2-pentanone came from a screening test which includes evaluation of fewer endpoints than a full multi-generation reproduction toxicity test.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2003a, ECHA 2023c
  - *Oral: Surrogate: 2-Butanol (CAS #78-92-2):* In a pre-GLP two-generation study conducted in a manner similar to OECD Guideline 416 (F2 pups not necropsied), male and female Wistar rats (30/sex/dose) were provided drinking water containing the surrogate 2-butanol (assumed to be 100% pure) at 0, 0.3, 1, or 3% (contributing doses of 0, 538, 1,644, and 5,089 mg/kg/day for males and 0, 594, 1,771, and 4,571 mg/kg/day for females, respectively according to study authors) for nine weeks prior to mating, through mating, and until lactation day 21 (F0 generation). The high dose was reduced to 2% (contributing a dose of approximately 3,122 mg/kg/day) prior to the second mating. A second mating was performed after a two-week rest period. After weaning, the F1 generation was maintained on the same treatment, with the exception of the high dose which was reduced to 2% (approximately 3,122 mg/kg/day), and animals were mated after 8 weeks of treatment. The F2 generation received the same treatment as the F1 generation through lactation day 21. Treatment significantly decreased F0 body weights of both sexes at the 3% dose. The fertility rate in the F0 animals at the high concentration decreased to 73% which was below historical values for the rat colony, but such a reduction was not detected after the dose was reduced from 3% to 2%. In the F0 generation, copulatory success decreased at the highest (3%) dose but U.S. EPA (2003a) notes that the biological significance is unknown as effects may be due to reduced body weight gain at this dose. After reduction of the high dose to 2% and second mating, treatment reduced female body weight gain but did not adversely affect

reproduction. Additionally, treatment did not adversely affect F1 generation reproduction. U.S. EPA (2003a) concluded that 2-butanol did not affect reproduction at drinking water concentrations up to 3%. However, U.S. EPA (2003a) notes that estrous cyclicity, sperm parameters, and uterus, epididymides, and seminal vesicles weights were not measured or evaluated in this study. ToxServices identified a reproductive toxicity NOAEL of 2% (3,122 mg/kg/day) based on the lack of effects on reproduction at this dose and the decreased fertility rate in the presence of decreased body weights at 3% (4,571 mg/kg/day). The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

- ECHA 2023d
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A reproductive toxicity test was performed with male Wistar rats (10/group) provided drinking water containing acetone (analytical grade) at 0 or 5,000 mg/L (equivalent to 650 mg/kg/day) for nine weeks or 0 or 10,000 mg/L (equivalent to 1,300 mg/kg/day) for four weeks. In the four-week study, treated males were mated with untreated females. Males were evaluated for sperm parameters (testes, epididymis, and seminal vesicles) and reproductive indices (number of males without recognized mating, pregnant females, implantations, and dead or retarded fetuses). Treatment did not adversely affect male fertility at up to the highest dose tested. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A reproductive toxicity test was performed with male Wistar rats (10/group) provided drinking water containing acetone (purity not specified) at 0 or 5,000 mg/L for six weeks. Treated males were then mated with untreated females. Treatment did not adversely affect testis weights, tubuli diameter, or pathological findings in the testis or the number of pregnant females or fetuses, and tubuli diameter. The authors concluded that acetone treatment did not adversely affect male fertility at the only dose tested. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A repeated dose toxicity test was performed with Fischer 344 rats (10/sex/group) provided drinking water containing acetone (> 99% purity) at 2,500, 5,000, 10,000, 20,000, or 50,000 ppm for 13 weeks (ToxServices notes that the REACH dossier did not identify the 5,000 or 20,000 ppm concentrations in the "Doses/Concentrations" section). These concentrations contributed equivalent time-weighted average doses of 200, 400, 900, 1,700, and 3,400 mg/kg/day for males and 300, 600, 1,200, 1,600, and 3,100 mg/kg/day for females, respectively. The animals were evaluated for estrous cyclicity (estrous cycle stage and length), sperm parameters (sperm morphology, density, and motility), and reproductive organ histopathology. Systemic toxicity was evident in males at ≥ 1,700 mg/kg/day as adverse effects to the kidneys (mild renal nephropathy) and hematopoietic system (mild leukocytosis and depression of erythrocytes, hemosiderosis in spleen). In the high dose group, males exhibited decreased cauda epididymal and right epididymal weights, sperm density, and sperm motility and increased incidence of abnormal sperm. The authors identified a male reproductive toxicity NOAEL of 900 mg/kg/day based on adverse effects to the male reproductive tract at 3,400 mg/kg/day. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A repeated dose toxicity test was performed with B6C3F1 mice (10/sex/group) provided drinking water containing acetone (> 99% purity) for 13 weeks. Males were exposed to 1,250, 2,500, 5,000, 10,000, or 20,000 ppm (contributing time-weighted average doses of 380, 611, 1,353, 2,258, and 4,858 mg/kg/day, respectively) and females were exposed to 2,500, 5,000, 10,000, 20,000, or 50,000 ppm

(contributing time-weighted average doses of 892, 2,007, 4,156, 5,945, and 11,298 mg/kg/day, respectively) (ToxServices notes that the REACH dossier did not identify all of the dose groups in the "Doses/Concentrations" section). The animals were evaluated for estrous cyclicity (estrous cycle stage and length), sperm parameters (sperm morphology, density, and motility), and reproductive organ histopathology. Treatment did not produce adverse effects on these parameters up to the highest dose tested. The authors identified a reproductive toxicity NOAEL of 4,858 mg/kg/day, the highest dose tested in males. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

- ECHA 2023e
  - *Inhalation: Surrogate: 2-Pentanone (CAS #107-87-9):* A GLP-compliant, OECD Guideline 421 reproduction / developmental toxicity screening test was performed with Sprague-Dawley rats (12/sex/group) administered whole body inhalation exposures to 2-pentanone vapor (≥ 99.8% purity) at 0, 1, 2.5, or 5 mg/L for 6 hours/day. Males were exposed for two weeks prior to mating, during the two-week mating period, and post mating for a total of 51 consecutive exposures. Females were exposed for two weeks prior to mating, during the two-week mating period, during pregnancy, and up to postnatal day 4 for a total of 35-48 consecutive exposures. Males were evaluated for sperm parameters (sperm and sperm head counts, sperm motility, testes weights, and epididymis weights), reproductive organ weights, and reproductive performance (not specified). Treatment did not adversely affect these parameters and the study authors identified a reproductive NOAEC of 5 mg/L, the highest concentration tested. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Inhalation exposures to methyl ethyl ketone produced developmental toxicity (increased incidence of developmental variations or abnormalities, decreased fetal and/or litter weights) at the highest concentrations tested, usually co-occurring with maternal toxicity (decreased body weight gain, altered organ weights). Since one study in Sprague-Dawley rats identified developmental toxicity, including increased incidences of rare malformities, in the absence of maternal toxicity, ToxServices classified methyl ethyl ketone as a Category 2 developmental toxicant following inhalation exposures under GHS criteria (UN 2021). In addition, treatment of rats with drinking water containing the surrogate 2-butanol caused developmental toxicity (reduced the number of liveborn offspring, number of pups alive at postnatal day 4, mean pup body weight, reduced fetal body weights, and increased incidence of skeletal variations) in the presence of maternal toxicity (decreased body weights and body weight gains). ToxServices conservatively assumed direct developmental toxicity, as U.S. EPA used developmental effects in this multi-generation reproductive toxicity study as the critical effects to derive the oral reference dose (RfD) for methyl ethyl ketone (U.S. EPA 2003a). GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity is available in animal studies (CPA 2018b). The confidence in the score is low as it is unclear whether the developmental toxicity was a direct effect of methyl ethyl ketone or was secondary to maternal toxicity, and secondary developmental toxicity is not classifiable under GHS.

- Authoritative and Screening Lists
  - *Authoritative:*
    - MAK - Pregnancy Risk Group C ("There is no reason to fear damage to the embryo or foetus when MAK and BAT values are observed").
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b

- *Inhalation*: In a non-GLP-compliant developmental toxicity study conducted in a manner similar to OECD Guideline 414, pregnant female Sprague-Dawley rats (25/group, 35/control) were administered whole body inhalation exposures to methyl ethyl ketone (99.605% purity, form not specified) at 400 ppm, 1,000 ppm, or 3,000 ppm [equivalent to 1.18, 2.95, and 8.85 mg/L, respectively, based on a chemical-specific adjustment factor of 1 ppm = 2.95 mg/m^3 for methyl ethyl ketone (NIOSH 2019) and a conversion factor of 1 m^3 = 1,000 L] for 7 hours/day on gestation days (GD) 6-15. Animals were sacrificed on GD 21. Treatment significantly decreased maternal body weights on GD 16 and decreased body weight gain on GD 10-15 in the high concentration group. Fetuses in the high concentration group exhibited a significant decrease in delayed ossification of inter-parietal bones and increase in the incidence of extra lumbar ribs. The authors identified maternal toxicity and developmental toxicity NOAECs of 1,000 ppm (2.95 mg/L) based on the effects identified at 3,000 ppm (8.85 mg/L). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- *Inhalation*: In a GLP-compliant developmental toxicity study conducted according to an NTP protocol, pregnant female Swiss CD-1 mice (30/group, 10/treatment) were administered whole body inhalation exposures to methyl ethyl ketone vapor (> 99.9% purity) at 0, 400, 1,000, or 3,000 ppm [equivalent to 1.18, 2.95, and 8.85 mg/L, respectively, based on a chemical-specific adjustment factor of 1 ppm = 2.95 mg/m^3 for methyl ethyl ketone (NIOSH 2019) and a conversion factor of 1 m^3 = 1,000 L] for 7 hours/day on GD 6-15. Animals were sacrificed on GD 18. Treatment did not produce overt maternal toxicity but significantly increased maternal relative liver and kidney weights at the high concentration. Treatment reduced fetal body weight at the high concentration; the relative decrease in body weight was the same for both sexes but was statistically significant in males only. Treatment also increased the incidence of misaligned sternebrae with increasing concentration, with a statistically significantly increased incidence identified in the high concentration. Treatment did not affect the incidence of malformations. The authors identified maternal and developmental toxicity NOAECs of 1,000 ppm (2.95 mg/L) based on adverse effects identified at 3,000 ppm (8.85 mg/L). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- *Inhalation*: In an OECD Guideline 414 prenatal developmental toxicity study (GLP status not specified), pregnant female Sprague-Dawley rats (15-19/group) were administered whole body inhalation exposures to methyl ethyl ketone vapor (>99.5% purity) at 0, 1,000, or 3,000 ppm [equivalent to 2.95 and 8.85 mg/L, respectively, based on a chemical-specific adjustment factor of 1 ppm = 2.95 mg/m^3 for methyl ethyl ketone (NIOSH 2019) and a conversion factor of 1 m^3 = 1,000 L] for 6 hours/day on GD 6-20. Animals were sacrificed on GD 21. Treatment reduced dam corrected body weight gain and food consumption at the high concentration. Treatment also decreased fetal body weights at the high concentration, but did not increase embryo lethality or induce skeletal or visceral malformations. The authors identified maternal and developmental toxicity NOAECs of 1,000 ppm (2.95 mg/L) based on adverse effects identified at 3,000 ppm (8.85 mg/L). The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).

- U.S. EPA 2003a
  - *Inhalation:* In a developmental toxicity study in Sprague-Dawley rats, pregnant dams (21-23/group, 42/control, 47/sham control) were administered whole body exposures to methyl ethyl ketone vapor (purity not specified) at 1,000 or 3,000 ppm (2,950 and 8,850 mg/m^3, or 2.95 and 8.85 mg/L) on GD 6-15. Treatment did not induce maternal toxicity. Fetuses exhibited a 5% decrease in mean litter weight and a 3% decrease in crown-rump length at

the low concentration, but treatment did not adversely affect these parameters at the high concentration. Treatment increased the percent of litters with fetuses exhibiting gross abnormalities at the high concentration (19% vs. 0% for concurrent control group), and four high concentration fetuses exhibited malformations not previously been observed in historical controls (imperforate anus and brachygnathia, also known as overbite or short lower jaw). Additionally, treatment in the high concentration group increased the percentage of litters with sternebral skeletal variations (43% vs. 11% for concurrent control group). The percent of litters with any skeletal anomaly was increased at the low concentration (95% vs. 58% for the concurrent control group), but not at the high concentration (81%). The percent of litters with any soft tissue anomaly was increased at the high concentration (76% vs. 51% for the concurrent control group) but not the low concentration (70%). The U.S. EPA identified a maternal toxicity NOAEC of 8.85 mg/L based on the lack of maternal toxicity identified with treatment, and a developmental toxicity NOAEC and LOAEC of 2.95 mg/L and 8.85 mg/L, respectively, based primarily on the increased incidence of rare malformations at the high concentration.

- U.S. EPA 2003a, ECHA 2023c
    - *Oral: Surrogate: 2-Butanol (CAS #78-92-2):* In the previously described pre-GLP two-generation study conducted in a manner similar to OECD Guideline 416 (F2 pups not necropsied), male and female Wistar rats (30/sex/dose) were provided drinking water containing the surrogate 2-butanol (assumed to be 100% pure) at 0, 0.3, 1, or 3% (contributing doses of 0, 538, 1,644, and 5,089 mg/kg/day for males and 0, 594, 1,771, and 4,571 mg/kg/day for females, respectively, according to the study authors) for nine weeks prior to mating, through mating, and until lactation day 21 (F0 generation). The high dose was reduced to 2% (contributing a dose of approximately 3,122 mg/kg/day) prior to the second mating. A second mating was performed after a two-week rest period. After weaning, the F1 generation was maintained on the same treatment, with the exception of the high dose which was reduced to 2% (approximately 3,122 mg/kg/day), and animals were mated after 8 weeks of treatment. The F2 generation received the same treatment as the F1 generation through lactation day 21. Treatment induced maternal toxicity in the high dose group as reduced body weights (3%) and reduced body weight gains (2%). Treatment in the high dose group F1a generation reduced the number of live born pups, number of pups alive before culling at postnatal day 4, and mean pup body weight at day 21. In the F1b generation, treatment reduced mean fetal body weights at the high dose, and increased the incidence of skeletal variations compared to the 1% dose but not to the concurrent controls. In the F2 generation, treatment reduced mean pup body weights at day 4 and day 21 at the high dose. The study and U.S. EPA (2003a) authors identified a maternal toxicity NOAEL of 1% (1,771 mg/kg/day) and LOAEL of 2% (3,122 mg/kg/day) based on decreased body weight gain, and a developmental toxicity NOAEL of 1% (1,771 mg/kg/day) and LOAEL of 2% (3,122 mg/kg/day) based on decreased pup and fetal weights. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
        - *ToxServices notes that the U.S. EPA IRIS summary document (U.S. EPA 2003b) identifies a lower NOAEL of 594 mg/kg/day for decreased pup body weight which is discordant from the NOAEL identification in the IRIS toxicological review document (U.S. EPA 2003a).*

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

Methyl ethyl ketone was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint. While the Mitran et al. (1997) study provided evidence of methyl ethyl

ketone's neurotoxicity, it does not provide evidence indicating this chemical is endocrine active. Reliable modeled results from both Danish QSAR and VEGA predict that methyl ethyl ketone is not endocrine-active. However, ToxServices identified no data for *in vivo* endocrine hormone signaling for methyl ethyl ketone.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - TEDX - Potential Endocrine Disruptors - Potential Endocrine Disruptor.
- The following study was identified in the TEDX database entry for methyl ethyl ketone.
  - Mitran et al. 1997
    - An occupational study was performed with 41 Romanian workers exposed to methyl ethyl ketone and 63 matched controls from a cable factory. The subjects' mean age was 36 years and the mean length of exposure was 14 years. The participants completed a questionnaire, responded to questions regarding consumption of alcoholic drinks, submitted to a clinical examination, submitted biological samples for identification of biomarkers of exposure, and were assessed for motor nerve conduction velocity and neurobehavior. The results indicated that workers exposed to methyl ethyl ketone exhibited evidence of neurotoxicity (no further details provided). Based on these results, the study authors proposed that the 6-hour permissible exposure limit for methyl ethyl ketone be reduced to less than 200 mg/m^3.
- U.S. EPA 2023b
  - Methyl ethyl ketone 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
  - Methyl ethyl ketone was predicted to be inactive in the Estrogen Receptor Relative Binding Affinity model (IRFMN) with strong reliability (Global AD Index = 0.853) (Appendix H).
  - Methyl ethyl ketone 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 = 0.93) (Appendix H).
  - Methyl ethyl ketone was predicted to be non-active in the Androgen Receptor-mediated effect (IRFMN/COMPARA) 1.0.0 model with strong reliability (Global AD Index = 0.95) (Appendix H).
- DTU 2023
  - Methyl ethyl ketone, 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 J).
  - Methyl ethyl ketone 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 J).
  - Methyl ethyl ketone 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 J).

- Methyl ethyl ketone was predicted to be negative and in domain for TPO inhibition QSAR1 (Rat *in vitro*) and QSAR2 (Rat *in vitro*) (Appendix J).

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

Methyl ethyl ketone was assigned a score of Low for acute toxicity based on oral LD_{50} values as low as 2,600 mg/kg, dermal LD_{50} values as low as 6,400 mg/kg, and vapor inhalation LC_{50} values as low as 34.515 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and vapor inhalation LC_{50} values are greater than 20 mg/L (CPA 2018b). The confidence in the score is high as it is based on measured values.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Japan - GHS - Acute toxicity (inhalation: vapor) - Category 4
      - No rationale provided (NITE 2014). Classified to Category 5 in 2006 (NITE 2006).
- ECHA 2023b
  - *Oral*: LD_{50} (female Harlan-Wistar rat) = 3,460 mg/kg (pre-GLP, similar to OECD Guideline 423)
    - Note: this study was reported in ECHA with a score of 4 (not assignable) for reliability due to insufficient documentation.
  - *Dermal*: LD_{50} (male New Zealand white rabbit) > 10 mL/kg (>8.06 g/kg[9]) (pre-GLP, similar to OECD Guideline 402)
- ECB 2000, OECD 2011
  - *Oral*: LD_{50} (rat, sex and strain not specified) = 2,600-5,400 mg/kg
  - *Dermal*: LD_{50} (rabbit, sex and strain not specified) = 6,400 – 8,000 mg/kg
  - *Inhalation*: LC_{50} (rat, sex and strain not specified) > 5,000 ppm/6 h (>14.7 mg/L[10]) based on 90-day inhalation toxicity study)
- U.S. EPA 2003a
  - *Oral*: LD_{50} (rat, sex and strain not specified) = 5,522 mg/kg
  - *Oral*: LD_{50} (rat, sex and strain not specified) = 2,737 mg/kg
  - *Oral*: LD_{50} (mouse, sex and strain not specified) = 4,044 mg/kg
  - *Inhalation*: LC_{50} (rat, sex and strain not specified) = 34.515 mg/L/4h

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

Methyl ethyl ketone was assigned a score of High for systemic toxicity (single dose) based on renal tubular necrosis effects at an oral dose of 1,082 mg/kg in rats. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (single dose) when systemic toxicity is evident following oral doses between 300 and 2,000 mg/kg (CPA 2018b). The confidence in the score is low due to the insufficient documentation and supporting classification only by a screening list.

- Authoritative and Screening Lists

[9] Based on a density of 0.806 g/mL: 10 mL/kg * 0.806 g/mL = 8.06 g/kg
[10] 5,000 ppm * 72.1062 / 24,450 = 14.7 mg/L

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Japan - GHS - Specific target organs/systemic toxicity following single exposure - Category 2, Category 3 (respiratory irritation).
      - Category 2 is based on adverse effects on the kidneys in rats (NITE 2006, 2014). Respiratory irritation is based on human evidence following inhalation exposure.
    - Australia - GHS - H335 - May cause respiratory irritation.
- ECHA 2023b
  - *Oral*: No data regarding clinical signs of toxicity, body weight changes, or gross pathological findings were reported for the acute oral toxicity study that identified an oral LD_{50} of 3,460 mg/kg in female Harlan-Wistar rats. The REACH dossier reported this study with a reliability score of 4 (not assignable).
  - *Dermal*: No data regarding clinical signs of toxicity, body weight changes, or gross pathological findings were reported for the acute dermal toxicity study that identified a dermal LD_{50} > 8,050 mg/kg in male New Zealand white rabbits. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
- U.S. EPA 2003a
  - *Inhalation:* No evidence of airway irritation was seen in 13 men and 11 women exposed to 200 ppm (590 mg/m^3 or 0.59 mg/L) methyl ethyl ketone for 4 hours.
  - *Oral*: A single oral dose of 1,082 mg/kg methyl ethyl ketone to male Fischer 344 rats resulted in no mortality or histological changes to the liver, but caused tubular necrosis to the kidneys. No additional details were provided.

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

Methyl ethyl ketone was assigned a score of Low for systemic toxicity (repeated dose) based on a NOAEC of 14.87 mg/L in a 90-day inhalation toxicity study in rats. Additionally, in subchronic repeated oral dose toxicity studies, the surrogate acetone produced systemic toxicity NOAELs of 900 and 4,858 mg/kg/day in rats and mice, respectively. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data are available and no adverse effects are detected below the guidance value of 1 mg/L for a subchronic vapor inhalation toxicity study or below the guidance value of 100 mg/kg/day for a subchronic oral toxicity study (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study on the target compound.

- 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 2003a, ECHA 2023b
  - *Inhalation*: In a GLP-compliant 90-day inhalation toxicity study conducted in a manner similar to OECD Guideline 413, Fischer 344 rats (15/sex/dose) were administered 1,254, 2,518, or 5,041 ppm (0, 3,700, 7,430, or 14,870 mg/m^3, or 3.7, 7.43, or 14.87 mg/L[11]) methyl ethyl ketone vapor (> 99.9% purity) via whole body inhalation for 6 hours/day, 5 days/week. Animals were evaluated for body weight, clinical signs, food consumption, ophthalmoscopic examination, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. No mortality was observed. Transient effects on body weight were seen. Absolute liver weight was increased in females at all doses, and relative liver weight

[11] 3,700 mg/m^3 * 1 m^3 / 1,000 L = 3.7 mg/L

was increased at the high dose. Absolute and relative brain weight and absolute spleen weight were decreased, and relative kidney weights were increased at this dose. Absolute and relative liver weights were increased in males at the high dose. Significant increases in serum potassium, alkaline phosphatase and glucose, and a significant decrease in SGPT activity were seen in females at the high dose. As no histopathological changes were seen in the liver, changes were thought to be adaptive. Mean corpuscular hemoglobin was increased in both sexes at the high dose. U.S. EPA concluded that effects at the high dose (14.87 mg/L) are of uncertain toxicological significance, and that liver effects likely represent an adaptive response. Therefore, ToxServices identified a systemic toxicity NOAEC of 14.87 mg/L, the highest concentration tested. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).

- ECHA 2023d
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A repeated dose toxicity test conducted in a manner similar to OECD Guideline 408 was performed with Fischer 344 rats (10/sex/group) provided drinking water containing acetone (> 99% purity) at 2,500, 5,000, 10,000, 20,000, or 50,000 ppm (contributing equivalent time-weighted average doses of 200, 400, 900, 1,700, and 3,400 mg/kg/day for males and 300, 600, 1,200, 1,600, and 3,100 mg/kg/day for females, respectively) for 13 weeks. The animals were evaluated for clinical signs of toxicity, body weight, water consumption, hematology, ophthalmology, organ weights, and histopathology. Treatment did not induce clinical signs of toxicity or ophthalmological changes. High dose males and females exhibited 27.5% and 13.5% decreased weight gains, respectively. Treatment reduced water intake levels in high dose males and in females of the two highest dose groups. Treatment-related effects to hematology parameters in male rats included increased leukocyte, and lymphocyte counts and hemoglobin levels ≥ 20,000 ppm, decreased platelet and erythrocyte counts ≥ 20,000 ppm, increased mean cell volume and mean corpuscular hemoglobin ≥ 10,000 ppm, and increased reticulocyte counts ≥ 5,000 ppm. Some of these parameters were also statistically significantly different from controls at lower doses but did not demonstrate dose responses or were only slight in magnitude. High dose females exhibited increased leukocyte and lymphocyte counts, mean corpuscular hemoglobin, and mean cell volume and females in the two highest dose groups exhibited decreased platelet counts. Treatment-related organ weight changes included increased relative liver weights in mid and high dose males and mid and high dose females, increased relative kidney weights in high dose males and mid and high dose females, increased absolute kidney weights in high dose females, and increased relative testis weights in high dose males. Treatment-related histopathological changes included increased incidences of spleen pigmentation (hemosiderin) in males in the two highest dose groups and increased incidence and severity of kidney nephropathy (characterized by foci of regenerating cortical tubules lined by basophilic cuboidal epithelial cells) in males in the two highest dose groups. Female rats did not exhibit treatment-related histopathological changes. High dose males also exhibited treatment-related effects to the reproductive tract, with decreased caudal epididymal and right epididymal weights, increased percent abnormal sperm, and decreased sperm motility. The REACH dossier authors identified a systemic toxicity NOAEL of 10,000 ppm (900 mg/kg/day) based on histopathological changes to the kidney and spleen at ≥ 20,000 ppm (≥ 1,700 mg/kg/day) in treated males. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* A repeated dose toxicity test conducted in a manner similar to OECD Guideline 408 was performed with B6C3F1 mice (10/sex/group) provided drinking water containing acetone (> 99% purity) for 13 weeks. Males were

exposed to 1,250, 2,500, 5,000, 10,000, or 20,000 ppm (contributing time-weighted average doses of 380, 611, 1,353, 2,258, and 4,858 mg/kg/day, respectively) and females were exposed to 2,500, 5,000, 10,000, 20,000, or 50,000 ppm (contributing time-weighted average doses of 892, 2,007, 4,156, 5,945, and 11,298 mg/kg/day, respectively). The animals were evaluated for clinical signs of toxicity, body weight, water consumption, hematology, ophthalmology, organ weights, and histopathology. Treatment did not adversely affect clinical signs of toxicity, body weights, or ophthalmology findings. Treatment-related changes to hematology parameters included increased hematocrit in high dose females, increased hemoglobin levels in females in the two highest dose groups, increased mean corpuscular hemoglobin in high dose males, and increased hemoglobin levels in males at ≥ 5,000 ppm. High dose females exhibited increased absolute and relative liver weights. Two high dose females exhibited minimal centrilobular hepatocellular hypertrophy. The authors identified a systemic toxicity NOAEL of 20,000 ppm (5,945 mg/kg/day) based on increased liver weights and liver histopathological changes in treated females, and a systemic toxicity NOAEL of 20,000 ppm (4,858 mg/kg/day) for males based on the lack of systemic toxic effects at up to the highest dose tested. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): M
Methyl ethyl ketone was assigned a score of Moderate for neurotoxicity (single dose) based on an authoritative listing and animal data supporting a GHS Category 3 classification for transient narcotic effects. Methyl ethyl ketone is associated with H Statement H336 (May cause drowsiness or dizziness). These classifications correspond to a score of Low-Moderate. Evidence of narcotic effects in several acute inhalation toxicity studies in rats and mice indicate that GHS Category 3 classification is warranted. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified as a GHS Category 3 specific target organ toxicant following single exposures for narcotic effects (CPA 2018b). The confidence in the score is high as it is based on an authoritative list.

- 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 (narcotic effects)
      - No rationale provided (NITE 2014). Not classified in 2006 (NITE 2006).
    - Korea - GHS - Specific target organ toxicity - Single exposure - Category 3 [H336 - May cause drowsiness or dizziness]
    - Australia - GHS - H336 - May cause drowsiness or dizziness
    - Malaysia - GHS - H336 - May cause drowsiness or dizziness
    - Grandjean and Landrigan - Neurotoxic Chemicals - Neurotoxic
    - Boyes - Neurotoxicants – Neurotoxic
- U.S. EPA 2003a
  - *Inhalation:* Methyl ethyl ketone vapors are expected to cause reversible nervous system depression. In a human case study, nausea, headaches, dizziness, and respiratory distress were seen in a 38-year old male worker exposed to a paint base containing methyl ethyl ketone at an unknown concentration for an unspecified period of time. Symptoms progressed to impaired concentration, memory loss, tremor, gait ataxia, and dysarthria, and toxic encephalopathy with dementia and cerebellar ataxia was diagnosed upon MRI. Effects

persisted for more than 30 months but it is unclear whether they could be attributed to methyl ethyl ketone or other solvents in the mixture. No effects on psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), postural sway, and a profile of mood states were seen in human volunteers exposed to 200 ppm (equivalent to 590 mg/m^3 or 0.59 mg/L) for 4 hours in a study conducted by NIOSH. Psychomotor tests (choice reaction time, visual vigilance, dual task, and memory scanning), a sensorimotor test, and a test of mood were performed on 13 men and 11 women exposed to 200 ppm (590 mg/m^3 or 0.59 mg/L) methyl ethyl ketone for 4 hours. Effects on 2 of 32 measures (choice reaction time in males and percent incorrect responses for dual task in females) were seen but were attributed to chance due to the large number of comparisons performed.

- *Inhalation:* In the acute inhalation toxicity study that identified an LC_{50} of 34.515 mg/L in rats, narcosis was observed. No additional details were provided.
- *Inhalation:* In a study of mice (sex and strain not specified) exposed to methyl ethyl ketone at 300, 1,000, 3,000, 5,600, or 10,000 ppm (equivalent to 885, 2,950, 8,850, 16,520, and 29,500 mg/m^3, respectively, and 0.885, 2.95, 8.85, 16.52, and 29.5 mg/L, respectively) at 30 minute intervals for a total exposure of 2 hours, an EC_{10} for failure to respond to a visual stimulus of 300 ppm (0.085 mg/L) was calculated.
- *Inhalation:* In a study of 10 Swiss mice exposed to methyl ethyl ketone via whole body inhalation at 0, 1,602, 1,848, 2,050, or 2,438 ppm (equivalent to 0, 4,726, 5,452, 6,048, and 7,192 mg/m^3, respectively, and 0, 4.726, 5.452, 6.048, and 7.192 mg/L, respectively) for 4 hours, a significant decrease in immobility in a behavioral despair swimming test was seen at all doses.

- ECHA 2023b
  - *Dermal:* No data regarding clinical signs of toxicity or gross pathological findings were reported for the acute dermal toxicity study that identified a dermal $LD_{50} > 8{,}050$ mg/kg in male New Zealand white rabbits treated with methyl ethyl ketone. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
- ECHA 2023c
  - *Oral: Surrogate: Acetone (CAS #67-64-1):* In an acute oral toxicity study in female Sprague-Dawley rats that identified an LD_{50} of 5,800 mg/kg, animals were administered acetone at doses of 5,370-6,980 mg/kg. Initial signs of toxicity include decreased activity and ataxia within 3 hours, and the signs resolved by 24 hours. Animals that died displayed tremors, tonus, and convulsions (Klimisch 2, reliable with restrictions).

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

Methyl ethyl ketone was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurological effects in repeated dose inhalation studies in rats. Although there is some evidence of neurobehavioral effects in occupational populations exposed to butyl ketone, this relationship is confounded by co-exposure with other solvents that may also act as neurotoxicants. In addition, available data on the surrogate acetone indicate that neurological effects are observed only at high doses in animals that exceed the guidance value of 100 mg/kg/day for an oral study. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and adverse effects are not seen below the guidance value of 1 mg/L for a subchronic inhalation toxicity study or the guidance value of 100 mg/kg/day for a subchronic oral toxicity study (CPA 2018b). The confidence in the score is high based on reliable measured data on the target chemical and a strong surrogate.

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

  - *Screening:*
    - Japan - GHS - Specific target organs/systemic toxicity following single exposure - Category 1 (nervous system)
      - Based on sensory paralysis of the hand and arm following human occupational exposure (NITE 2006, 2014).
    - New Zealand - GHS – Category 2 (inhalation) - Harmful to human target organs or systems
      - Based on adverse neurological effects detected in humans following chronic inhalation exposures (CCID 2023).
    - Grandjean and Landrigan - Neurotoxic Chemicals - Neurotoxic
    - Boyes - Neurotoxicants – Neurotoxic
    - Classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- U.S. EPA 2003a
  - *Inhalation*: In a previously described 90-day inhalation toxicity study, Fisher 344 rats (15/sex/dose) were administered whole body inhalation exposures of methyl ethyl ketone vapor (> 99.9% purity) at 1,254, 2,518, or 5,041 ppm [equivalent to 0, 3.7, 7.43, and 14.87 mg/L, respectively, based on a chemical-specific adjustment factor of 1 ppm = 2.95 mg/m^3 for methyl ethyl ketone (NIOSH 2019) and a conversion factor of 1 m^3 = 1,000 L] for 6 hours/day, 5 days/week, for 89-90 days. Treatment did not adversely affect neurological function (assessments of posture, gait, facial muscular tone, or symmetry, and four neuromuscular reflexes). At necropsy, no histopathological lesions were detected in the brain.
  - No evidence of peripheral neuropathy was detected in 12 Sprague-Dawley rats (sex not specified) that were administered 1,125 ppm methyl ethyl ketone (equivalent to 3,318 mg/m^3 and 3.318 mg/L) for 16, 25, 35, or 55 days. No histological changes were seen in sciatic nerve and foot muscle or spinal cord and dorsal root ganglia.
  - Motor nerve conduction velocity, distal motor nerve latency, and tail nerve conduction velocity were measured in male Wistar rats (8/group) that were administered 0 or 200 ppm methyl ethyl ketone (equivalent to 590 mg/m^3 and 0.590 mg/L) for 12 hours/day for 24 weeks, and histopathology was performed on one tail nerve per rat. A slight increase in motor nerve conduction velocity and mixed nerve conduction velocity and a decrease in distal motor latency was seen at 4 weeks but not at 8, 12, 16, 20, or 24 weeks. No histopathological lesions were seen in the tail nerve at 24 weeks.
  - In its evaluation of methyl ethyl ketone, U.S. EPA concluded that there is some evidence of neurological effects in humans with repeated exposures to methyl ethyl ketone, but those exposures occurred in conjunction with other solvents. U.S. EPA also noted that animal studies do not support the case for persistent neurological effects.
- ECHA 2023c
  - *Oral: <u>Surrogate: Acetone (CAS #67-64-1):</u>* In a non-guideline toxicity study with specific investigation of effects on male fertility (GLP not specified), male Wistar rats (10/dose) were administered 0 or 1% acetone in drinking water for 4 weeks, or 0 and 0.5% acetone in drinking water for 9 weeks. A functional observation battery (FOB) was conducted to observe sensory, motor, and physiological endpoints. A reduction in hindlimb and forelimb grip strength was noted after the 4-week exposure to 1% acetone. There were no adverse effects after the 9-week exposure to 0.5% acetone. The authors reported neurobehavioral toxicity NOAEL and LOAEL values of 650 (0.5%) and 1,300 mg/kg/day (1%), respectively (Klimisch 2, reliable with restrictions). *ToxServices notes these values significantly exceed*

the duration-adjusted GHS guidance value of 300 mg/kg/day for a 4-week study for Category 2 classification.

- *Oral: Surrogate: Acetone (CAS #67-64-1):* Acetone was evaluated as a vehicle control substance in a non-guideline (GLP not specified) 6-week study in rats. Male Wistar rats were exposed to acetone at 0.5% in the drinking water (5,000 mg/L, corresponding to 600 mg/kg/day based on water consumption) for 6 weeks (9-11 animals per group). Nerve conduction velocity was measured in the tails of rats weekly in weeks 3-6, and performance on rotarod was measured weekly in weeks 1-6. Animals were also evaluated for body weight gain and water consumption. Exposed and control animals demonstrated a constant increase in nerve conduction velocity each week, however the week 6 values were statistically significantly lower for exposed rats compared to controls (29.5 +/- 1.1 compared to 31.5 +/- 2.1 m/sec, respectively, $p < 0.05$). As the difference was slight and occurred only at a single time point, authors speculated the findings were not toxicologically significant (Klimisch 2, reliable with restrictions). *ToxServices notes also control rats had greater variability in weekly values and did not show a constant increase (i.e., control values at week 5 were decreased). This also suggests the week 6 decreased value for exposed rats to controls was spurious and not toxicologically significant. No historical data for this species, endpoint, and laboratory were provided.*

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

Methyl ethyl ketone was assigned a score of Low for skin sensitization based on the lack of dermal sensitization detected in a Buehler test. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - A GLP-compliant, OECD Guideline 406/EU Method B.6 Buehler test was performed with female Dunkin-Hartley guinea pigs (20/treatment, 10/control) administered topical applications of methyl ethyl ketone (99.7% purity). The induction doses were administered as topical applications of 0.3 mL undiluted methyl ethyl ketone to the skin under occlusive dressing for 24 hours once per week for three weeks. The challenge dose was applied on day 29 as a topical application of 0.1 mL undiluted methyl ethyl ketone and a 50% dilution in Alembicol "D" (fractionated coconut oil) under occlusive dressing for 6 hours. The dermal reactions were evaluated 24 and 48 hours after the challenge dose. Challenge with the undiluted methyl ethyl ketone resulted in 2/20 and 0/20 positive reactions after 24 and 48 hours, respectively, while challenge with the 50% solution resulted in 1/20 and 0/20 positive reactions after 24 and 48 hours, respectively. The study authors concluded that methyl ethyl ketone was not sensitizing to the skin under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction)

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

Methyl ethyl ketone was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential and according to ECHA's guidance on respiratory sensitization evaluation. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization,

which is generally based on observations in humans, 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
  - Methyl ethyl ketone does not contain any structural alerts for respiratory sensitization (Appendix K)
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As methyl ethyl ketone 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 methyl ethyl ketone, and as methyl ethyl ketone does not contain any structural alerts for respiratory sensitization (OECD 2022), methyl ethyl ketone is not expected to be a respiratory sensitizer.

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

Methyl ethyl ketone was assigned a score of High for skin irritation/corrosivity based on reports of mild to moderate irritation in humans and animals following repeated or extended exposures. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when available data indicate that GHS Category 2 classification may be warranted (CPA 2018b). The confidence in the classification is low as erythema and edema scores were not identified in the available study summaries.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - Japan - GHS - Skin corrosion / irritation - Category 2
      - Based on moderate irritation following application to rabbit skin (NITE 2006, 2014).
- HSDB 2015
  - Methyl ethyl ketone damaged only the stratum corneum when applied to the forearm skin of two volunteers for 1 hour/day on 6 consecutive days.
  - A 20% solution of methyl ethyl ketone in petrolatum did not cause any irritation when applied to the skin of 24 human volunteers for 48 hours.
  - Prolonged contact may cause defatting and dermatitis.
- ECB 2000, OECD 2011
  - Methyl ethyl ketone produced mild to moderate skin irritation following topical application to the skin of rabbits with and without occlusion for 24 hours in a non-GLP-compliant test. No further details were provided.
- Based on the weight of evidence, a score of High was assigned. No standard dermal irritation studies were available for methyl ethyl ketone. Studies of repeated exposures in humans and prolonged exposures to methyl ethyl ketone in rabbits report at most mild to moderate irritation, possibly due to defatting of the skin. Although effects due to defatting of the skin are not considered in GHS classification, in the absence of standard toxicity tests, ToxServices conservatively assumes that effects seen with repeated and extended exposures may occur after a standard duration study.

Based on the mild to moderate skin irritation identified in rabbits exposed for 24 hours and stratum corneum damage identified in human volunteers, ToxServices adopted the Japanese GHS skin irritation classification and classified methyl ethyl ketone as a Category 2 skin irritant under GHS criteria (UN 2021). GHS criteria define Category 2 skin irritants as chemicals that produce mean scores of 2.3-4.0 for erythema and/or edema in at least 2 of 3 animals following readings at 24, 48, and 72 hours.

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

Methyl ethyl ketone was assigned a score of High for eye irritation/corrosivity based on an authoritative listing. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified by the EU as GHS Category 2A ocular irritants (H319) (CPA 2018b). The confidence in the score is high as it is based on an authoritative A list with support from experimental data.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H319 - Causes serious eye irritation.
  - *Screening:*
    - Japan - GHS - Serious eye damage / eye irritation - Category 2A.
      - No explanation provided (NITE 2014). Previously a Category 2B eye irritant based on evidence in humans and rabbits (NITE 2006).
    - Korea - GHS - Serious eye damage/irritation - Category 2 [H319 - Causes serious eye irritation]
    - Australia - GHS - H319 - Causes serious eye irritation.
    - Malaysia - GHS - H319 - Causes serious eye irritation.
    - New Zealand - GHS – Cat. 2A - Irritating to the eye.
      - Based on significant irritation detected in the eyes of rabbits (CCID 2023).
- ECHA 2023b
  - In a pre-GLP ocular irritation study conducted in a manner similar to OECD Guideline 405 (observations continued only until day 7), male albino rabbits (6 total) were administered ocular instillations of 0.1 mL undiluted methyl ethyl ketone (purity not specified). An observation period of 7 days following the instillations. The mean overall irritation score was 19.2/110 at 24 hours, 10.8/110 at 72 hours, and 0.8/110 at 7 days. Authors concluded that methyl ethyl ketone is irritating but that as the mean score was close to 0 at day 7, it can be surmised that effects are reversible. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
  - A GLP-compliant ocular irritation study conducted in a manner similar to OECD Guideline 405 was performed with rabbits (4 total, strain not specified) administered single ocular instillations of an unspecified volume of methyl ethyl ketone (99% purity). An observation period of 10 days followed the instillations. After 1 day, the mean modified maximum average irritation score was 50/110. The ocular irritation effects were fully reversible within 10 days. The study authors concluded that methyl ethyl ketone was irritating to the eyes under the conditions of the study. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).

Ecotoxicity (Ecotox)

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

Methyl ethyl ketone was assigned a score of Low for acute aquatic toxicity based on acute aquatic L/EC_{50} values as low as 308 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when aquatic L/EC_{50} values are greater than 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on measured data on all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) = 2,973 mg/L (measured) (GLP-compliant, OECD Guideline 203)
  - 48-hour LC_{50} (*Leuciscus idus melanotus*) = 4,600-4,880 mg/L (nominal)
  - 48-hour mobility EC_{50} (*Daphnia magna*) = 308 mg/L (measured) (GLP-compliant, OECD Guideline 202)
  - 24-hour mobility EC_{50} (*D. magna*) = 7,060 mg/L (nominal) (non-GLP-compliant, similar to OECD Guideline 202)
  - 24-hour mobility EC_{50} (*D. magna*) = 8,890 mg/L (nominal) (non-GLP-compliant, similar to OECD Guideline 202)
  - 72-hour growth rate EC_{50} (*Pseudokirchneriella subcapitata*, algae) = 1,220 mg/L (measured) (GLP-compliant, OECD Guideline 201)
  - 96-hour growth rate EC_{50} (*P. subcapitata*, algae) = 2,029 mg/L (measured) (GLP-compliant, OECD Guideline 201)

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

Methyl ethyl ketone was assigned a score of Low for chronic aquatic toxicity based on the lowest predicted chronic aquatic toxicity value of 60.92 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2018b). The confidence in the score is low as only measured data were identified for the algae trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - Methyl ethyl ketone (100% purity) has a measured 72-hour growth rate NOEC of 566 mg/L in algae (*Raphidocelis subcapitata*) as identified in a GLP-compliant, OECD Guideline 201 test. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- U.S. EPA 2017a
  - Methyl ethyl ketone is designated to the neutral organics ECOSAR chemical class (Appendix L). The most conservative predicted chronic aquatic toxicity values are 161.82 mg/L in fish, 60.92 mg/L in daphnia, and 69.49 mg/L in green algae.

Environmental Fate (Fate)

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

Methyl ethyl ketone was assigned a score of Very Low for persistence based on it meeting the 10-day window in a ready biodegradability test, and soil being predicted as it is dominant environmental compartment. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil is the dominant environmental compartment and they are readily biodegradable, meeting the 10-day window (CPA 2018b). The confidence in the score is high as it is based on a reliable experimental study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - EC - CEPA DSL – Persistent
      - Based on a predicted ozone reaction half-life of 999 days (OECD 2023).
- ECHA 2023b
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 D/EU Method C.4E/EPA OTS 796.3200 was performed with activated domestic sewage (adaptation not specified) exposed to methyl ethyl ketone (100% purity) at 2 or 5 mg/L for 28 days. Biodegradation (as measured by DOC removal) reached 70 and 61% on day 7 for 2 and 5 mg/L, respectively. At the end of the exposure period, the level of degradation was 98% for the 2 mg/L sample and ≥ 57% for the 5 mg/L. The authors note that the "5 mg/L concentration achieved the maximum percent biodegradation possible based on the theoretical oxygen demand of the test substance and the amount of oxygen present in the test system," and concluded that methyl ethyl ketone was readily biodegradable under the conditions of this study. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
    - Meeting the pass level (70% DOC removal) in 7 days indicates that the 10-day window is met.
- U.S. EPA 2017b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that methyl ethyl ketone is expected to be readily biodegradable (Appendix M). Fugacity modeling predicts 53.9% will partition to soil with a half-life of 30 days, 45.7% will partition to water with a half-life of 15 days, and 0.339% will partition to air with a half-life of 1.33 hours.

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

Methyl ethyl ketone was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 0.3 and an estimated BCF of 1.035. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4 and BCF values are no greater than 100 (CPA 2018b). The confidence in the score is high as it is based in part on a measured log K_{ow} that is less than 4.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - Methyl ethyl ketone has a log K_{ow} of 0.3 at 40°C as identified in a test conducted in a manner similar to OECD Guideline 117. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction).
- U.S. EPA 2017b

- BCFBAF predicts a BCF of 3.162 L/kg using the regression-based method, and 1.035 using the Arnot-Gobas method for the upper trophic level, based on a log K_{ow} of 0.3 (Appendix M).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Methyl ethyl ketone was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score is low as no authoritative listings or measured data were identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECB 2000
  - Methyl ethyl ketone is not explosive and has no oxidizing properties.
- Pharmco 2018
  - A safety data sheet for methyl ethyl ketone indicates that it has a physical/reactivity hazard of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives (e.g., helium)").
- No other measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of methyl ethyl ketone. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, methyl ethyl ketone is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (Appendix N).
  - Based on the structure of its components or moieties, methyl ethyl ketone is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of methyl ethyl ketone has 1 oxygen, which is bonded only to carbon and hydrogen, classification is not warranted.

Flammability (F) Score (vH, H, M, or L): H
Methyl ethyl ketone was assigned a score of High for flammability based on an authoritative listing. GreenScreen® criteria classify chemicals as a High hazard for flammability when they are classified by the EU as GHS Category 2 flammable liquids (H225) (CPA 2018b). The confidence in the score is high as it is based on an authoritative listing supported by experimental data.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU - GHS (H-Statements) - H225 - Highly flammable liquid and vapour
  - *Screening:*
    - Australia - GHS - H225 - Highly flammable liquid and vapour
    - Japan - GHS - Flammable liquids - Category 2
      - Based on a flash point < 23°C and a boiling point >35°C (NITE 2006, 2014).

        - Korea - GHS - Flammable liquids - Category 2 [H225 - Highly flammable liquid and vapour]
        - Malaysia - GHS - H225 - Highly flammable liquid and vapour
        - New Zealand - GHS - 3.1B - Flammable Liquids: high hazard
            - Based on a flash point of -9°C in a closed cup test and a boiling point of 79.6°C (CCID 2023).
        - Québec CSST - WHMIS 1988 - Class B2 - Flammable liquids
- ECHA 2023b
    - Methyl ethyl ketone (purity not specified) has a boiling point of 79.59°C. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
    - Methyl ethyl ketone (purity not specified) has a boiling point of 79.6°C. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
    - Methyl ethyl ketone (purity not specified) has a flash point of -9°C as identified in a non-GLP-compliant test. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
    - Methyl ethyl ketone (purity not specified) has a flash point of -6°C as identified in a non-GLP-compliant closed cup test. The REACH dossier reported this study with a reliability score of 2 (reliable with restrictions).
- U.S. DOT 2008a
    - Methyl ethyl ketone is designated to hazard class or division 3 (flammable liquid), packaging group II, and label code 3.
- Based on the weight of evidence, a score of High is assigned. Based on a boiling point of 79.59°C and a flash point of -9°C to -6°C, ToxServices classified methyl ethyl ketone as a Category 2 flammable liquid under GHS criteria (UN 2021). GHS defined Category 2 flammable liquids as chemicals with flash points < 23°C and initial boiling points > 35°C. This classification agrees with the EU classification.

Use of New Approach Methodologies (NAMs)[12] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation; and *in vitro* assays for genotoxicity. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 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 4, Type I (input data) uncertainties in methyl ethyl ketone's NAMs dataset include no or insufficient experimental data for carcinogenicity and for respiratory sensitization, lack of *in vivo* data on circulating hormones for endocrine activity assessments, and lack of established test methods for respiratory sensitization. Methyl ethyl ketone's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, use of non-validated or deleted *in vitro* genotoxicity test methods, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of OncoLogic to evaluate methyl ethyl ketone's carcinogenic potential, the inaccuracy/non-transparency of VEGA carcinogenicity database, the uncertain *in vivo* relevance of *in silico* prediction of receptor binding, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of methyl ethyl ketone's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available for the oral and inhalation routes, and insufficient experimental data are available for the dermal route. **Endocrine activity:** No *in vivo* data are available on circulating hormones. **Respiratory sensitization**: No experimental data are available, and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). OncoLogic could not evaluate carcinogenic potential of this chemical (U.S. EPA 2021). Two VEGA models' predictions were based on

[12] 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).

	measured data on the target chemical, which ToxServices could not identify. **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[13]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[14] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[15]. The *in vitro* UDS assay detects "longpatch repair" but is less sensitive for detection of "shortpatch repair". Mutagenic events may result from non-repair, misrepair, or misreplication of DNA lesions, and UDS gives no indication of fidelity of the repair process. It is possible that a mutagen interacts with DNA but damage is not repaired by an excision repair process.[16] Identification of morphologically transformed colonies in the *in vitro* mammalian cell transformation assay could be subjective. The mechanism leading to cell transformations is not fully understood. The test does not inform *in vivo* potency, species-specificity or tissue-specificity of cell transformations, and is being validated for mono-constituent substances only[17]. The yeast gene mutation assay test guideline (OECD Guideline 480) has been deleted from the recommended OECD test guidelines due to lack of use under regulatory settings, and inferior performance compared to other tests.[18] **Endocrine activity:** The *in vivo* relevance of *in silico* modeling of receptor binding is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.

[13] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[14] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[15] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[16] https://www.oecd-ilibrary.org/environment/test-no-486-unscheduled-dna-synthesis-uds-test-with-mammalian-liver-cells-in-vivo_9789264071520-en#:~:text=The%20purpose%20of%20the%20unscheduled,physical%20agents%20in%20the%20liver.
[17] https://www.oecd.org/env/ehs/testing/Guidance-Document-on-the-in-vitro-Syrian-Hamster-Embryo-Cell-Transformation-Assay.pdf
[18] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

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/Toxtree/OncoLogic/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay/ *in vitro* cell transformation assay/ *in vitro* UDS assay/ fungal gene mutation assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: ToxCast/VEGA/Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301D Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Methyl Ethyl Ketone (CAS #78-93-3)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / **Chemical Name** / **CAS#**	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Methyl Ethyl Ketone / 78-93-3	L	L	*L*	M	DG	L	*H*	L	M	L	L	*L*	*H*	H	L	*L*	vL	vL	*L*	H

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Methyl Ethyl Ketone	2

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

Table 6

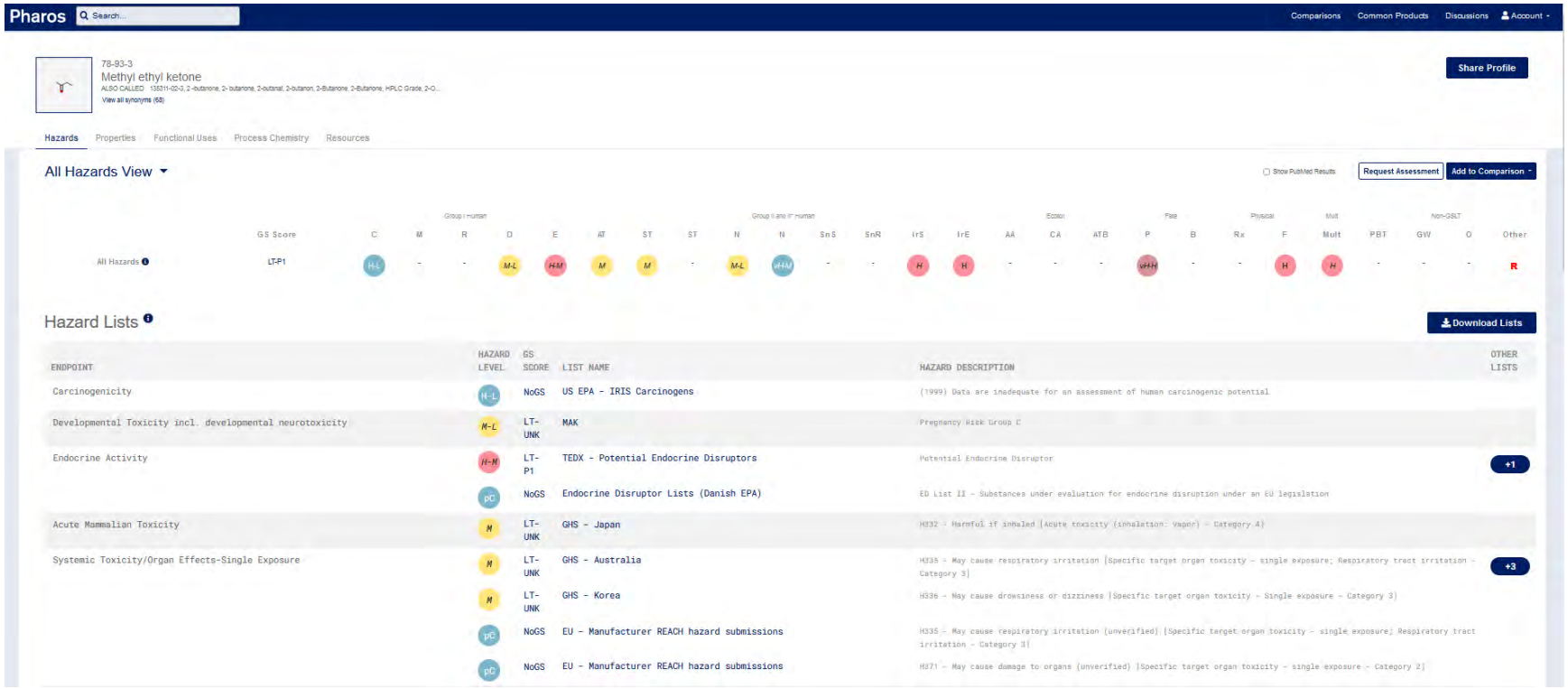
Chemical Name	Final GreenScreen® Benchmark Score
Methyl Ethyl Ketone	2

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

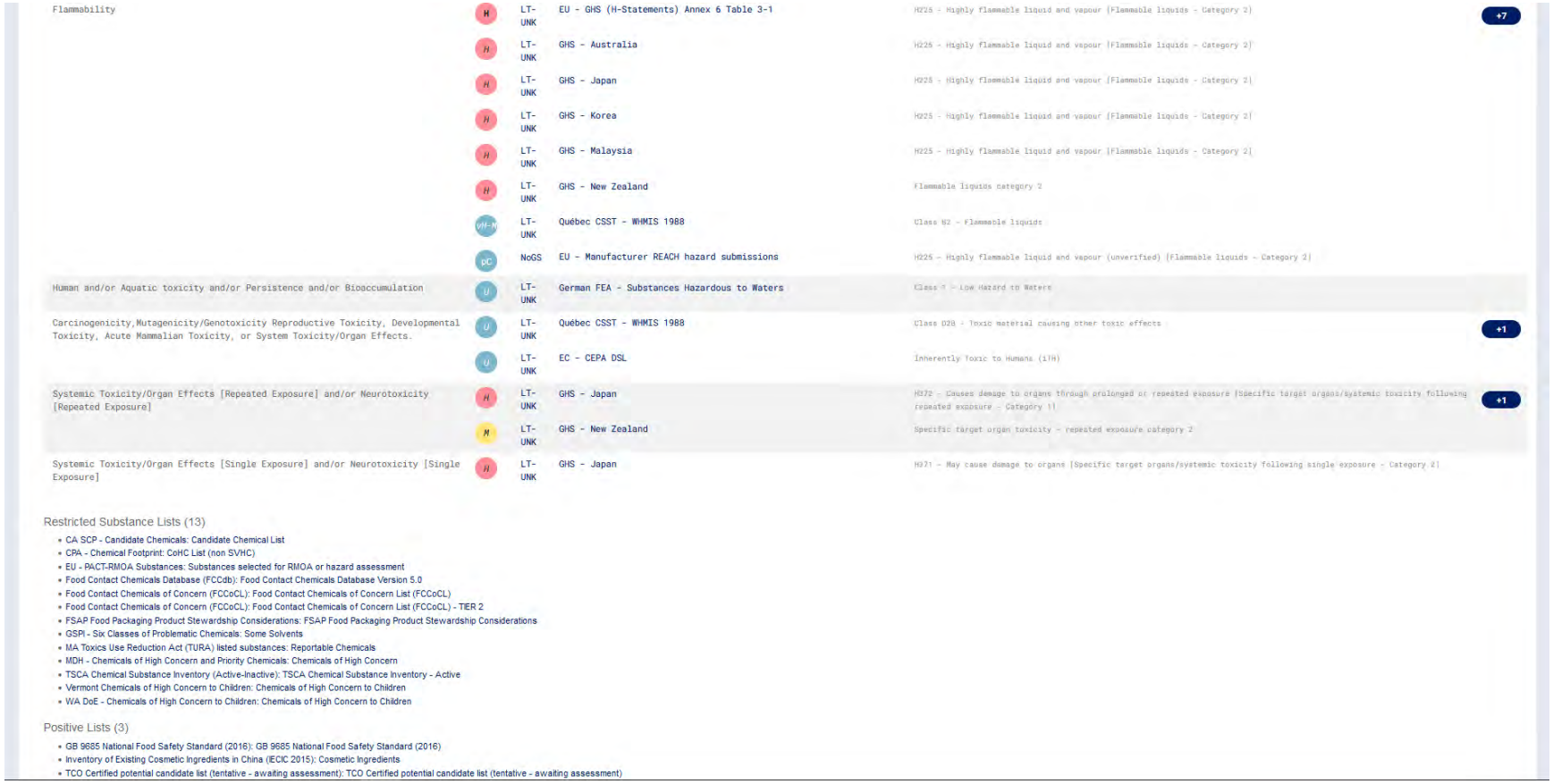
Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for Methyl Ethyl Ketone (CAS #78-93-3)



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]	
	DG	NoGS	EU - Manufacturer REACH hazard submissions	H336 - May cause drowsiness or dizziness (unverified) [Specific target organ toxicity - single exposure; Narcotic effects - Category 3]	
Neurotoxicity-Repeated Exposure	vH-M	LT-UNK	G&L - Neurotoxic Chemicals	Neurotoxic	+1
	vH-L	LT-UNK	Boyes - Neurotoxicants	Neurotoxic	
Skin Irritation/Corrosivity	H	LT-UNK	GHS - Japan	H315 - Causes skin irritation [Skin corrosion / irritation - Category 2]	
Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+6
	H	LT-UNK	GHS - Japan	H319 - Causes serious eye irritation [Serious eye damage / eye irritation - Category 2A]	
	H	LT-UNK	GHS - Korea	H319 - Causes serious eye irritation [Serious eye damage/irritation - Category 2]	
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - Malaysia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	
	DG	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Persistence	vH-M	LT-UNK	EC - CEPA DSL	Persistent	



Flammability	H	LT-UNK	EU - GHS (H-Statements) Annex 6 Table 3-1	H225 - Highly flammable liquid and vapour (Flammable liquids - Category 2)	+7
	H	LT-UNK	GHS - Australia	H225 - Highly flammable liquid and vapour (Flammable liquids - Category 2)	
	H	LT-UNK	GHS - Japan	H225 - Highly flammable liquid and vapour (Flammable liquids - Category 2)	
	H	LT-UNK	GHS - Korea	H225 - Highly flammable liquid and vapour (Flammable liquids - Category 2)	
	H	LT-UNK	GHS - Malaysia	H225 - Highly flammable liquid and vapour (Flammable liquids - Category 2)	
	H	LT-UNK	GHS - New Zealand	Flammable liquids category 2	
	vH-N	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)	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 0 - Low Hazard to Waters	
Carcinogenicity, Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	Québec CSST - WHMIS 1988	Class D2B - Toxic material causing other toxic effects	+1
	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (ITH)	
Systemic Toxicity/Organ Effects [Repeated Exposure] and/or Neurotoxicity [Repeated Exposure]	H	LT-UNK	GHS - Japan	H372 - Causes damage to organs through prolonged or repeated exposure (Specific target organs/systemic toxicity following repeated exposure - Category 1)	+1
	M	LT-UNK	GHS - New Zealand	Specific target organ toxicity - repeated exposure category 2	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	H	LT-UNK	GHS - Japan	H371 - May cause damage to organs (Specific target organs/systemic toxicity following single exposure - Category 2)	

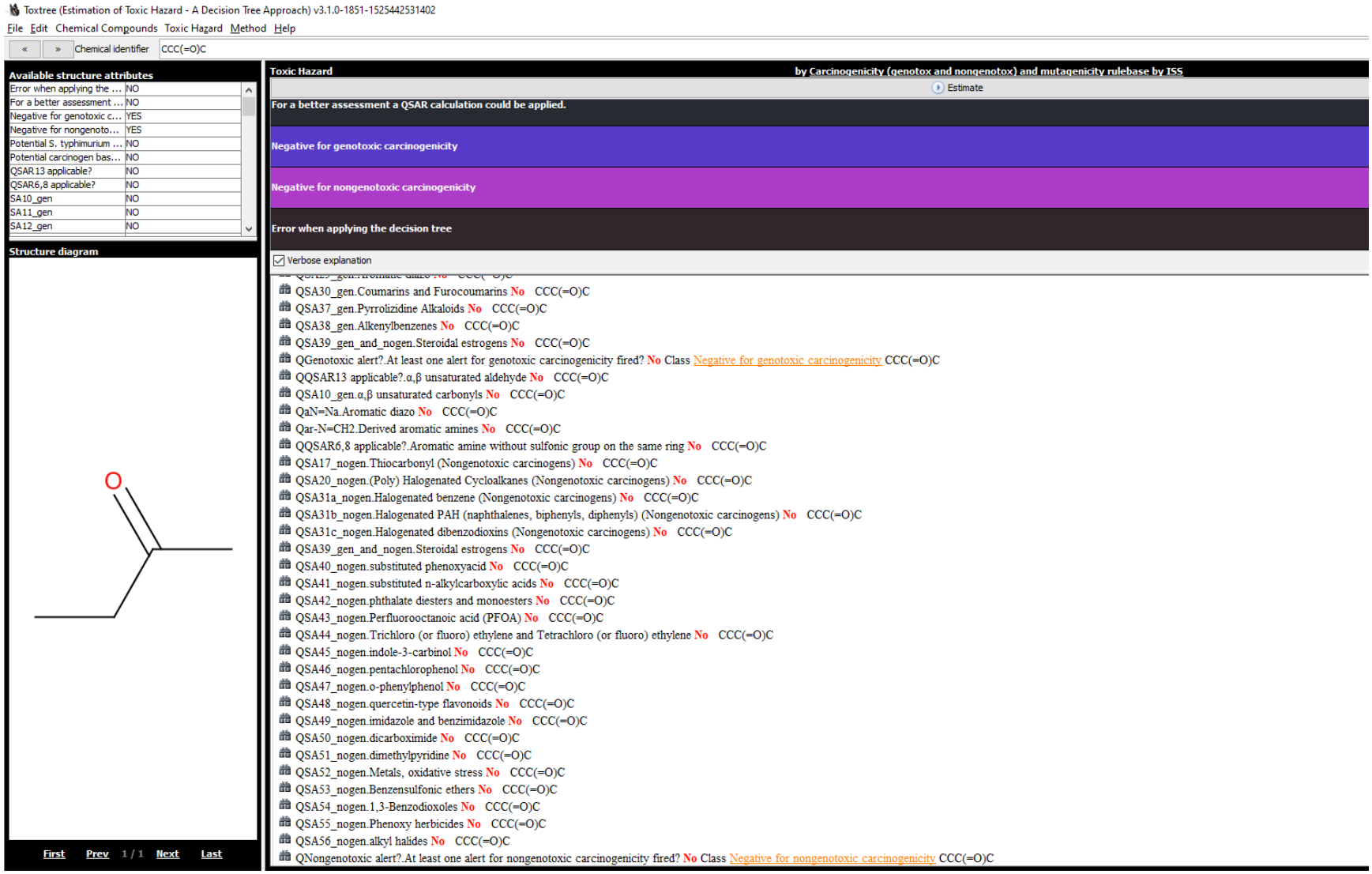
Restricted Substance Lists (13)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- CPA - Chemical Footprint: CoHC List (non SVHC)
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- Food Contact Chemicals of Concern (FCCoCL): Food Contact Chemicals of Concern List (FCCoCL)
- Food Contact Chemicals of Concern (FCCoCL): Food Contact Chemicals of Concern List (FCCoCL) - TIER 2
- FSAP Food Packaging Product Stewardship Considerations: FSAP Food Packaging Product Stewardship Considerations
- GSPI - Six Classes of Problematic Chemicals: Some Solvents
- MA Toxics Use Reduction Act (TURA) listed substances: Reportable Chemicals
- MDH - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active
- Vermont Chemicals of High Concern to Children: Chemicals of High Concern to Children
- WA DoE - Chemicals of High Concern to Children: Chemicals of High Concern to Children

Positive Lists (3)

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

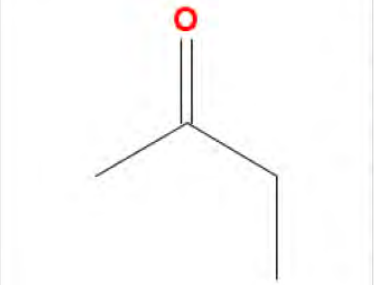
APPENDIX D: Toxtree Carcinogenicity Results for Methyl Ethyl Ketone (CAS #78-93-3)



APPENDIX E: VEGA Carcinogenicity Results for Methyl Ethyl Ketone (CAS #78-93-3)

1. Prediction Summary

Prediction for compound Molecule 0

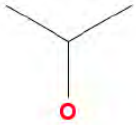


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- similar molecules found in the training set have experimental values that disagree with the predicted value
- predicted substance falls into a neuron that is populated by no compounds of the training set

Compound: Molecule 0
Compound SMILES: O=C(C)CC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.647
P(NON-Carcinogen): 0.353
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



Compound #1

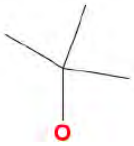
CAS: 67-63-0
Dataset id: 406 (Training set)
SMILES: OC(C)C
Similarity: 0.833

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

Compound #2

CAS: 75-07-0
Dataset id: 1 (Training set)
SMILES: O=CC
Similarity: 0.809

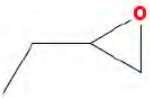
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #3

CAS: 75-65-0
Dataset id: 108 (Training set)
SMILES: OC(C)(C)C
Similarity: 0.791

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 106-88-7
Dataset id: 295 (Test set)
SMILES: O1CC1CC
Similarity: 0.789

Experimental value: Carcinogen
Predicted value: Carcinogen

Compound #5

CAS: 1634-04-4
Dataset id: 444 (Training set)
SMILES: O(C)C(C)(C)C
Similarity: 0.783

Experimental value: Carcinogen
Predicted value: Carcinogen

Compound #6

CAS: 75-56-9
Dataset id: 678 (Training set)
SMILES: O1CC1C
Similarity: 0.776

Experimental value: Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.379
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.821
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 = 0.491
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 = 0.295
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:

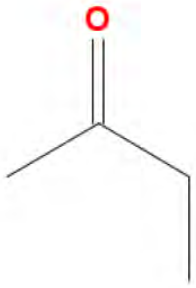
The feature has a good assessment, model is reliable regarding this aspect.

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.

1. Prediction Summary

Prediction for compound Molecule 0



Prediction: Reliability:

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

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

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

Compound #1

CAS: 78-84-2
Dataset id: 585 (Training set)
SMILES: O=CC(C)C
Similarity: 0.913

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

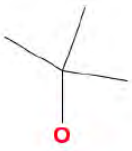
Alerts (not found in the target): SA11 Simple aldehyde

Compound #2

CAS: 75-07-0
Dataset id: 321 (Training set)
SMILES: O=CC
Similarity: 0.809

Experimental value: Carcinogen
Predicted value: Carcinogen

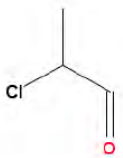
Alerts (not found in the target): SA11 Simple aldehyde



Compound #3

CAS: 75-65-0
Dataset id: 304 (Training set)
SMILES: OC(C)(C)C
Similarity: 0.791

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

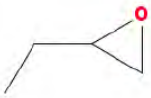


Compound #4

CAS: 683-50-1
Dataset id: 440 (Training set)
SMILES: O=CC(C)Cl
Similarity: 0.791

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA8 Aliphatic halogens; SA11 Simple aldehyde



Compound #5

CAS: 106-88-7
Dataset id: 263 (Training set)
SMILES: O1CC1CC
Similarity: 0.789

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA7 Epoxides and aziridines

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

Compound #6

CAS: 75-56-9
Dataset id: 63 (Training set)
SMILES: O1CC1C
Similarity: 0.776

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA7 Epoxides and aziridines

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.652
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.852
Explanation: strongly similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.464
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.536
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

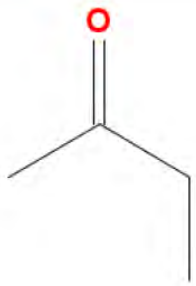
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

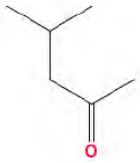


Prediction: Reliability:

Prediction is 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(C)CC
Experimental value: -
Predicted Carcinogenic 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

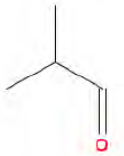
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 1337 (Training set)
SMILES: O=C(C)CC(C)C
Similarity: 0.915

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #2

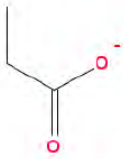
CAS: N.A.
Dataset id: 995 (Training set)
SMILES: O=CC(C)C
Similarity: 0.913

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

Compound #3

CAS: N.A.
Dataset id: 406 (Training set)
SMILES: OC(C)C
Similarity: 0.833

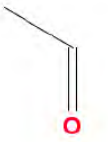
Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: N.A.
Dataset id: 1122 (Training set)
SMILES: O=C([O-])CC
Similarity: 0.817

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



Compound #5

CAS: N.A.
Dataset id: 1 (Training set)
SMILES: O=CC
Similarity: 0.809

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #6

CAS: N.A.
Dataset id: 108 (Training set)
SMILES: OC(C)(C)C
Similarity: 0.791

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.759
Explanation: the predicted compound could be out of the Applicability Domain of the model.

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

Accuracy of prediction for similar molecules
Accuracy index = 0.655
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.655
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

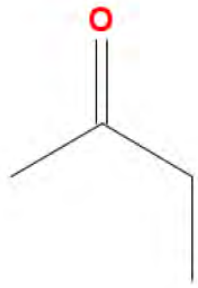
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

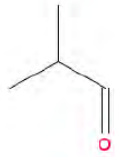


Prediction: Reliability:

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

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



Compound #1

CAS: 78-84-2
Dataset id: 678 (Training set)
SMILES: O=CC(C)C
Similarity: 0.913

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

Compound #2

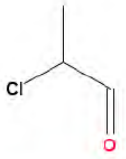
CAS: 75-07-0
Dataset id: 258 (Training set)
SMILES: O=CC
Similarity: 0.809

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

Compound #3

CAS: 75-65-0
Dataset id: 246 (Training set)
SMILES: OC(C)(C)C
Similarity: 0.791

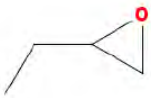
Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #4

CAS: 683-50-1
Dataset id: 365 (Training set)
SMILES: O=CC(C)Cl
Similarity: 0.791

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen



Compound #5

CAS: 106-88-7
Dataset id: 216 (Training set)
SMILES: O1CC1CC
Similarity: 0.789

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 23

Compound #6

CAS: 1634-04-4
Dataset id: 863 (Training set)
SMILES: O(C)C(C)(C)C
Similarity: 0.783

Experimental value: Carcinogen
Predicted value: Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.552
Explanation: the predicted compound is outside 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 = 0.369
Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.

Concordance for similar molecules
Concordance index = 0.369
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

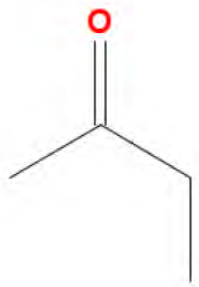
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

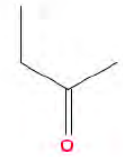


EXPERIMENTAL DATA

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

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

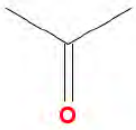
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 78-93-3
Dataset id: 580 (Training set)
SMILES: O=C(C)CC
Similarity: 1

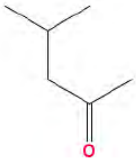
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 67-64-1
Dataset id: 321 (Training set)
SMILES: O=C(C)C
Similarity: 0.93

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



Compound #3

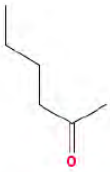
CAS: 108-10-1
Dataset id: 581 (Test set)
SMILES: O=C(C)CC(C)C
Similarity: 0.915

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

Compound #4

CAS: 123-38-6
Dataset id: 658 (Test set)
SMILES: O=CCC
Similarity: 0.906

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 591-78-6
Dataset id: 542 (Training set)
SMILES: O=C(C)CCCC
Similarity: 0.897

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

Compound #6

CAS: 78-92-2
Dataset id: 363 (Training set)
SMILES: OC(C)CC
Similarity: 0.837

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

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

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

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

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

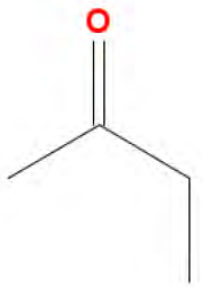
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

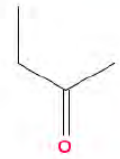


EXPERIMENTAL DATA

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

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

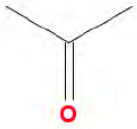
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 78-93-3
Dataset id: 559 (Training set)
SMILES: O=C(C)CC
Similarity: 1

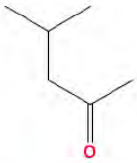
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 67-64-1
Dataset id: 267 (Training set)
SMILES: O=C(C)C
Similarity: 0.93

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



Compound #3

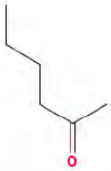
CAS: 108-10-1
Dataset id: 560 (Test set)
SMILES: O=C(C)CC(C)C
Similarity: 0.915

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

Compound #4

CAS: 123-38-6
Dataset id: 647 (Training set)
SMILES: O=CCC
Similarity: 0.906

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



Compound #5

CAS: 591-78-6
Dataset id: 518 (Training set)
SMILES: O=C(C)CCCC
Similarity: 0.897

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

Compound #6

CAS: 78-92-2
Dataset id: 316 (Training set)
SMILES: OC(C)CC
Similarity: 0.837

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

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

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

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

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

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

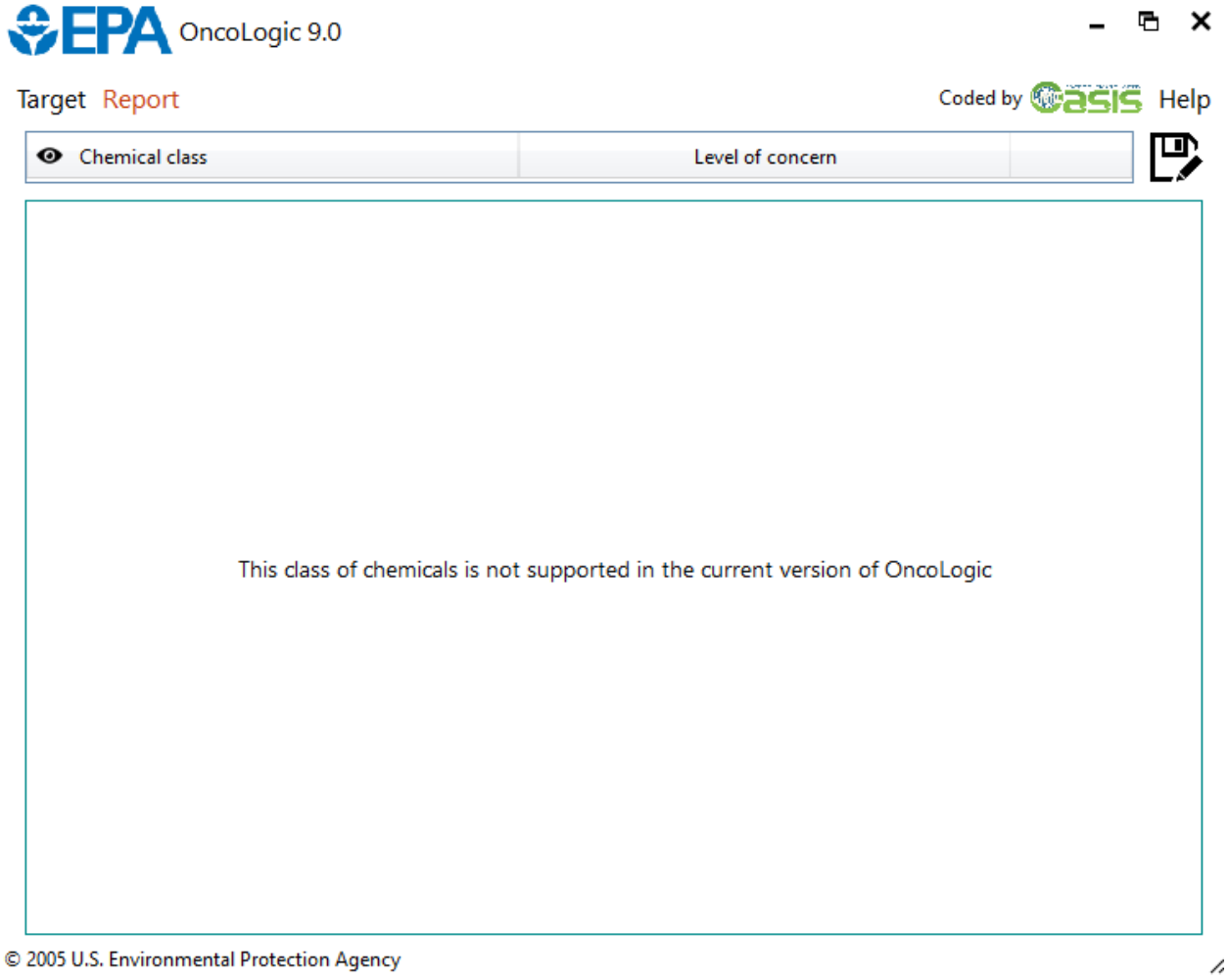
Symbols explanation:

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

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

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

APPENDIX F: Oncologic Carcinogenicity Results for Methyl Ethyl Ketone (CAS #78-93-3)



APPENDIX G: Danish QSAR Carcinogenicity Results for Methyl Ethyl Ketone (CAS #78-93-3)

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

Commercial models from CASE Ultra and Leadscope

FDA RCA: Data from US Food and Drug Administration as part of Research Cooperation Agreement

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

OECD QSAR Toolbox v.4.2 profilers

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

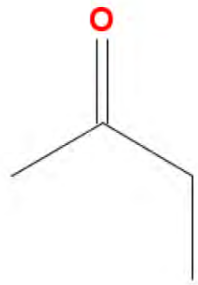
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		NEG_IN	NEG_IN	NEG_OUT	NEG_IN

DTU-developed models

APPENDIX H: VEGA Endocrine Endpoint for Methyl Ethyl Ketone (CAS #78-93-3)

1. Prediction Summary

Prediction for compound Molecule 0

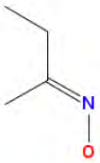


Prediction: Reliability:

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(C)CC
Experimental value: -
Predicted activity: Inactive
Classification tree final node: 4
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

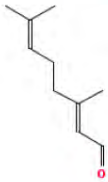
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 96-29-7
Dataset id: 7 (Training set)
SMILES: ON=C(C)CC
Similarity: 0.769

Experimental value: Inactive
Predicted value: Inactive



Compound #2

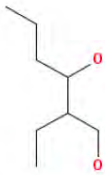
CAS: 5392-40-5
Dataset id: 15 (Training set)
SMILES: O=CC=C(C)CCC=C(C)C
Similarity: 0.693

Experimental value: Inactive
Predicted value: Inactive

Compound #3

CAS: 107-21-1
Dataset id: 22 (Training set)
SMILES: OCCO
Similarity: 0.693

Experimental value: Inactive
Predicted value: Inactive



Compound #4

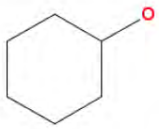
CAS: 94-96-2
Dataset id: 17 (Training set)
SMILES: OCC(CC)C(O)CCC
Similarity: 0.666

Experimental value: Inactive
Predicted value: Inactive

Compound #5

CAS: 68-12-2
Dataset id: 23 (Test set)
SMILES: O=CN(C)C
Similarity: 0.653

Experimental value: Inactive
Predicted value: Inactive



Compound #6

CAS: 108-93-0
Dataset id: 876 (Test set)
SMILES: OC1CCCCC1
Similarity: 0.653

Experimental value: Inactive
Predicted value: Inactive

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.853
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.727
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

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

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

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

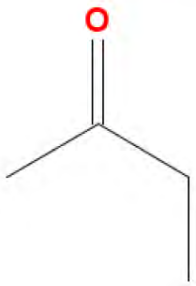
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0

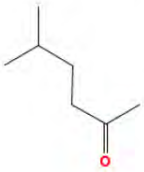


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(C)CC
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: 1
Structural alerts: ER possible non-activity alert no. 9
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

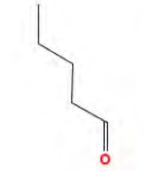


Compound #1

CAS: N.A.
Dataset id: 456 (Training set)
SMILES: O=C(C)CCC(C)C
Similarity: 0.871

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

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

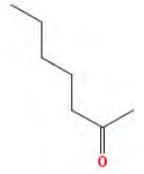


Compound #2

CAS: N.A.
Dataset id: 465 (Training set)
SMILES: O=CCCCC
Similarity: 0.865

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

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



Compound #3

CAS: N.A.
Dataset id: 463 (Training set)
SMILES: O=C(C)CCCC
Similarity: 0.857

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

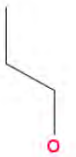
Alerts (found also in the target): ER possible non-activity alert no. 9

Compound #4

CAS: N.A.
Dataset id: 414 (Training set)
SMILES: O=C(CC)CCCC
Similarity: 0.828

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

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

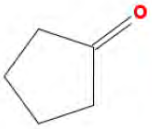


Compound #5

CAS: N.A.
Dataset id: 110 (Training set)
SMILES: OCCC
Similarity: 0.825

Experimental value: NON-active
Predicted value: Not predicted

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



Compound #6

CAS: N.A.
Dataset id: 562 (Training set)
SMILES: O=C1CCCC1
Similarity: 0.811

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

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.93
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.864
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

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

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

Symbols explanation:

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

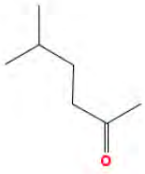
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

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)

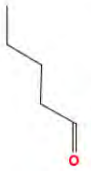
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: N.A.
Dataset id: 456 (Training set)
SMILES: O=C(C)CCC(C)C
Similarity: 0.871

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

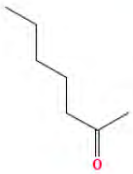
Alerts (found also in the target): ER possible non-activity alert no. 9



CAS: N.A.
Dataset id: 465 (Training set)
SMILES: O=CCCCC
Similarity: 0.865

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

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



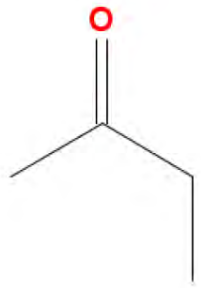
CAS: N.A.
Dataset id: 463 (Training set)
SMILES: O=C(C)CCCCC
Similarity: 0.857

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

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

1. Prediction Summary

Prediction for compound Molecule 0

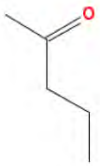


Prediction: Reliability:

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

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

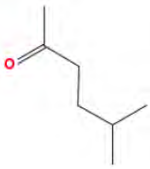
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 107-87-9
Dataset id: 545 (Training set)
SMILES: CCCC(C)=O
Similarity: 0.944

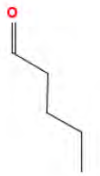
Experimental value: NON-active
Predicted value: NON-active



Compound #2

CAS: 110-12-3
Dataset id: 549 (Training set)
SMILES: CC(C)CCC(C)=O
Similarity: 0.871

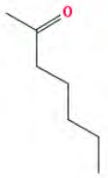
Experimental value: NON-active
Predicted value: NON-active



Compound #3

CAS: 110-62-3
Dataset id: 503 (Training set)
SMILES: CCCCC=O
Similarity: 0.865

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



Compound #4

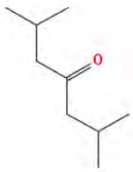
CAS: 110-43-0
Dataset id: 550 (Training set)
SMILES: CCCCCC(C)=O
Similarity: 0.857

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

Compound #5

CAS: 106-68-3
Dataset id: 1302 (Training set)
SMILES: CCCCCC(=O)CC
Similarity: 0.828

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



Compound #6

CAS: 108-83-8
Dataset id: 792 (Training set)
SMILES: CC(C)CC(=O)CC(C)C
Similarity: 0.826

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.95
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.903
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

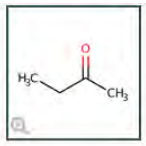
Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

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

Symbols explanation:

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

APPENDIX I: ToxCast Endocrine Bioactivity Model Predictions for Methyl Ethyl Ketone (CAS #78-93-3)



Methyl ethyl ketone

78-93-3 | DTXSID3021516

Searched by DTXSID

Bioactivity - ToxCast: Models

EXPORT

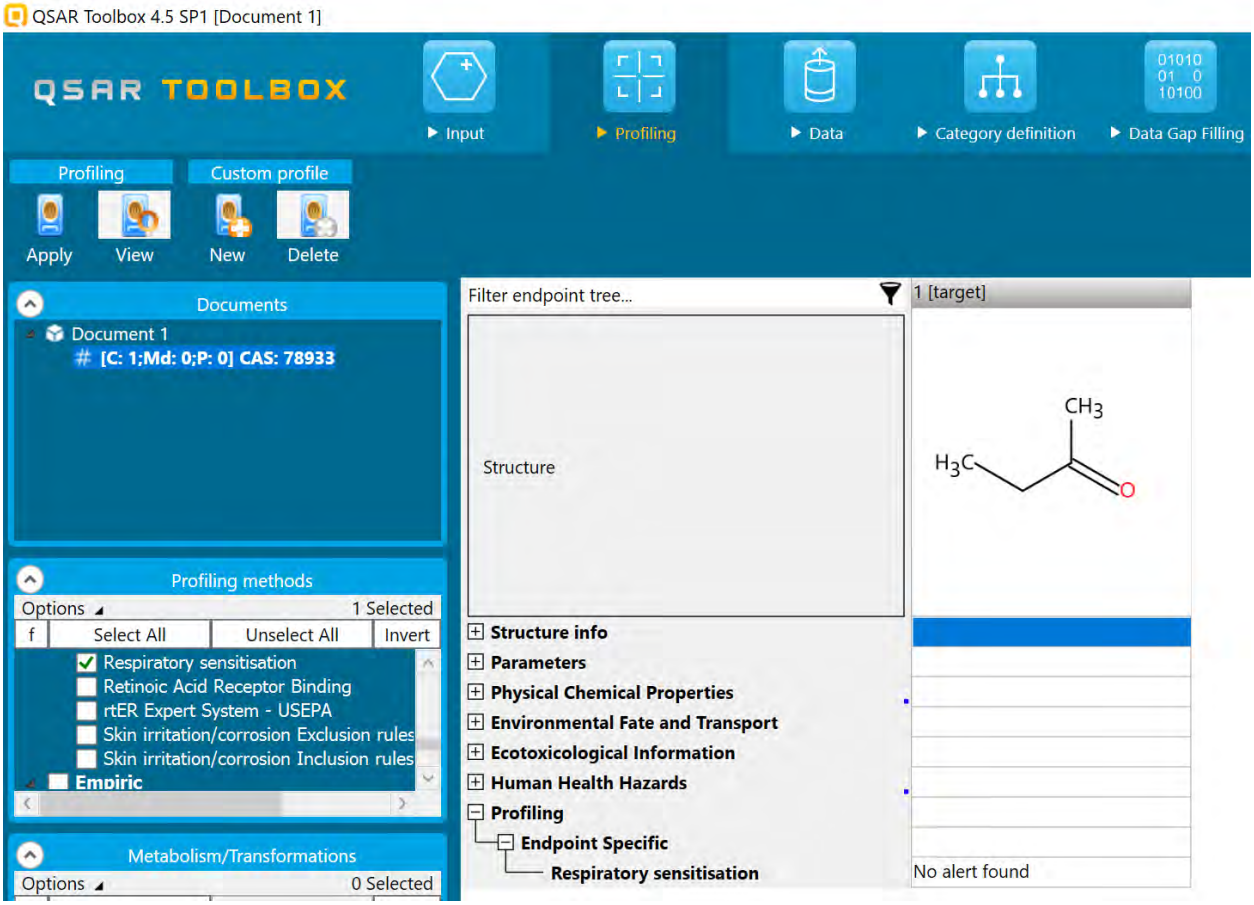
ToxCast Model Predictions

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

APPENDIX J: Danish (Q)SAR Endocrine and Molecular Endpoints for Methyl Ethyl Ketone (CAS #78-93-3)

	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
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			11534.41	995.0058	34.16611
- µM			159955.8	13798.44	473.8055
- Positive for $IC_{50} \leq 10$ µM					
- Positive for $IC_{50} \leq 100$ µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			2333.435	43.56878	199.4324
- µM			32359.38	604.1989	2765.668
- Positive for $IC_{50} \leq 10$ µM					
- Positive for $IC_{50} \leq 100$ µM					
- Domain		OUT	OUT	OUT	OUT

APPENDIX K: OECD Toolbox Respiratory Sensitization for Methyl Ethyl Ketone (CAS #78-93-3)



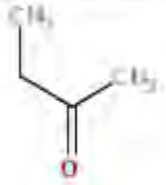
APPENDIX L: ECOSAR Modeling Results for Methyl Ethyl Ketone (CAS #78-93-3)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
78933	2-Butanone	O=C(CC)C

Structure



Details	
Mol Wt	72.11
Selected LogKow	0.3
Selected Water Solubility (mg/L)	223000
Selected Melting Point (°C)	-86.6
Estimated LogKow	0.26
Estimated Water Solubility (mg/L)	106783.68
Measured LogKow	0.29
Measured Water Solubility (mg/L)	223000
Measured Melting Point (°C)	-86.6

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	1992.29	5	
Daphnid	48h	LC50	966.9	5	
Green Algae	96h	EC50	376.38	6.4	
Fish		ChV	161.82	8	
Daphnid		ChV	60.92	8	
Green Algae		ChV	59.49	8	
Fish (SW)	96h	LC50	2482.75	5	
Mysid	96h	LC50	5836.77	5	

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)		ChV	95.43	8	
Mysid (SW)		ChV	834.95	8	
Earthworm	14d	LC50	188.14	6	

APPENDIX M: EPI Suite™ Modeling Results for Methyl Ethyl Ketone (CAS #78-93-3)

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

CAS Number: 78-93-3
SMILES : O=C(CC)C
CHEM : 2-Butanone
MOL FOR: C4 H8 O1
MOL WT : 72.11
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 0.30
Boiling Point (deg C) : 79.60
Melting Point (deg C) : -86.00
Vapor Pressure (mm Hg) : 78
Water Solubility (mg/L): 10000
Henry LC (atm-m3/mole) : 5.69E-005

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.26
Log Kow (Exper. database match) = 0.29
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 70.36 (Adapted Stein & Brown method)
Melting Pt (deg C): -80.48 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 98.1 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.31E+004 (Mean VP of Antoine & Grain methods)
MP (exp database): -86.67 deg C
BP (exp database): 79.6 deg C
VP (exp database): 9.06E+01 mm Hg (1.21E+004 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1.088e+005
log Kow used: 0.30 (user entered)
melt pt used: -86.00 deg C
Water Sol (Exper. database match) = 2.11e+005 mg/L (25 deg C)
Exper. Ref: YALKOWSKY,SH ET AL. (2010)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 96451 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 6.58E-005 atm-m3/mole (6.67E+000 Pa-m3/mole)
Group Method: 5.60E-005 atm-m3/mole (5.68E+000 Pa-m3/mole)

Exper Database: 4.67E-05 atm-m3/mole (4.73E+000 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC: 5.690E-005 atm-m3/mole (5.765E+000 Pa-m3/mole)
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 7.401E-004 atm-m3/mole (7.499E+001 Pa-m3/mole)
VP: 78 mm Hg (source: User-Entered)
WS: 1E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 0.30 (user entered)
Log Kaw used: -2.633 (user entered)
Log Koa (KOAWIN v1.10 estimate): 2.933
Log Koa (experimental database): 2.710

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.7200
Biowin2 (Non-Linear Model) : 0.8223
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0173 (weeks)
Biowin4 (Primary Survey Model) : 3.7215 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5967
Biowin6 (MITI Non-Linear Model): 0.7988
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.3110
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): 1.04E+004 Pa (78 mm Hg)
Log Koa (Exp database): 2.710
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 2.88E-010
Octanol/air (Koa) model: 1.26E-010
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.04E-008
Mackay model : 2.31E-008
Octanol/air (Koa) model: 1.01E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 1.3329 E-12 cm3/molecule-sec
Half-Life = 8.025 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 96.295 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

1.67E-008 (Junge-Pankow, Mackay avg)
1.01E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 4.51 L/kg (MCI method)
Log Koc: 0.654 (MCI method)
Koc : 19.35 L/kg (Kow method)
Log Koc: 1.287 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.2954 days (HL = 0.05065 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.015 (BCF = 1.035)
Log BAF Arnot-Gobas method (upper trophic) = 0.015 (BAF = 1.035)
log Kow used: 0.30 (user entered)

Volatilization from Water:
Henry LC: 5.69E-005 atm-m3/mole (entered by user)
Half-Life from Model River: 9.604 hours
Half-Life from Model Lake : 176 hours (7.332 days)

Removal In Wastewater Treatment:
Total removal: 4.75 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.72 percent
Total to Air: 2.95 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.339**	**1.33**	**1000**
Water	**45.7**	**360**	**1000**
Soil	**53.9**	**720**	**1000**
Sediment	**0.0922**	**3.24e+003**	**0**

Persistence Time: 273 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.339	1.33	1000
Water	45.7	360	1000

water (45.7)
biota (4.55e-006)
suspended sediment (0.000309)

Soil	53.9	720	1000
Sediment	0.0922	3.24e+003	0

Persistence Time: 273 hr

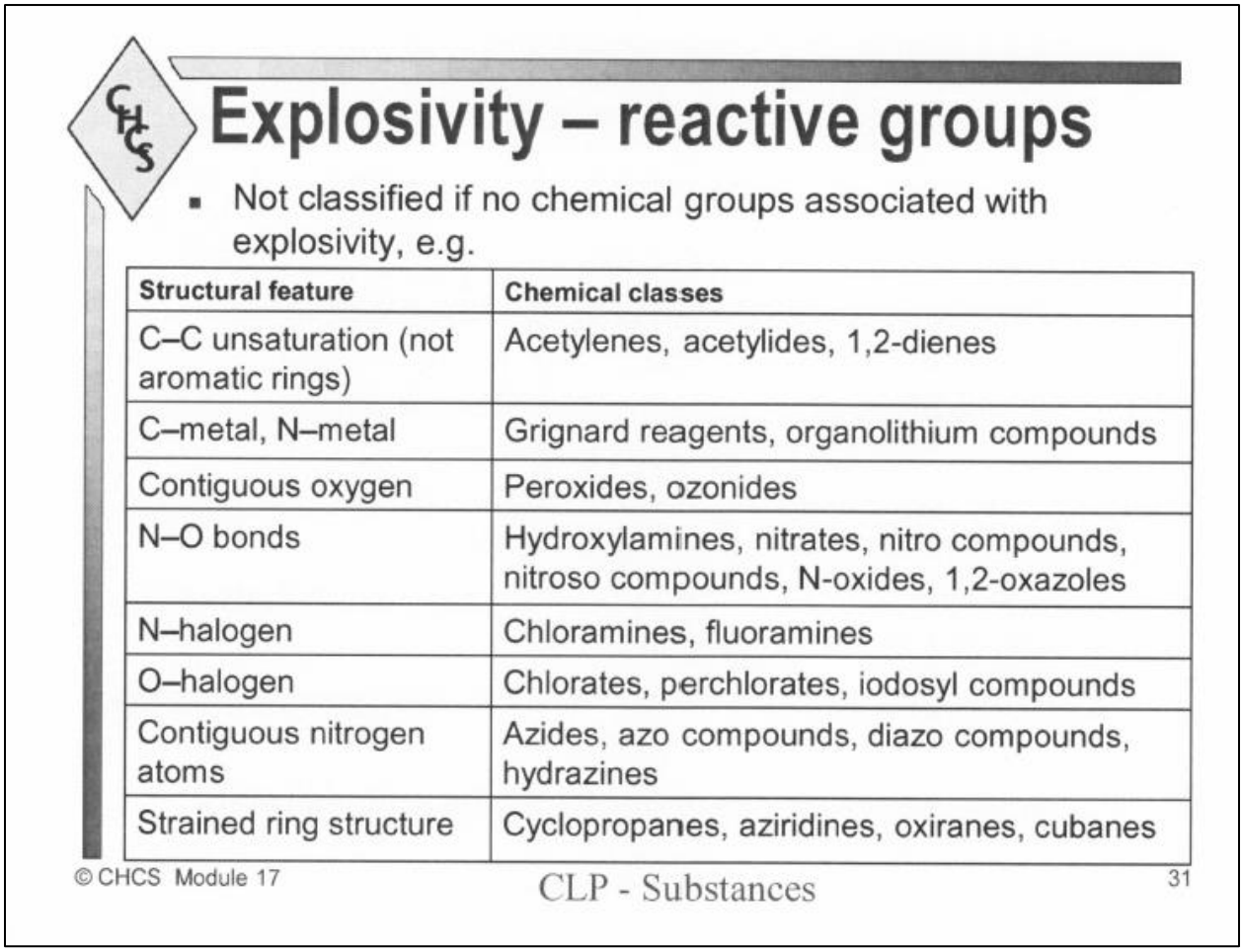
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.371	1.33	1000
Water	49.8	360	1000
water	(49.8)		
biota	(4.97e-006)		
suspended sediment	(6.11e-005)		
Soil	49.7	720	1000
Sediment	0.0929	3.24e+003	0

Persistence Time: 256 hr

APPENDIX N: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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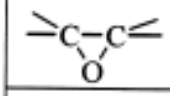
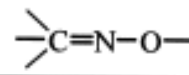
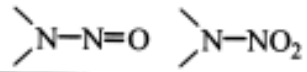
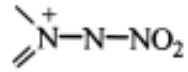
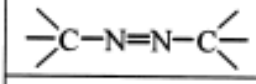
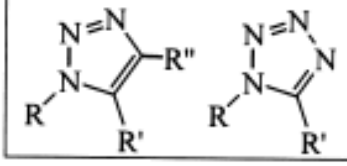
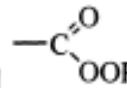
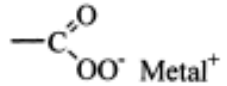
Explosivity – Full List

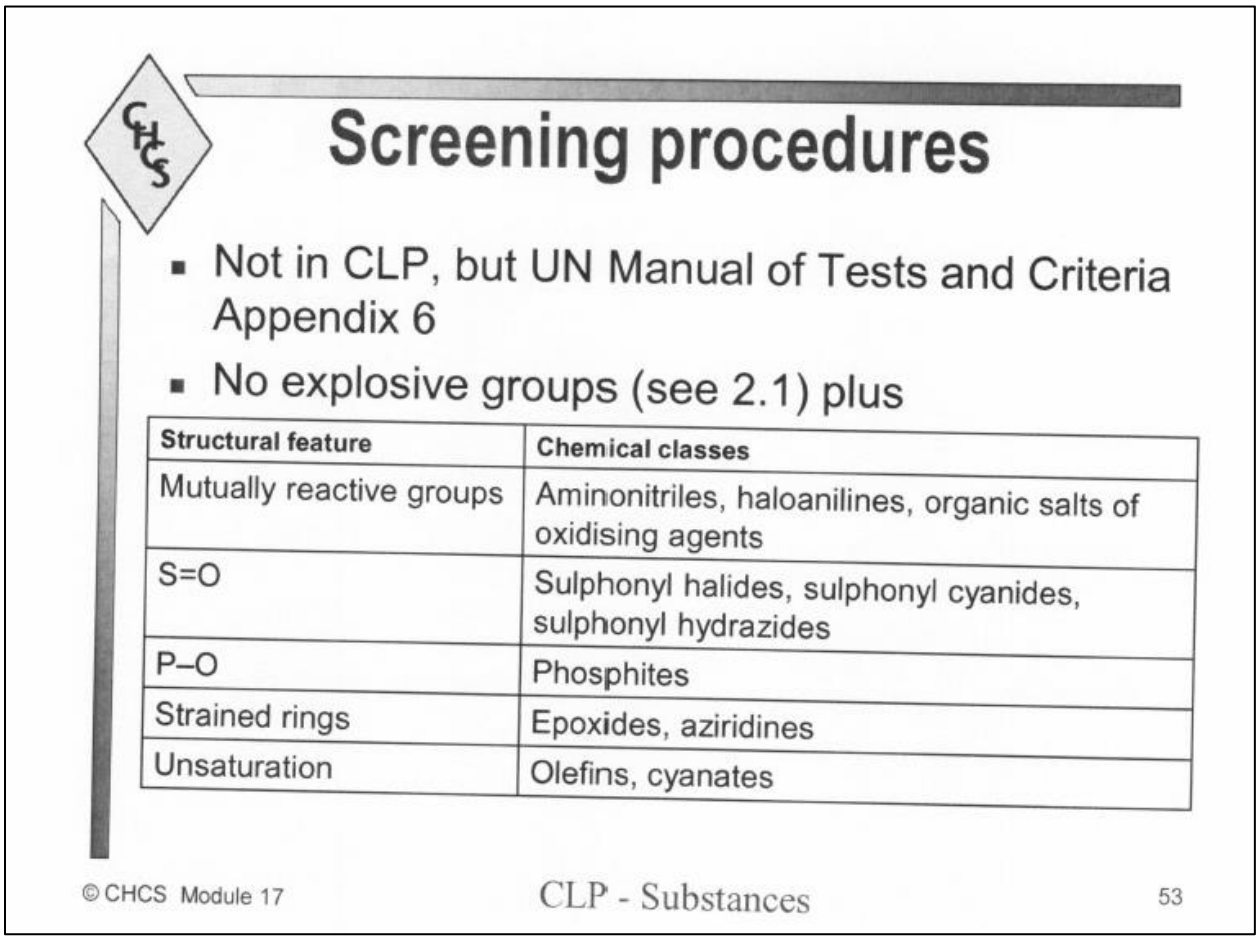
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



APPENDIX O: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for methyl ethyl ketone. The GreenScreen® Benchmark Score for methyl ethyl 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 1.4 update in 2019. The BM-2 score was also maintained with a version 1.4 update in this 2023 report.

Table 5: Change in GreenScreen® Benchmark™ for Methyl Ethyl Ketone

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
August 1, 2014	BM-2	v. 1.2	New assessment
February 21, 2019	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
December 22, 2022	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template. Score for skin irritation changed from *Moderate* (low confidence) to **High** (low confidence), but this did not impact the overall BM score.
January 30, 2023	BM-2	v. 1.4	No change in BM score. The assessment is slightly updated to address Washington Department of Ecology's comments.

Licensed GreenScreen® Profilers

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