# CYCLOPENTANONE

## (CAS #120-92-3)

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

**Prepared by:**

**ToxServices LLC**

**Assessment Date: June 14, 2021**

**Expiration Date: June 14, 2026**

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## GreenScreen® Executive Summary for Cyclopentanone (CAS #120-92-3)

Cyclopentanone is an organic chemical with reported functions including a chemical intermediate for pharmaceuticals, biologicals, insecticides, rubber chemicals, and a fragrance. It is a clear, colorless liquid with an ethereal odor somewhat like peppermint. It has a low boiling point and high vapor pressure, therefore it may be considered a volatile organic compound (VOC). It is flammable but not explosive, oxidizing, or self-reactive.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental Toxicity-D)

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

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

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

Type I (input data) uncertainties in cyclopentanone's NAMs dataset include limited or lack of experimental data for some endpoints, particularly endocrine activity, skin sensitization, respiratory sensitization and chronic aquatic toxicity. Cyclopentanone's Type II (extrapolation output) uncertainties include several uses of QSAR models using structural alerts without defined applicability domains (OECD Toolbox and Toxtree), use of *in vitro* data that may not accurately reflect *in vivo* conditions, and assessment of respiratory sensitization without consideration for non-immunologic mechanisms. Some of cyclopentanone'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 Cyclopentanone

| Group I Human | | | | | Group II and II* Human | | | | | | | | | Ecotox | | Fate | | Physical | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C | M | R | D | E | AT | ST | | N | | SnS | SnR | IrS | IrE | AA | CA | P | B | Rx | F |
| | | | | | | s | r* | s | r* | * | * | | | | | | | | |
| **M** | **L** | *M* | *M* | DG | *L* | **M** | *M* | **M** | *M* | *L* | *L* | **H** | **H** | **L** | *L* | **vL** | **vL** | **L** | **M** |

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

# GreenScreen® Chemical Assessment for Cyclopentanone (CAS #120-92-3)

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

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Date: June 10, 2021

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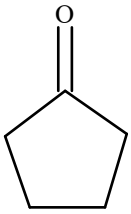
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: June 14, 2021

Expiration Date: June 14, 2026[2]

**Chemical Name:** Cyclopentanone

**CAS Number:** 120-92-3

**Chemical Structure(s):**

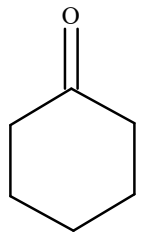



Cyclopentanone (ChemIDplus 2021)

**Also called:** Adipic ketone, EC 204-435-9, ketocyclopentane, and ketopentamethylene (ChemIDplus 2021).

**Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):** One chemical, cyclohexanone (CAS 108-94-1), identified as a read-across chemical in the REACH dossier for cyclopentanone (ECHA 2021a) is used as a surrogate for multiple endpoints. ToxServices notes that cyclopentanone and cyclohexanone are both cyclic ketones that differ by only 1 carbon, and are expected to have similar bioavailability and metabolism. Therefore, cyclohexanone may be considered a strong surrogate.

[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).




Surrogate: Cyclohexanone (CAS 108-94-1) (ChemIDplus 2021)

**Identify Applications/Functional Uses:**
1. Chemical intermediate for pharmaceuticals, biologicals, insecticides, rubber chemicals (HSDB 2003)
2. Fragrance (RIFM 2012).

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

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental Toxicity-D)

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

| Group I Human | | | | | Group II and II* Human | | | | | | | | | Ecotox | | Fate | | Physical | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| C | M | R | D | E | AT | ST | | N | | SnS | SnR | IrS | IrE | AA | CA | P | B | Rx | F |
| | | | | | | s | r* | s | r* | * | * | | | | | | | | |
| **M** | **L** | *M* | *M* | DG | *L* | **M** | *M* | **M** | *M* | *L* | *L* | **H** | **H** | **L** | *L* | **vL** | **vL** | **L** | **M** |

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect lower confidence in the hazard classification while hazard levels in **BOLD** font reflect higher confidence in the hazard classification. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of

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

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 cyclopentanone is readily biodegradable (see persistence section below), it is not expected to have relevant transformation products.

## Introduction

Cyclopentanone is manufactured by heating adipic acid in the presence of barium hydroxide, distilling, extracting with ether, and fractionating (HSDB 2003, RIFM 2012).

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

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

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

Cyclopentanone is not currently on the SCIL.

## GreenScreen® List Translator Screening Results

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

- Cyclopentanone is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Cyclopentanone is listed on the U.S. DOT list as a Hazard Class 3 chemical, Packing Group III.
- Cyclopentanone 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.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low Hazard to Waters
    - Québec CSST – WHMIS 1988 – Class D2B – Toxic material causing other toxic effects

## Hazard Statement and Occupational Control

Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for cyclopentanone that are harmonized across European Union (EU) as reported by the European Chemicals Agency (ECHA), and indicated in Table 1. As shown in Table 2, personal

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

protective equipment (PPE) recommendations were summarized, and no occupational exposure limits (OEL) were identified.

| Table 1: GHS H Statements for Cyclopentanone (CAS #120-92-3) (ECHA 2021b) | |
|---|---|
| **H Statement** | **H Statement Details** |
| H226 | Flammable liquid and vapor |
| H315 | Causes skin irritation |
| H319 | Causes serious eye irritation |

| Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Cyclopentanone (CAS #120-92-3) | | | |
|---|---|---|---|
| **Personal Protective Equipment (PPE)** | **Reference** | **Occupational Exposure Limits (OEL)** | **Reference** |
| Hand: appropriate gloves;<br>Eye: goggles;<br>Skin and body: protective clothing; | ECHA 2021a | None | NIOSH 1997 |

**Physicochemical Properties of Cyclopentanone**

Cyclopentanone is a colorless liquid with ethereal odor. It is volatile and highly soluble in water. Cyclopentanone is slightly more soluble in the organic phase than in water, according to the log $K_{ow}$ of 0.7.

| Table 3: Physical and Chemical Properties of Cyclopentanone (CAS #120-92-3) | | |
|---|---|---|
| **Property** | **Value** | **Reference** |
| Molecular formula | C5H8O | ChemIDplus 2021 |
| SMILES Notation | O=C1CCCC1 | ChemIDplus 2021 |
| Molecular weight | 84.1172 | ChemIDplus 2021 |
| Physical state | Liquid | ECHA 2021a |
| Appearance | Colorless liquid with ethereal odor, somewhat like peppermint | ECHA 2021a; HSDB 2003 |
| Melting point | -58.2 to -51°C | ECHA 2021a |
| Boiling point | 131 to 130°C | ECHA 2021a |
| Vapor pressure | 8.35 mmHg at 20.0°C | ECHA 2021a |
| Water solubility | 301 g/L at 20°C (OECD 105) | ECHA 2021a |
| Dissociation constant | Not applicable | |
| Density/specific gravity | 0.95 g/cm$^3$ at 18°C;<br>2.3 relative to air | ECHA 2021a |
| Partition coefficient | 0.7 at 25°C (OECD 117) | ECHA 2021a |

**Toxicokinetics**

Cyclopentanone is an alicyclic ketone. Following ingestion, it is rapidly absorbed, reduced to its corresponding secondary alcohol, and excreted in the urine primarily as the glucuronic acid conjugate (JECFA 2003). In a gavage study in rabbits exposed to approximately 193 mg/kg cyclopentanone, about 47% was excreted in the urine as the glucuronide conjugate, and about 5% as unidentified sulfur-containing metabolites (RIFM 2012). No additional toxicokinetic data were identified.

## Hazard Classification Summary

### Group I Human Health Effects (Group I Human)

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

Cyclopentanone was assigned a score of Low for carcinogenicity based on surrogate data providing evidence of tumor formation in chronic oral studies of rats and mice. This is also supported by the MAK 3B classification for the surrogate. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals and then they are classified as MAK Category 3 (CPA 2018b). The confidence in the score is high as it is based on experimental data as well as an authoritative A list for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021c
  - *Surrogate: Cyclohexanone (CAS #108-94-1):* In a combined chronic toxicity and carcinogenicity study similar to OECD Guideline 453 in male and female C57BL/6xC3H)F1 mice, animals (41-52/sex/dose) were administered cyclohexanone (purity not reported) in drinking water at concentrations of 0, 6,500, or 13,000 ppm for males (equivalent to oral doses of 0, 1,612, and 3,224 mg/kg/day, respectively[9]) and 0, 6,500, 13,000 or 25,000 ppm for females (equivalent to oral doses of 0, 1,664, 3,328, and 6,400 mg/kg/day, respectively[10]) for 104 weeks. There was an increase in the incidence of malignant lymphoma in females at 6,500 ppm and an increase in hepatocellular neoplasms (combined adenomas and carcinomas) in males at 6,500 ppm. Authors concluded that evidence of carcinogenicity is marginal due to the lack of a dose response (Reliability 2, reliable with restrictions).
  - *Surrogate: Cyclohexanone (CAS #108-94-1):* In a combined chronic toxicity and carcinogenicity study similar to EPA OPP 83-5 in male and female Fischer 344 rats, animals (50-52/sex/dose) were administered 0, 3,300, or 6,500 ppm cyclohexanone (96% purity, 3% water; equivalent to oral doses of 462 and 910 mg/kg/day, respectively) in drinking water continuously for 104 weeks. Adenomas of the adrenal cortex were significantly increased in males at the 3,300 ppm dose. Incidence rates for these adenomas in treated animals and historical controls were 13% (7/52), 0.02% (1/52), and 1%, respectively. Authors concluded that evidence for carcinogenicity is marginal (Reliability 2, reliable with restrictions). The study summary notes that although authors did not consider thyroid tumors, which were seen in 1/52 control animals, 0/52 low dose animals, and 6/51 high dose animals, the MAK commission considered these tumors to be treatment-related based on the increased tumor incidence in the high dose group.
- Pharos 2021
  - *Surrogate: Cyclohexanone (CAS #108-94-1):* MAK Carcinogen Group 3B - Evidence of carcinogenic effects but not sufficient for classification.

[9] 6,500 ppm = 6,500 mg/L water * 0.248 L water/kg BW/day = 1,612 mg/kg/day (male mouse average water factor for chronic study from TERA undated); 13,000 ppm = 13,000 mg/L water * 0.248 L water/kg BW/day = 3,224 mg/kg/day (male mouse average water factor for chronic study from TERA undated)

[10] 6,500 ppm = 6,500 mg/L water * 0.256 L water/kg BW/day = 1,664 mg/kg/day (female mouse average water factor for chronic study from TERA undated); 13,000 ppm = 13,000 mg/L water * 0.256 L water/kg BW/day = 3,328 mg/kg/day (female mouse average water factor for chronic study from TERA undated); 25,000 ppm = 25,000 mg/L water * 0.256 L water/kg BW/day = 6,400 mg/kg/day (female mouse average water factor for chronic study from TERA undated)

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

Cyclopentanone was assigned a score of Low for mutagenicity/genotoxicity based on negative results in multiple reverse mutation assays in bacteria, negative results in an *in vitro* chromosomal aberration assay in mammalian cells, and negative results in an *in vitro* mammalian gene cell mutation 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 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 2021a
  - Cyclopentanone was evaluated in a GLP-compliant bacterial reverse mutation assay performed according to OECD 471 and EU Method B.13/14. *Salmonella typhimurium* strains TA1535, TA100, TA1537, and TA98, and *Escherichia coli* $WP_2$ *uvr*A were exposed to the test substance (purity not specified) at up to 5,000 µg/plate, in water, with and without metabolic activation. Exposure was performed using the Direct place incorporation method with and without activation in Experiment 1, and using Direct plate incorporation without activation or Pre-incubation with activation in Experiment 2. Results were negative for increased mutations in all strains, with and without activation, at all concentrations, in both experiments. There were no observations of cytotoxicity or precipitation, and testing was performed up to the recommended dose limit. Controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 1, reliable without restriction).
  - Cyclopentanone was evaluated in a bacterial reverse mutation assay similar to OECD 471 (non-GLP). *S. typhimurium* strains TA98 and TA100 were exposed to the test substance (purity not specified) at up to 5,000 µg/plate, in DMSO, with and without metabolic activation. Results were negative for increased mutations in both strains, with and without activation, at all concentrations. There were no observations of cytotoxicity, and testing was performed up to the recommended dose limit. Controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).
  - Cyclopentanone was evaluated in a bacterial reverse mutation assay similar to OECD 471 (non-GLP). *S. typhimurium* strains TA1535, TA1537, TA98, and TA100 were exposed to the test substance (purity not specified) at up to 3 µmol/plate (252 µg/plate) for TA1535, TA1537, and TA98, and up to 30 µmol/plate with TA100, in ethanol, with and without metabolic activation. Results were negative for increased mutations in all strains, with and without activation, at all concentrations. There were no observations of cytotoxicity. Results of controls were not reported. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).
  - Cyclopentanone distilled (99.9%) was evaluated in a GLP-compliant *in vitro* mammalian chromosome aberration test performed according to OECD 473. Human lymphocytes were exposed to the test substance in deionized water at 0, 277.6, 485.7, or 850 µg/mL, with and without exogenous metabolic activation. Results were negative for increased chromosomal aberrations at all concentrations, with and without activation. There were no observations of cytotoxicity or precipitation, and testing was performed up to the recommended dose limit. Controls performed as expected. Authors concluded the test substance was not clastogenic under the conditions of the test (Reliability 1, reliable without restriction).

- *Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was evaluated in an *in vitro* mammalian gene cell mutation test equivalent or similar to OECD 476 (GLP not specified). Mouse lymphoma L5178Y cells were exposed to the test substance (purity not specified) in distilled water or DMSO, at 0, 312.5, 625, 1,750, 2,500, or 5,000 µg/mL, with and without exogenous metabolic activation. Results were negative for increased mutations at the tk+/- locus of the L5178Y cells at all concentrations, with and without activation. There were no observations of cytotoxicity or precipitation, and testing was performed up to the recommended dose limit. Controls performed as expected. Authors concluded the test substance was not mutagenic under the conditions of the test (Reliability 2, reliable with restrictions).

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

Cyclopentanone was assigned a score of Moderate for reproductive toxicity based on multiple studies on the surrogate demonstrating decreased male fertility and mating indices, which coincided with parental systemic toxicity, and therefore meets the criteria for GHS Category 2 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when data meet GHS Category 2 classification (CPA 2018b). The confidence in the score is low as it is unclear if reproductive effects were secondary to systemic toxicity.

- 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 2021a
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone (≥ 99.9% purity, with 0.01% water, 0.02% cyclohexanol, 0.058% esters (as cyclohexylformate), and 0.003% acidity (as formic acid)) was evaluated in a GLP-compliant two-generation reproductive toxicity study equivalent or similar to OECD 416. Sprague-Dawley rats were exposed to the test substance by whole body inhalation (no vehicle) 6 hours day, 5 to 7 days/week as follows: parental (P) males were exposed 5 days/week before mating (at least 10 weeks), during mating (maximum 15 days), and until initiation of the F1a weanlings; P females were exposed 5-7 days/week before mating (7-10 weeks) 7 days/week during mating (15 days max), 7 days/week during pregnancy, and 7 days/week through weaning of F1 offspring; F1 males were exposed 5 days/week before mating (at least 15 weeks), 5 days/week during mating (15 days max), and until sacrifice; and F1 females were exposed 5-7 days/week before mating (12-15 weeks), 7 days/week during mating (15 days max), and until sacrifice. Exposure concentrations for F0 animals were 0, 250, 500, or 1,000 ppm (equivalent to 0, 1.0, 2.0, or 4.0 mg/L, respectively), and for F1 animals were 0, 250, 500, or 1,400 ppm (equivalent to 0, 1.0, 2.0, or 5.6 mg/L, respectively). There were 30 animals/sex/dose/generation. Litters were standardized to 4/sex/litter on postpartum day 4.
    - For P0 animals there were no effects observed on body weight and weight changes, food consumption, urinalysis, non-neoplastic histopathology, or reproductive performance based on mating indices. In P0 animals at 1,000 ppm, there were observations of lacrimation, ataxia, and irregular breathing following the first two exposures. **Authors assigned the NOAEC and LOAEC in P0 animals at 500 ppm, and 1,000 ppm, based on clinical signs.**
    - In P1 animals, irregular breathing, urine soaked fur, prostration, lacrimation, and ataxia were the predominant observations at 1,400 ppm. During week 16, these animals appeared to have acclimated with only lethargy being the predominant post-exposure observation. Body weight was reduced in 1,400 ppm group males up

through week 33, and in 500 ppm males only during the first week. **Authors assigned the NOAEC and LOAEC in parental F1 animals at 500 ppm, and 1,400 ppm, based on clinical signs and body weight reduction.**

- In F1 pups, there were no effects observed on mortality, gross pathology, or histopathology. **On lactation day 15, 31-56% fewer test progeny had open eyelids** compared to controls, however no dose-response was apparent and there were no corresponding pathological findings, including ophthalmology of the eyes. Authors assigned the NOAEC in F1 animals at 1,000 ppm, the highest concentration tested.
- In F2a and F2b, the male fertility and mating indices were significantly reduced at 1,400 ppm, compared to the untreated controls, and compared to males at 250 and 500 ppm. There was a decreased number of viable fetuses during the lactation period at 1,400 ppm. The % of 1,400 ppm F2a and F2b progeny delivered viable and surviving to lactation days 1 and 4 (but not at lactation days 14, 21, and 28) were significantly less than seen for untreated controls. There was a significant reduction in pup body weights at 1,400 ppm in F2a and F2b, compared to untreated controls. **Authors assigned the NOAEC at 500 ppm, and the LOAEC at 1,400 ppm, based on decreased male fertility and mating indices,** and decreased pup viability, body weight, and weight gain.
- Authors concluded there were no significant effects on growth, development, or reproductive performance, and that evaluation for behavioral / neurotoxicological development of selected F1a progeny revealed no consistent difference between treated groups and controls. High dose males had decreased weights, and their progeny had reduced survival and body weights, indicative of systemic toxicity, and not reproductive or developmental toxicity (Reliability 2, reliable with restrictions). *ToxServices more conservatively considers the decreased male fertility and mating indices a reproductive effect, in accordance with sections 3.7.1.2 and 3.7.1.3 of the GHS guidance, respectively (UN 2019). Whereas the next study (summary below) was intended to show recovery of reproductive performance, ToxServices considers even a temporary effect as undesirable and adverse.*

- *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone (≥ 99.9% purity, with 0.01% water, 0.02% cyclohexanol, 0.058% esters (as cyclohexylformate), and 0.003% acidity (as formic acid)) was evaluated in a GLP-compliant, non-guideline, one-generation reproductive toxicity study with a post-exposure recovery period for males. The F1 males had previously been exposed to the test substance at 0, 250, 500, or 1,400 ppm (equivalent to 0, 1.0, 2.0, or 5.6 mg/L) 6 hours/day. Fertile males of the same strain and similar age were injected intraperitoneally with 1 mL/kg of 0.05% (w/v) triethylenemelamine as a positive control. All males were rested 2 days following the last exposure of the test or control substance. Males were paired weekly with 2 untreated virgin females for 4 consecutive weeks. They were rested during the 5$^{th}$ and 7$^{th}$ weeks of the recovery period, and paired again during the 6$^{th}$ and 8$^{th}$ weeks. Females were examined daily during mating to determine if copulation had occurred. Females were sacrificed on gestation day (GD) 20 and uterine contents were examined. Fetuses were sexed, weighed, and examined externally.
    - Fertility of treated males during the post-exposure recovery period was comparable to the negative control group. At termination, mean body weights of all groups were similar. Although the high-dose group weighted less (9%) than negative controls at the start of the mating, they gained twice as much weight during the recovery period

compared to negative controls. One male in the 1,400 ppm group was found dead on the day of scheduled sacrifice with a diffuse red exudate in the nasal region, but study authors did not consider this related to previous exposure to cyclohexanone. The mean number of corpora lutea, implantation sites, early/late resorption sites, and viable fetuses obtained from females bred with the test groups revealed no significant differences compared to negative controls. The females bred with positive controls had significant increases in early resorption sites and significant decreases in viable fetuses during weeks 1, 2, 3, 4 and 6. Statistical analysis of the male/female fertility indices and pre-/post-implantation losses calculated for the test groups revealed no significant treatment-related differences compared to negative controls. Authors assigned the NOAEC for reproductive toxicity at 1,400 ppm, the highest concentration tested.

- In F1 animals, there were no effects on fetal body weight or external development and authors assigned the NOAEC at 1,400 ppm, the highest concentration tested (Reliability 2, reliable with restrictions).

**Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L):** *M*
Cyclopentanone was assigned a score of Moderate for developmental toxicity based on multiple studies on the surrogate demonstrating developmental effects including delayed eye opening, decreased pup survival, decreased pup body weight gain, and delayed ossification, which coincided with parental systemic toxicity, and therefore meets the criteria for GHS Category 2 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when data meet GHS Category 2 classification (CPA 2018b). The confidence in the score is low as it is unclear if developmental effects were secondary to parental systemic toxicity.

- 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 2021a
  - *Oral:* Cyclopentanone was evaluated in a non-guideline teratology screening study in rats (GLP not specified) (reported in 1988). Wistar rats were exposed to the test substance (purity not specified) by gavage in corn oil at 0, 50 or 300 mg/kg, on GD 6 to 15 (25 rats/dose). Dams were assessed for appearance and behavior, body weights, and ovaries and uterine content. Fetuses were assessed via external examination, soft-tissue examination, and skeletal examination.
    - In the dams there were no significant findings based on maternal toxicity, embryotoxicity, or teratology and authors assigned the NOAEL at 300 mg/kg, the highest dose tested.
    - In fetuses, there was a slight decrease in mean fetal body weight at 300 mg/kg compared to concurrent controls, but the value was within the range of historical controls. There were increased number of litters with fetal variant mal-aligned sternebrae at 50 mg/kg, but not at 300 mg/kg, therefore authors did not consider the effect treatment-related. Authors assigned the NOAEL for teratogenicity at 300 mg/kg, the highest dose tested (Reliability 2, reliable with restrictions, only the study abstract is available).
  - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was evaluated in a non-guideline developmental toxicity screening study in mice (GLP not specified) (reported in 1986). ICR mice were exposed to the test substance (purity not specified) by gavage in corn oil at 0 or 2,200 mg/kg, on GD 8 to 12 (28 rats/dose). Animals were evaluated from GD 8

through PND 3. All dams were examined for body weights, and dams that had not given birth by GD 21 or 22 were killed and their uteri were examined. Litters were counted and weighted at 1 and 3 days of age. Pups found dead were necropsied and assessed for abnormalities. Indices were calculated for maternal toxicity, number of litters born, number of litters resorbed, average number of pups/litter alive on PND 1, and pup survival, weight, and weigh gain from PND1 to PND 3. **Exposed dams had significantly reduced body weight gain and increased mortality (6/28 died) compared to controls. Average neonate weight was significantly reduced at PND 1 and PND 3 compared to controls.** Necropsy of neonates did not result in any significant findings. A NOAEL could not be assigned based on effects at the only dose tested. Authors concluded the decreased pup body weights were probably due to marked maternal toxicity and were not a frank developmental effect (Reliability 2, reliable with restrictions).

- *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone (≥ 99.9% purity, with 0.01% water, 0.02% cyclohexanol, 0.058% esters (as cyclohexylformate), and 0.003% acidity (as formic acid)) was evaluated as previously described in a GLP-compliant two-generation reproductive toxicity study performed equivalent or similar to OECD 416. Sprague-Dawley rats were exposed to the test substance by whole body inhalation (no vehicle) 6 hours day, 5 to 7 days/week as follows: parental (P) males were exposed 5 days/week before mating (at least 10 weeks), during mating (maximum 15 days), and until initiation of the F1a weanlings; P females were exposed 5-7 days/week before mating (7-10 weeks) 7 days/week during mating (15 days max), 7 days/week during pregnancy, and 7 days/week through weaning of F1 offspring; F1 males were exposed 5 days/week before mating (at least 15 weeks), 5 days/week during mating (15 days max), and until sacrifice; and F1 females were exposed 5-7 days/week before mating (12-15 weeks), 7 days/week during mating (15 days max), and until sacrifice. Exposure concentrations for F0 animals were 0, 250, 500, or 1,000 ppm (equivalent to 0, 1.0, 2.0, or 4.0 mg/L, respectively), and for F1 animals were 0, 250, 500, or 1,400 ppm (equivalent to 0, 1.0, 2.0, or 5.6 mg/L, respectively). There were 30 animals/sex/dose/generation. Litters were standardized to 4/sex/litter on postpartum day 4.
    - For P0 animals there were no effects observed on body weight and weight changes, food consumption, urinalysis, non-neoplastic histopathology, or reproductive performance based on mating indices. In P0 animals at 1,000 ppm, there were observations of lacrimation, ataxia, and irregular breathing following the first two exposures. Authors assigned the NOAEC and LOAEC in P0 animals at 500 ppm, and 1,000 ppm, based on clinical signs.
    - In P1 animals, irregular breathing, urine soaked fur, prostration, lacrimation, and ataxia were the predominant observations at 1,400 ppm. During week 16, these animals appeared to have acclimated with only lethargy being the predominant post-exposure observation. Body weigh was reduced in 1,400 ppm group males up through week 33, and in 500 ppm males only during the first week. Authors assigned the NOAEC and LOAEC in parental F1 animals at 500 ppm, and 1,400 ppm, based on clinical signs and body weight reduction.
    - In F1 pups, there were no effects observed on mortality, gross pathology, or histopathology. **On lactation day 15, 31-56% fewer test progeny had open eyelids compared to controls, however no dose-response was apparent and there were no corresponding pathological findings, including ophthalmology of the eyes.** Authors assigned the NOAEC in F1 animals at 1,000 ppm, the highest concentration tested.

- In F2a and F2b, the male fertility and mating indices were significantly reduced at 1,400 ppm, compared to the untreated controls, and compared to males at 250 and 500 ppm. There was a decreased number of viable fetuses during the lactation period at 1,400 ppm. The % of 1,400 ppm F2a and F2b progeny delivered viable and surviving to lactation days 1 and 4 (but not at lactation days 14, 21, and 28) were significantly less than seen for untreated controls. There was a significant reduction in pup body weights at 1,400 ppm in F2a and F2b, compared to untreated controls. Authors assigned the NOAEC at 500 ppm, and the **LOAEC at 1,400 ppm, based on** decreased male fertility and mating indices, and **decreased pup viability, body weight, and weight gain.**
- Authors concluded there were no significant effects on growth, development, or reproductive performance, and that evaluation for behavioral / neurotoxicological development of selected F1a progeny revealed no consistent difference between treated groups and controls. High dose males had decreased weights, and their progeny had reduced survival and body weights, indicative of systemic toxicity, and not reproductive or developmental toxicity (Reliability 2, reliable with restrictions). *ToxServices more conservatively considers the decreased pup weights and decreased pup survival as adverse effects on the developmental of the offspring, in accordance with sections 3.7.1.2 and 3.7.1.3 of the GHS guidance, respectively (UN 2019). Whereas the next study (summary below) was intended to show recovery of reproductive performance, ToxServices considers even a temporary effect as undesirable and adverse.*

- *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone (≥ 99.9% purity, with 0.01% water, 0.02% cyclohexanol, 0.058% esters (as cyclohexylformate), and 0.003% acidity (as formic acid)) was evaluated in a GLP-compliant, non-guideline, one-generation reproductive toxicity study with a post-exposure recovery period for males. The F1 males had previously been exposed to the test substance at 0, 250, 500, or 1,400 ppm (equivalent to 0, 1.0, 2.0, or 5.6 mg/L) 6 hours/day. Fertile males of the same strain and similar age were injected intraperitoneally with 1 mL/kg of 0.05% (w/v) triethylenemelamine as a positive control. All males were rested 2 days following the last exposure of the test or control substance. Males were paired weekly with 2 untreated virgin females for 4 consecutive weeks. They were rested during the 5$^{th}$ and 7$^{th}$ weeks of the recovery period, and paired again during the 6$^{th}$ and 8$^{th}$ weeks. Females were examined daily during mating to determine if copulation had occurred. Females were sacrificed on GD 20 and uterine contents were examined. Fetuses were sexed, weighed, and examined externally.
  - Fertility of treated males during the post-exposure recovery period was comparable to the negative control group. At termination, mean body weights of all groups were similar. Although the high-dose group weighted less (9%) than negative controls at the start of the mating, they gained twice as much weight during the recovery period compared to negative controls. One male in the 1,400 ppm group was found dead on the day of scheduled sacrifice with a diffuse red exudate in the nasal region, but study authors did not consider this related to previous exposure to cyclohexanone. The mean number of corpora lutea, implantation sites, early/late resorption sites, and viable fetuses obtained from females bred with the test groups revealed no significant differences compared to negative controls. The females bred with positive controls had significant increases in early resorption sites and significant decreases in viable fetuses during weeks 1, 2, 3, 4 and 6. Statistical analysis of the male/female fertility indices and pre-/post-implantation losses calculated for the test

groups revealed no significant treatment-related differences compared to negative controls. Authors assigned the NOAEC for reproductive toxicity at 1,400 ppm, the highest concentration tested.
    - In F1 animals, there were no effects on fetal body weight or external development and authors assigned the NOAEC at 1,400 ppm, the highest concentration tested (Reliability 2, reliable with restrictions).
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone (97% purity) was evaluated in a non-guideline, teratology study that focused on postnatal growth and viability in mice (GLP not specified) (reported in 1983). CD-1 mice were exposed to the test substance by gavage in corn oil at 0 or 800 mg/kg, on GD 8-12. Animals were evaluated from GD 8 through day 250 of the offspring. All dams were examined for body weights, and dams that had not given birth by postnatal day (PND) 3 were killed and examined for the presence of resorptions. Litters were counted and weighted at 1 and 3 days of age. Pups found dead were necropsied and assessed for abnormalities. Calculated indices were for number of pregnant, average weight on day 1 and 3, and number of live on day 1 and 3. There were no significant findings on mortality, body weight or weight changes, dead fetuses, number of pregnant, or maternal toxicity. Authors assigned the NOAEL at 800 mg/kg/day, the only dose tested and concluded the test substance was not a developmental toxicant in this study (Reliability 2, reliable with restrictions).
  - *Inhalation*: *Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was evaluated in a prenatal developmental toxicity study performed according to EPA OPPTS 870.3700 which is similar to OECD 414 (GLP not specified). Sprague-Dawley rats were exposed to the test substance as vapor (99.9% purity) via whole-body inhalation (no vehicle) at 0, 300, 650, or 1,400 ppm, 6 hours/day, on GD 6 to 19.
    - There were no effects observed on early and late resorptions or dead fetuses. High dose dams had decreased mean body weight gain during GD 6-20, as well as lacrimation, lethargy, nasal and brown/red vaginal discharge in several females. **Authors assigned the parental NOAEC at 650 ppm based on decreased body weight and weight gain at 1,400 ppm.**
    - High dose fetuses had decreased body weights, and generally delayed ossification based on incidence of incomplete ossification, particularly in cranial ossifications, sternebrae and phalanges, compared to controls. **Authors assigned the pup NOAEC at 650 ppm based on decreased pup body weight gain and delayed ossification at 1,400 ppm.**
    - The executive summary of the REACH dossier states cyclohexanone is not expected to induce effects on development (Reliability 2, reliable with restrictions).
- U.S. EPA 1987
  - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* Pregnant mice were administered a diet containing 1% cyclohexanone, approximately 1,300 mg/kg/day, throughout gestation and lactation. **Neonatal mortality was increased during the first 21 days of life** (Gondry 1973) (no further details were reported).
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Embryotoxicity and teratogenicity were examined in rats exposed to cyclohexanone via inhalation at 0, 320, 680, or 1,430 ppm on GD 9-16. **At the highest dose there was significant depression of maternal and fetal body weights.** No other adverse effects were reported. Authors assigned the NOAEC at 668 ppm (219 mg/kg/day), and the LOAEC at 1,430 ppm (457 mg/kg/day) (Schroeder 1984) (no further details were reported).

- *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Developmental toxicity was examined in rats exposed to cyclohexanone vapor (99.8% purity) via inhalation in a non-guideline study (GLP not specified) (reported in 1989). Sprague-Dawley rats were exposed to the test substance by whole body inhalation at 0, 100, 200, or 500 ppm (10/dose, 5 positive controls, and 5 negative controls), 7 hours/day, for 16 days on GD 5-20. 2-Ethoxyethanol was the positive control. Dams were assessed for appearance and behavior, body weights, and ovaries and uterine content. Fetuses were assessed via external examination, soft-tissue examination, skeletal examination, and half the fetuses had head examinations.
  - There was slightly decreased body weight gain in exposed dams compared to controls, and a grey mottling of the lungs in a few treated animals, but there were no corresponding pathological findings. There were no significant findings on clinical signs, mortality, body weight or weight changes, or gross pathology.
  - In fetuses, there were no significant effects on body weight changes, number of live offspring, sex ratios, skeletal malformation, or teratogenic effects. Authors assigned the teratogenic NOAEC at 500 ppm, the highest concentration tested (Reliability 2, reliable with restrictions, only the study abstract is available).

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

Cyclopentanone was assigned a score of Data Gap for endocrine activity based on insufficient data. There were no observations of endocrine activity found in the public literature, and the weight of evidence from the bioassays in U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century suggest low concerns, however there are no robust studies found in which endocrine activity was a key endpoint, thus a Data Gap is assigned.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021c
  - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* In a combined chronic toxicity and carcinogenicity study described previously, similar to EPA OPP 83-5 in male and female Fischer 344 rats, animals (50-52/sex/dose) were administered 0, 3,300, or 6,500 ppm cyclohexanone (equivalent to oral doses of 0, 462, and 910 mg/kg/day, respectively) in drinking water continuously for 104 weeks. The incidence of adenomas of the adrenal cortex was significantly increased in males at the 3,300 ppm dose. Authors concluded that evidence for carcinogenicity is marginal. The study summary notes that although authors did not consider thyroid tumors, which were seen in 1/52 control animals, 0/52 low dose animals, and 6/51 high dose animals, the MAK commission considered these tumors to be treatment-related based on occurrence in the high dose group. *ToxServices notes that the authors did not collect endocrine signaling data or evaluate levels of circulating endocrine hormone levels in this study. Therefore, it is not clear that the adrenal or thyroid tumors arose due to an endocrine-related mechanism.*
- U.S. EPA 2021a
  - Cyclopentanone was active in 1/18 estrogen receptor (ER) assays, 0/14 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/9 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.

**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*

Cyclopentanone was assigned a score of Low for acute toxicity based on acute oral and dermal $LD_{50}$ values > 2,000 mg/kg, and a 4-hour $LC_{50}$ in male rats at ≥ 19.5 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal $LD_{50}$ values are >2,000 mg/kg, and the 4-hour inhalation $LC_{50}$ is >20 mg/L (CPA 2018b). The confidence in the score is low as the inhalation toxicity study in male rats did not test up to the GHS guidance value of 20 mg/L, and limited data in female rats provide an extrapolated 4-hour $LC_{50}$ at < 23.4 mg/L.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – Japan – Acute Toxicity (oral) – Category 4 [H302]
- ECHA 2021a (note: due to sufficient data availability for studies with Reliability ratings of 1 and/or 2, studies with reliability ratings of 3 and 4 were not included in the weight of evidence and are not summarized here)
  - *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1999) similar to OECD 401 (non-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 500 mg/kg (3 males), or 2,000 mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. No deaths were reported and **the $LD_{50}$ was assigned at >2,000 mg/kg** (Reliability 2, reliable with restrictions).
  - *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1964) equivalent or similar to OECD 401 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 34.6, 120, 417, 1,450, 5,000, or 10,000 mg/kg (5 males/group), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. All animals died at ⩾5,000 mg/kg within 24 hours of exposure. The **$LD_{50}$ was calculated at 2,690 mg/kg** (Reliability 2, reliable with restrictions).
  - *Dermal:* Sprague-Dawley rats were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1999) similar to OECD 402 (non-GLP). Animals were exposed to cyclopentanone (99.8% purity) (vehicle, duration, and occlusion not specified) undiluted at 400 mg/kg (3 males), or 2,000 mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. The **$LD_{50}$ was assigned at >2,000** mg/kg (Reliability 2, reliable with restrictions).
  - *Dermal:* Albino rabbits (strain not specified) were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1964) similar to OECD 402 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) at 50, 200, 794, or 3,160 mg/kg, under semi occlusion (no vehicle) for 24 hours (4/sex/dose), and were observed for 14 days. Necropsy was performed on surviving animals. One death occurred at 3,160 mg/kg. The **$LD_{50}$ was assigned at >3,160 mg/kg** (Reliability 2, reliable with restrictions).
  - *Inhalation:* Male Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1965) similar to OECD 403 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure at 4.7, 12, 15, 17.8, or 19.5 mg/L (10 animals/dose) for 4 hours, and were observed for 14 days.

Deaths were 0/10, 1/10, 3/10, 3/10, and 4/10 at 4.7, 12, 15, 17.8 and 19.5 mg/L, respectively. **The 4-hr $LC_{50}$ was assigned at ⩾19.5 mg/L** (Reliability 2, reliable with restrictions).

- *Inhalation:* Female Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1964) (guideline not specified, pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure **at 15.6 mg/L (10 animals/dose) for 6 hours**, and were observed for 14 days. **All animals died**, and the $LC_{50}$ could not be determined (Reliability 3, not reliable). *ToxServices notes the exposure duration was 6 hours instead of 4 as recommended by current guidelines, and there were no control animals. However, the above study with Reliability rating of 2 tested only males, which may be less sensitive than females. Using the equation of $LC_{50}$ at 4 hours = $LC_{50}$ at Y hours x (Y hours)$^{1/2}$/2 for vapors (WorkSafeBC 2007), 15.6 mg/L for 6 hours is equivalent to 15.6 mg/L x $6^{1/2}$/2 = 19.1 mg/L for 4 hours. Therefore, if 100% of the animals died at this concentration, the $LC_{50}$ would be less than 19.1 mg/L. Substances with 4h $LC_{50}$ (vapor) values between 10 and 20 mg/L is classified to GHS Category 4. However, since this study was deemed unreliable, ToxServices did not rely on this study to score this endpoint.*

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

Cyclopentanone was assigned a score of Moderate for systemic toxicity (single dose) based on aspiration hazard consistent with GHS Category 2 classification, and evidence of respiratory tract irritation based on a human volunteer study which established a throat and nose irritation threshold, and several animal studies with reports of labored breathing and dyspnea at sub-lethal doses, which meets the criteria for GHS Category 3 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when data suggest an aspiration hazard consistent with GHS Category 2 classification, or when there is evidence of respiratory tract irritation consistent with GHS Category 3 classification (CPA 2018b). Confidence is high based on the respiratory tract irritation measured in humans and animals.

- 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 2021a (note: due to sufficient data availability for studies with Reliability ratings of 1 and/or 2, studies with reliability ratings of 3 and 4 were not included in the weight of evidence and are not summarized here)
  - *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1999) similar to OECD 401 (non-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 500 mg/kg (3 males), or 2,000 mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination**. Reduced activity, piloerection, and hunched posture** were observed at both doses. Hair loss was observed only at the lowest dose. **Lethargy, part-closed eyes, and staining of skin and fur** were observed at 2,000 mg/kg following dosing. Low dose animals recovered by day 10, and high dose animals by day 14. No abnormalities were found at necropsy. There was a **dose-related decrease in body weight gain** (statistical significance not reported). No deaths were reported and the $LD_{50}$ was assigned at >2,000 mg/kg (Reliability 2, reliable with restrictions).
  - *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1964) equivalent or similar to OECD 401 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 34.6, 120, 417, 1,450, 5,000, or 10,000 mg/kg (5 males/group), and were observed for 14 days. Necropsy was performed

on surviving animals at study termination. All animals died at ⩾5,000 mg/kg within 24 hours of exposure. **Slight depression, labored breathing, and decreased body weight gain** were observed at 1,450 mg/kg, with complete recovery by day 8. At ⩾5,000 mg/kg, **depression, lacrimation, slow labored breathing, vasodilation, coma, and death** were observed. At necropsy, animals at ⩾5,000 mg/kg had **congestion of the lungs, liver, and kidney, gastrointestinal inflammation, and hemorrhage**. The $LD_{50}$ was calculated at 2,690 mg/kg (Reliability 2, reliable with restrictions).

- *Dermal:* Sprague-Dawley rats were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1999) similar to OECD 402 (non-GLP). Animals were exposed to cyclopentanone (99.8% purity) (vehicle, duration, and occlusion not specified) undiluted at 400 mg/kg (3 males), or 2,000 mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. There were no clinical signs of toxicity observed in low dose animals. At 2,000 mg/kg, **piloerection and staining of the skin/fur were observed during exposure but disappeared within 24 hours**. There were no mortalities and no abnormalities found at necropsy. The $LD_{50}$ was assigned at >2,000 mg/kg (Reliability 2, reliable with restrictions).
- *Dermal:* Albino rabbits (strain not specified) were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1964) similar to OECD 402 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) at 50, 200, 794, or 3,160 mg/kg, under semi occlusion (no vehicle) for 24 hours (4/sex/dose), and were observed for 14 days. Necropsy was performed on surviving animals. One death occurred at 3,160 mg/kg. This animal exhibited **depression, phonation, excessive masticatory movements, labored breathing, gasping, stiffness of body, and intermittent convulsions at 24 hours**. One or two animals at each of the 3 lower doses had **diarrhea** for one to four days. Two of the animals that presented diarrhea had body weight loss. At necropsy, the one animal that died during exposure had **congestion of the lungs, liver, and kidney (fibrous), fluid in the cranial cavity, and soft brain tissue**. There were no other findings at necropsy. The $LD_{50}$ was assigned at >3,160 mg/kg (Reliability 2, reliable with restrictions).
- *Inhalation:* Male Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1965) similar to OECD 403 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure at 4.7, 12, 15, 17.8, or 19.5 mg/L (10 animals/dose) for 4 hours, and were observed for 14 days. Necropsy was performed on surviving animals. Mortality occurred in 1, 1, 3, 3, and 4/10 animals at 12, 15, 17.8, and 19.5 mg/L, respectively. **During exposure, dyspnea, depression, and decreased activity were observed, and ataxia and prostration were noted at the two highest levels but disappeared within 48 hours**. At necropsy, there were observations of **moderate congestion in the lungs, liver, and kidneys, but there were no gross pathological findings** at study termination. The $LC_{50}$ was assigned at ⩾19.5 mg/L (Reliability 2, reliable with restrictions).
- *Inhalation:* Female Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1964) (guideline not specified, pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure at 15.6 mg/L (10 animals/dose) for 6 hours, and were observed for 14 days. All animals died, and ptosis, lacrimation, dyspnea, and ataxia were observed during the exposure period. At necropsy, yellow-gray coloration of the lung surface was observed. The $LC_{50}$ was not determined (Reliability 3, not reliable).
- *Inhalation:* Cyclopentanone was evaluated for eye, nose, and throat irritation, and odor detection, in a non-GLP, non-guideline study (reported in 1965). Six volunteers were

exposed to methyl isobutyl ketone (MIBK) at the beginning of the study to familiarize themselves with their responsibilities during testing. In week 1, subjects were exposed to a documented ketone similar to those being tested. In week 2 they were exposed to one of the test compounds (unspecified) at increasing concentrations until a sensory irritation threshold was established. In week 4, they were exposed to the test substance at the previously determined irritation threshold, followed by additional concentrations if needed. Subjects were exposed via masks for 7 minutes and were allowed to breathe only through the nose. **The throat irritation index was 0.518 mg/L (presumably for cyclopentanone), approximately 150 ppm as vapor concentration. Eye and nasal irritation were observed at 1.337 mg/L, approximately 390 ppm as vapor.** Odor detection was <0.158 mg/L, approximately 50 ppm as vapor (no Reliability rating was provided, study was disregarded due to major methodological deficiencies).

- *Aspiration:* Cyclopentanone has a measured kinematic viscosity of 1.132 $mm^2/s$ at 25.0°C based on testing to OECD 114 (GLP not specified) (Reliability 2, reliable with restrictions).
- *Aspiration:* Reported dynamic viscosity values are: 1.07 mPa s at 25.0°C, 0.992 mPa s at 30.0°C, 0.504-1.169 mPa s at 20°C, and 0.49-1.149 at 20°C (Reliability 2, reliable with restrictions).
- *Aspiration:* GHS criteria classify chemicals as aspiration hazards Category 2 when they are hydrocarbons, alcohols or ketones with a kinematic viscosity of ⩽14 $mm^2/s$ at 40°C along with consideration of surface tension, water solubility, boiling point and volatility (UN 2019). Whereas the kinematic viscosity is < 14 $mm^2/s$ at 25°C, it would be even lower at 40°C. Therefore, as cyclopentanone is a ketone and has kinematic viscosity <14 $mm^2/s$, it meets the criteria for **GHS Category 2 classification for aspiration**.

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

Cyclopentanone was assigned a score of Moderate for systemic toxicity (repeated dose) based on epidemiological data for a strong surrogate suggesting liver disorders in exposed workers, which meets the criteria for GHS Category 2 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when data support GHS Category 2 classification (CPA 2018b). The confidence in the score is low because there are limited experimental details available for the key study, and animal data do not warrant GHS classification.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NITE 2009
  - *Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was classified as GHS Category 1 in Japan based on effects on the central nervous system and bones of exposed humans. Neurotoxic effects were observed in a group of 75 works from a furniture factory. Reported neurotoxic symptoms included mood disorders, memory difficulty, and sleep disturbances. Based on this information and another study summarized by ACGIH also indicating central nervous system effects, cyclohexanone was classified as a GHS Category 1 (central nervous system). In the same set of 75 workers, an increase in the percentage of individuals reporting **rheumatic symptoms (bone pain, joint pain, and muscular pain)** was also observed. These bone-related effects were also noted in the ACGIH report. Therefore, cyclohexanone was also categorized as a GHS Category 1 (bone effects). The Japan classification did not take into consideration some data indicating liver and kidney

effects as this data were not detailed enough, the source was unknown, and no similar information was identified.

- U.S. EPA 1987
    - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* A chronic oral exposure study was performed in F344 rats and B6C3F1 mice. Male and female rats were exposed to cyclohexanone in the drinking water at 3,300 or 6,500 ppm, male mice were exposed at 6,500 or 13,000 ppm, and female mice were exposed at 6,500, 13,000, or 25,000 ppm (52/sex/species/dose). In rats there was decreased body weight gain at 6,500 ppm in both sexes. In mice there was decreased body weight gain and increased mortality at 13,000 ppm and higher in both sexes. No other adverse effects were reported. Authors reported a NOAEL of 3,300 ppm, equivalent to 462 mg/kg/day in rats (Lijinksy and Kovatch 1986) (no further details reported).
    - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* The National Cancer Institute conducted subchronic toxicity studies in rats and mice exposed to cyclohexanone in drinking water. Animals were evaluated for mortality, body and organ weight changes, clinical observations, and histopathology of the target organs. Mice were exposed at 0, 425, 2,400, 7,000, 14,000, 26,000, 36,000, or 50,000 ppm, for 95 days. Decreased body weight gain was measured at 14,000 ppm and higher in males, and at 36,000 ppm and higher in females. Decreased survival occurred in both sexes at 50,000 ppm. Rats were exposed to cyclohexanone at 0, 200, 425, 850, 1,700, 3,500, 5,000, or 7,000 ppm, for 175 days. There were no effects on mortality at any dose level for either sex. Decreased body weight gain was measured at 7,000 ppm in males and females. Authors assigned the NOAEL at 5,000 ppm, equivalent to 665 mg/kg/day (NCI 1979) (no further details reported).
- ECHA 2021a
    - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* The National Cancer Institute conducted subchronic toxicity studies in rats and mice exposed to cyclohexanone (96% purity, with 3% water and 1% unidentified compounds) in drinking water (Reliability 2, reliable with restrictions).
        - F344 rats were exposed to the test substance at 0, 190, 400, 800, 1,600, 3,300, 4,700, or 6,500 ppm (equivalent to 0, 29, 61, 122, 246, 508, 723, and 1,000 mg/kg, respectively) (5/sex/dose) for 25 weeks. Animals were evaluated based on clinical signs, mortality, body weights, gross pathology, and histopathology (there are no data for additional parameters such as hematology or clinical chemistry). Authors reported no findings on clinical signs and mortality. Moderate chronic respiratory disease was reported in all treated and control animals. Decreased body weight gain was measured in males and females at 6,500 ppm (1,000 mg/kg). A mild non-neoplastic degenerative change was observed in the thyroid gland in 2/5 males at 4,700 ppm, but was not seen in other animals. Authors reported the NOAEL at 4,700 ppm (723 mg/kg), and the LOAEL at 6,500 ppm (1,000 mg/kg) based on decreased body weight gain (no further details provided).
        - B6C3F1 mice were exposed to the test substance at 0, 400, 2,300, 6,500, 13,000, 25,000, 340,000, or 47,000 ppm (equivalent to 0, 100, 575, 1,625, 3,250, 6,250, 8500, and 11,750 mg/kg, respectively) (10/sex/dose) for 13 weeks. Animals were evaluated on clinical signs, mortality, body weights, gross pathology, and histopathology (there are no data for additional parameters such as hematology or clinical chemistry). Mortality occurred in 6/10 males and 47,000 ppm, 3/10 females at 47,000 ppm, and 1/10 males at 34,000 ppm. Body weight and weight gain was decreased in females at 34,000 ppm (by 15%), and in males at 34,000 ppm (by 24%)

and at 25,000 ppm (by 19%) compared to controls. At 47,000 ppm, there was focal coagulative liver necrosis in some mice, and hyperplasia of the thymus in 2 females. There were no other significant pathological findings. Males were more sensitive than females and authors assigned the NOAEL for males at 13,000 ppm (3,250 mg/kg), and the LOAEL at 25,000 ppm (6,250 mg/kg) based on decreased body weight gain (no further details provided).

- ECHA 2021c
  - *Oral: Surrogate: Cyclohexanone (CAS #108-94-1):* In a GLP-compliant subchronic oral toxicity study according to OECD Guideline 408 in male and female Wistar rats, animals (10/sex/dose) were administered 500, 2,000 or 7,000 ppm (40, 143 or 407 mg/kg/day) cyclohexanone (99.9% purity) continuously in drinking water for 90 days. There were no effects on clinical signs or ophthalmoscopic examination. Body weights were significantly reduced by approximately 10% at the high dose. Also, at the high dose, there was a significant increase in total cholesterol, total protein, and total globulins in both sexes and an increase in platelets in females. Effects on water consumption at lower doses were attributed to the odor and taste of the test substance. Authors noted that effects on cholesterol may be due to slight changes in lipid metabolism or reduced water consumption. Authors identified a NOAEL of 143 mg/kg/day.
- ECHA 2021a (it may be noted that studies with reliability ratings of 3 – not reliable – are not included in the weight of evidence and therefore are not summarized here due to major methodological deficiencies and insufficient data to assign NOAEC/LOAEC values).
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was evaluated in a pre-guideline, pre-GLP subchronic inhalation toxicity study. Rabbits (strain not specified) were exposed to cyclohexanone (purity not specified) vapor (nose-only or whole-body not specified) at 0, 190, 309, 773, 1,414 ppm (equivalent to 0, 0.75, 1.21, 3.04, or 5.56 mg/L) (4/sex/concentration) 6 hours/day, 5 days/week, for 10 weeks. Animals were observed for 2 months after the last exposure. Animals were evaluated for body weight, hematology, urinalysis, body temperature, gross pathology, and histopathology. Clinical observations included slight lethargy, distention of the ear veins, salivation, and conjunctival irritation manifested by congestion, lacrimation, and secretion of mucus at 1,414 ppm throughout the daily exposure periods. At 773 ppm, there was slight salivation during exposure, and at 309 and 773 ppm there was ocular irritation. There were no mortalities, and no significant effects on weight gain, hematology, or urinalysis. Authors assigned the NOAEC and LOAEC for local effects at 190 ppm and 309 ppm (equivalent to 0.075 and 1.21 mg/L, respectively) based on ocular irritation. Authors assigned the NOAEC and LOAEC for systemic effects at 773 ppm and 1,414 ppm (equivalent to 3.04 and 5.56 mg/L, respectively), and the critical effects was not specified. Authors of the REACH dossier suggest the critical effects for systemic toxicity were lethargy and distention of the ear veins (Reliability 2, reliable with restrictions).
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was evaluated in a pre-guideline, pre-GLP (reported in 1943) sub-acute inhalation toxicity study. Rabbits (strain not specified) were exposed to cyclohexanone (purity not specified) vapor (nose-only or whole-body not specified) at 0 or 12.12 mg/L (equivalent to 0 or 3,082 ppm, respectively) (it is unclear if 4/sex/concentration or 4/concentration) 6 hours/day, 5 days/week, for 3 weeks. Animals were observed for 2 months after the last exposure. Animals were evaluated for body weight, hematology, urinalysis, body temperature, gross pathology, and histopathology. Mortality occurred in 2/4 exposed animals. Decreased body temperature, light narcosis, labored breathing, incoordination, salivation, conjunctival irritation

manifested by congestion, lacrimation, and secretion of mucus were observed in treated animals throughout the exposure period. Authors assigned the LOAEC at 3,082 ppm (12.12 mg/L), the only concentration tested (Reliability 2, reliable with restrictions). *ToxServices notes 12.12 mg/L 6 hours/day, 5 days/week for 3 weeks, with application of Haber's rule, is comparable to approximately 2.0 mg/L administered 6 hours/day, 7 days/week, for 13 weeks[11], and thus is well above the GHS guidance values for sub-chronic exposure to vapor (UN 2019).*

- UNEP 1996
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* When 1 rhesus monkey was exposed to 2.432 mg/L cyclohexanone for 6 hours/day, 5 days/week, for 10 weeks, extensive injury to the heart, muscle, lungs, liver, and kidney were seen. There were no hematological or pathological changes. Authors note that effects may not be attributable to exposure because the animal was suffering from bronchopulmonary infection.
  - *Inhalation: Surrogate: Cyclohexanone (CAS #108-94-1):* When rabbits were exposed to 190 ppm (0.762 mg/L) cyclohexanone for 6 hours/day, 5 days/week, for a total of 300 hours (i.e., 10 weeks), barely demonstrable degenerative change in the liver and kidney were seen. *ToxServices notes in the absence of additional information, it is unclear if the referenced changes are adaptive or adverse changes, thus this is not a reliable information source.*
- IARC 1989
  - *Dermal: Surrogate: Cyclohexanone (CAS #108-94-1):* In 100 workers exposed occupationally to 3.7 $mg/m^3$ cyclohexanone via inhalation and $10^{-4}$ $mg/cm^2$ cyclohexanone dermally (on hands) during the production of caprolactam, there was some indication of liver disorders among a subgroup of workers 30-39 years old with more than 5 years of exposure to cyclohexanone. *ToxServices notes GHS criteria require reliable and good quality evidence from human cases or epidemiological studies for Category 1 classification, while Category 2 classification is warranted when the weight of evidence is not sufficiently convincing to warrant Category 1 classification. ToxServices does not consider the available epidemiological study to be sufficient to classify as GHS Category 1, due to limited reporting of study details, and instead classifies this study to GHS Category 2.*

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

Cyclopentanone was assigned a score of Moderate for neurotoxicity (single dose) based on several animal studies demonstrating transient narcotic effects such as reduced activity, hunched posture, depression, ataxia, and prostration. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when data meet the criteria for GHS Category 3 classification (CPA 2018b). The confidence in the score is high based on reliable and consistent data across multiple studies and exposure routes.

- 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 2021a (note due to sufficient data availability for studies with Reliability ratings of 1 and/or 2, studies with reliability ratings of 3 and 4 were not included in the weight of evidence and are not summarized here)
  - *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1999) similar to OECD 401 (non-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 500 mg/kg (3 males), or 2,000

[11] 12.12 mg/L x 6 hr/6 hr x 5days/7days x 3 weeks/13 weeks = 2.0 mg/L

mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. **Reduced activity, piloerection, hunched posture were observed at both doses.** Hair loss was observed only at the lowest dose. Lethargy, part-closed eyes, and staining of skin and fur were observed at 2,000 mg/kg following dosing. Low dose animals recovered by day 10, and high dose animals by day 14. No abnormalities were found at necropsy. There was a dose-related decrease in body weight gain (statistical significance not reported). No deaths were reported and the $LD_{50}$ was assigned at >2,000 mg/kg (Reliability 2, reliable with restrictions).

- *Oral:* Sprague-Dawley rats were exposed to cyclopentanone in an acute oral toxicity study (reported in 1964) equivalent or similar to OECD 401 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) by gavage in corn oil at 34.6, 120, 417, 1,450, 5,000, or 10,000 mg/kg (5 males/group), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. All animals died at ⩾5,000 mg/kg within 24 hours of exposure. **Slight depression,** labored breathing, and decreased body weight gain were observed **at 1,450 mg/kg, with complete recovery by day 8.** At ⩾5,000 mg/kg, depression, lacrimation, slow labored breathing, vasodilation, coma, and death were observed. At necropsy, animals at ⩾5,000 mg/kg had congestion of the lungs, liver, and kidney, gastrointestinal inflammation, and hemorrhage. The $LD_{50}$ was calculated at 2,690 mg/kg (Reliability 2, reliable with restrictions).
- *Dermal:* Sprague-Dawley rats were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1999) similar to OECD 402 (non-GLP). Animals were exposed to cyclopentanone (99.8% purity) (vehicle, duration, and occlusion not specified) undiluted at 400 mg/kg (3 males), or 2,000 mg/kg (3 females), and were observed for 14 days. Necropsy was performed on surviving animals at study termination. There were no clinical signs of toxicity observed in low dose animals. At 2,000 mg/kg, piloerection and staining of the skin/fur were observed during exposure but disappeared within 24 hours. There were no mortalities and no abnormalities found at necropsy. The $LD_{50}$ was assigned at >2,000 mg/kg (Reliability 2, reliable with restrictions).
- *Dermal:* Albino rabbits (strain not specified) were exposed to cyclopentanone in an acute dermal toxicity study (reported in 1964) similar to OECD 402 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) at 50, 200, 794, or 3,160 mg/kg, under semi occlusion (no vehicle) for 24 hours (4/sex/dose), and were observed for 14 days. Necropsy was performed on surviving animals. One death occurred at 3,160 mg/kg. **This animals exhibited depression, phonation, excessive masticatory movements, labored breathing, gasping, stiffness of body, and intermittent convulsions at 24 hours**. One or two animals at each of the 3 lower doses had diarrhea for one to four days. Two of the animals that presented diarrhea had body weight loss. At necropsy, the one animal that died during exposure had congestion of the lungs, liver, and kidney (fibrous), fluid in the cranial cavity, and soft brain tissue. There were no other findings at necropsy. The $LD_{50}$ was assigned at >3,160 mg/kg (Reliability 2, reliable with restrictions).
- *Inhalation:* Male Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1965) similar to OECD 403 (pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure at 4.7, 12, 15, 17.8, or 19.5 mg/L (10 animals/dose) for 4 hours, and were observed for 14 days. Necropsy was performed on surviving animals. Mortality occurred in 1, 1, 3, 3, and 4/10 animals at 12, 15, 17.8, and 19.5 mg/L, respectively. **During exposure,** dyspnea**, depression, and decreased activity were observed, and ataxia and prostration were noted at the two highest levels but disappeared within 48 hours**. At necropsy, there were observations of

moderate congestion in the lungs, liver, and kidneys, but there were no gross pathological findings at study termination. The $LC_{50}$ was assigned at ⩾19.5 mg/L (Reliability 2, reliable with restrictions).

- *Inhalation:* Female Wistar rats were exposed to cyclopentanone in an acute inhalation toxicity study (reported in 1964) (guideline not specified, pre-GLP). Animals were exposed to cyclopentanone (purity not specified) vapor (no vehicle) by whole body exposure at 15.6 mg/L (10 animals/dose) for 6 hours, and were observed for 14 days. All animals died, and ptosis, lacrimation, dyspnea, and ataxia were observed during the exposure period. At necropsy, yellow-gray coloration of the lung surface was observed. The $LC_{50}$ was not determined (Reliability 3, not reliable).

**Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L):** *M*
Cyclopentanone was assigned a score of Moderate for neurotoxicity (repeated dose) based on surrogate epidemiological data indicating effects on the nervous system in exposed workers, which meets the criteria for GHS Category 2 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (repeated dose) when data support GHS Category 2 classification (CPA 2018b). The confidence in the score is low because there are limited experimental details available for the key 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.
- NITE 2009
  - *Surrogate: Cyclohexanone (CAS #108-94-1):* Cyclohexanone was classified as GHS Category 1 in Japan based on effects on the central nervous system and bones of exposed humans. Neurotoxic effects were observed in a group of 75 works from a furniture factory. **Reported neurotoxic symptoms included mood disorders, memory difficulty, and sleep disturbances**. Based on this information and another study summarized by ACGIH also indicating central nervous system effects, cyclohexanone was classified as a GHS Category 1 (central nervous system). In the same set of 75 workers, an increase in the percentage of individuals reporting **rheumatic symptoms (bone pain, joint pain, and muscular pain)** was also observed. These bone-related effects were also noted in the ACGIH report. Therefore, cyclohexanone was also categorized as a GHS Category 1 (bone effects). *ToxServices notes rheumatic symptoms, particularly pain in the absence of swelling, along with mood disorders, memory difficulty, and sleep disturbances can also be indicative of effects on the nervous system (e.g., fibromyalgia). Additionally, as noted above, GHS criteria require reliable and good quality evidence from human cases or epidemiological studies for Category 1 classification, while Category 2 classification is warranted when the weight of evidence is not sufficiently convincing to warrant Category 1 classification. ToxServices does not consider the available epidemiological study to be sufficient to classify as GHS Category 1, due to limited reporting of study details, and instead classifies this study to GHS Category 2.*

**Skin Sensitization (SnS) (Group II*) Score (H, M, or L):** *L*
Cyclopentanone was assigned a score of Low for skin sensitization based on negative results in a guinea pig maximization test, which meets the criteria for GHS not classified. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). Confidence is low because the number of animals tested was half as many as

recommended by the OECD test guideline 406, which inherently reduces the statistical power of the test results, and QSAR modeling identified one alert for possible skin 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.
- ECHA 2021a
  - Cyclopentanone was evaluated for skin sensitization in a guinea pig maximization test equivalent or similar to OECD 406 (non-GLP). Dunkin-Hartley guinea pigs were induced with 5% test substance (purity not specified) in polyethylene glycol (PEG) 200 by intradermal injection, or by 100% topical application. The first challenge was performed at 100%, and the second challenge was performed one week later at 20% in PEG 200, as well as with Freund's Complete Adjuvant (FCA). Results were evaluated at 24 and 48 hours after each challenge. Results were negative based on lack of sensitization at all time points for each challenge group (Reliability 2, reliable with restrictions – only 5 animals were used in the treatment group, which is half the amount recommended in OECD 406).
- Toxtree 2018
  - Cyclopentanone does not have any structural alerts for skin sensitization (Appendix D).
- OECD 2020a
  - Cyclopentanone does not have any structural alerts for skin sensitization according to GHS, however it has one alert (i.e., nucleophilic addition to carbon-hetero double bond) according to OASIS (Appendix E).

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

Cyclopentanone was assigned a score of Low for respiratory sensitization based on extrapolation from negative skin sensitization data, and lack of structural alerts for respiratory sensitization. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020a
  - Cyclopentanone does not contain any structural alerts for respiratory sensitization (Appendix E).
- 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 cyclopentanone 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 cyclopentanone, and as cyclopentanone does not contain any structural alerts for respiratory sensitization (OECD 2020), cyclopentanone is not expected to be a respiratory sensitizer.

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

Cyclopentanone was assigned a score of High for skin irritation/corrosivity based on EU harmonized hazard statement H315 – Causes skin irritation. GreenScreen® criteria classify chemicals as a High

hazard for skin irritation/corrosivity when the harmonized EU hazard statement is H315 (CPA 2018b). The confidence in the score is high based on authoritative A listing, and is supported by data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-Statements) – H315 - Causes skin irritation
    - *Screening:*
        - GHS – Australia – H315 – Causes skin irritation
        - GHS – New Zealand – 6.3A – Irritating to the skin (Cat. 2)
- ECHA 2021a (note one study with Reliability rating 3, not reliable, was not included due to use of a non-standard protocol with significant deviations relative to typical skin irritation tests such as OECD 404. For example, a binding agent was applied to the test site of each animal, and the exposure duration was 24 hours instead of 4 hours).
    - Cyclopentanone was evaluated for skin irritation in a study performed according to OECD 404 (GLP not specified). The test substance (purity not specified) was applied undiluted with an occlusive patch (no vehicle) over a 4cm$^2$ area of the skin on New Zealand White rabbits (n=6) for 4 hours. Animals were observed for 72 hours post exposure. Based on observations at 24, 48, and 72 hours, the primary irritation index was 3 out of 8 and authors concluded the substance was slightly irritating (no further details provided) (Reliability 2, reliable with restrictions).
    - Cyclopentanone was evaluated for skin irritation in a study performed according to AFNOR 1984 (GLP not specified). The test substance (purity not specified) was applied undiluted with an occlusive patch (no vehicle) to shaved and abraded skin of New Zealand White rabbits (n=6) for 4 hours. Animals were observed for 48 hours, and up to 7 or 14 days post exposure if pronounced irritation was noted. The primary irritation index was 2.75 out of 8 using the Draize method of scoring, and authors concluded the substance was slightly irritating (no further details provided) (Reliability 2, reliable with restrictions).
    - Cyclopentanone was evaluated for skin irritation in a study performed according to the Cosmetic – official method for testing cosmetics and toiletries (Journal Officiel de al République Francaises, 1971 & 1973) (GLP not specified). The test substance (purity not specified) was applied undiluted with an occlusive patch (no vehicle) to shaved and abraded skin of New Zealand White rabbits (n=6) for 24 hours. Animals were observed for 48 hours. The primary irritation index was 2.21 out of 8 using the Draize method of scoring, and authors concluded the substance was slightly irritating (no further details provided) (Reliability 2, reliable with restrictions).

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

Cyclopentanone was assigned a score of High for eye irritation/corrosivity based on EU harmonized hazard statement H319 – Causes serious eye irritation. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when the harmonized EU hazard statement is H319 (CPA 2018b). The confidence in the score is high based on authoritative A listing, and is supported by data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-Statements) – H319 - Causes serious eye irritation
    - *Screening:*
        - GHS – Japan – Serious eye damage / eye irritation – Category 2A [H319]
        - GHS - Australia – H319 – Causes serious eye irritation
        - GHS – New Zealand – 6.4A – Irritating to the eye (Cat. 2A)
- ECHA 2021a

- Cyclopentanone was evaluated for eye irritation in a study equivalent or similar to OECD 405 (GLP not specified). The test substance (purity not specified) was instilled into one eye each at 0.1 mL (no vehicle) in six New Zealand White rabbits. Some animals did not get the exposed eye rinsed, and some did with Dacryoserum after 4 or 30 seconds. Observations were recorded at 1 hour, and 1, 2, 3, 4, and 7 days post exposure, or later where lesion persisted. Individual scores for cornea opacity, iris, conjunctivae, and chemosis were not reported. Results were reported using the AFNOR scale with a maximum index value of 110. The individual ocular irritation (IOI) at day 7 was >30 without rinsing in 4/6 rabbits, and with rinsing at 30 seconds in 1/3 rabbits. The mean ocular irritation (MOI) after 7 days was 43.67 without rinsing, 17.50 after rinsing at 30 seconds, and 20.67 after rinsing at 4 seconds. The average ocular irritation (AOI) was 54.33 without rinsing, 49.67 within rinsing at 30 seconds, and 54.66 with rinsing at 4 seconds. Authors concluded the test substance was irritating to the eye (Reliability 2, reliable with restrictions).
- Cyclopentanone was evaluated for eye irritation in a non-guideline, pre-GLP study (reported in 1964) using the Draize test. The test substance (purity not specified) was instilled into one eye each at 0.1 mL (no vehicle) in six rabbits (strain not specified). Observations were recorded at 1, 4, and 24 hours, and 2, 3, 4, 7, 10, and 14 days post exposure. The mean score for cornea opacity was 1.07 at 24, 48, and 72 hours, and effects were not fully reversible within 14 days for one of the animals. The mean score for the iris was 0.53 at 24, 48, and 72 hours, and effects were fully reversed within 7 days. The mean score for conjunctivae was 2.07 at 24, 48, and 72 hours, and effects were not fully reversible within 14 days for one of the rabbits. The mean score for chemosis was 1.6 at 24, 48, and 72 hours, and effects were not fully reversible within 14 days. Authors concluded the test substance was irritating to the eye. Authors noted the eye irritation was severe, and corneal lesions were noted on the 7$^{th}$ day and were still present at day 14 (Reliability 2, reliable with restrictions). *ToxServices notes that the mean cornea opacity of 1.07 and conjunctivae at 2.07 are in the range of criteria for GHS Category 2A, however, as observations were terminated at day 14, there is uncertainty if effects would have completely reversed by day 21.*

## Ecotoxicity (Ecotox)

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

Cyclopentanone was assigned a score of Low for acute aquatic toxicity based on LC/EC$_{50}$ values > 100 mg/L in fish, invertebrates, and algae. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when the LC/EC$_{50}$ value of the most sensitive trophic level is >100 mg/L (CPA 2018b). The confidence in the score is high based on high quality data and numerous studies.

- 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 2021a (note: due to available high reliability data, studies with reliability ratings of 3 (not reliable) were not included in the weight of evidence and are not summarized here)
  - Cyclopentanone was evaluated for acute toxicity to fish in a GLP-compliant study performed according to OECD 203. *Oncorhynchus mykiss* (rainbow trout) were exposed to the test substance (purity not specified) at up to 100 mg/L (nominal), or 109 mg/L (measured) for 96 hours under semi-static conditions. The 96-hr LC$_{50}$ was > 100 mg/L (Reliability 1, reliable without restriction).
  - Cyclopentanone was evaluated for acute toxicity to invertebrates in a GLP-compliant study performed according to OECD 202. *Daphnia magna* (water flea) were exposed to the test

substance (purity not specified) at up to 100 mg/L (nominal) (or 96.9 at T0, 80.2 at 24h, and 88.2 at 48h) for 48 hours under static conditions. The 48-hr $EC_{50}$ was > 100 mg/L (Reliability 1, reliable without restriction).
    - Cyclopentanone was evaluated for acute toxicity to algae in a GLP-compliant study performed according to OECD 201. *Desmodesmus subspicatus* (green algae) were exposed to the test substance (purity not specified) at up to 100 mg/L (nominal) for 72 hours under static conditions. The 72-hr $EC_{50}$ was > 100 mg/L based on growth rate and biomass (measured concentrations were within 20% of nominal throughout the study) (Reliability 1, reliable without restriction).
- U.S. EPA 2021b
    - The 48 hour $LC_{50}$ in *Leuciscus idus* (carp) is 3,320 mg/L (no further details provided).
    - The 48 hour $LC_{50}$ in *L. idus* (carp) is 2,950 mg/L (no further details provided).
    - The 24 hour $EC_{50}$ in *D. magna* (Water flea) is 1,435 mg/L (no further details provided).
    - The 24 hour $LC_{50}$ in *D. magna* (Water flea) is 1,800 mg/L (no further details provided).

**Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L):** *L*
Cyclopentanone was assigned a score of Low for chronic aquatic toxicity based on predicted chronic toxicity values (ChV) >10 mg/L in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when the ChV for the most sensitive trophic level is >10 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeling, and no chronic exposure data were identified for fish and aquatic invertebrates.

- 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 2021a
    - Cyclopentanone was evaluated for acute toxicity to algae in a GLP-compliant study performed according to OECD 201. *D. subspicatus* (green algae) were exposed to the test substance (purity not specified) at up to 100 mg/L (nominal) for 72 hours under static conditions. The 72-hr NOEC was > 100 mg/L based on growth rate and biomass (measured concentrations were within 20% of nominal throughout the study) (Reliability 1, reliable without restriction).
- U.S. EPA 2017a
    - Cyclopentanone belongs to the Neutral Organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 98.0 mg/L in fish, 40.0 mg/L in daphnia, and 50.9 mg/L in green algae (Appendix F).

## Environmental Fate (Fate)

**Persistence (P) Score (vH, H, M, L, or vL): vL**
Cyclopentanone was assigned a score of Very Low for persistence based on predicted partitioning to soil and measured ready biodegradability (>60% in 28 days, within the 10-day window). GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil is the dominant medium and the substance is readily biodegradable within the 10-day window (CPA 2018b). The confidence in the score is high based on measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - EC – CEPA DSL - Persistent

- ECHA 2021a (note due to the availability of a high reliability ready biodegradability study, additional data on inherently biodegradability was not included in the weight of evidence and is not summarized here).
    - Cyclopentanone was evaluated in GLP-compliant ready biodegradability test performed according to OECD 301F. The test substance (purity not specified) was exposed to domestic, non-adapted, activated sludge under aerobic conditions for 28 days at an initial concentration of 100 mg/L (nominal). Biodegradation was measured based on oxygen consumption. Biodegradation reached 10% by day 4 for both replicates, and >60% by days 6 and 7, thus the test substance met the 10-day window. The reference substance, sodium benzoate, performed as expected. Authors reported 102% degradation in 28 days, and within the 10-day window, and concluded the test substance was readily biodegradable (Reliability 1, reliable without restriction).
- U.S. EPA 2017b
    - Fugacity modeling (MCI method) predicts 55.7% will partition to soil with a half-life of 30 days, 38.7% will partition to water with a half-life of 15 days, 5.45% will partition to air with a half-life of <4 days, and 0.0865% will partition to sediment with a half-life of 135 days (Appendix G).

**Bioaccumulation (B) Score (vH, H, M, L, or vL): vL**
Cyclopentanone was assigned a score of Very Low for bioaccumulation based on predicted BCF values of 3.162 and 1.236, and a measured log $K_{ow}$ of 0.70. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the BCF is ≤100, and when the log $K_{ow}$ is ≤ 4 (CPA 2018b). The confidence in the score is high based on the measured log $K_{ow}$.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017b
    - BCFBAF predicts a BCF of 3.162 using the regression based model based on a measured log $K_{ow}$ of 0.70, and a BCF of 1.236 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix G).

**Physical Hazards (Physical)**

**Reactivity (Rx) Score (vH, H, M, or L): L**
Cyclopentanone was assigned a score of Low for reactivity based on data demonstrating auto-ignition at > 140°C, lack of shock- and thermal-sensitivity to explosion, and lack of functional groups associated with oxidation potential. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on measured data and physicochemical properties.

- 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 2021a
    - The auto-ignition temperature of cyclopentanone was 430°C at 1,025 hPa (EU Method A.15, GLP-compliant) (Reliability 1, reliable without restriction).
    - Cyclopentanone did not demonstrate shock-sensitivity or thermal-sensitivity to explosion (EU Method A.14, GLP-compliant) (Reliability 1, reliable without restriction).

    - Cyclopentanone does not have any functional groups associated with oxidizing properties, therefore testing is not necessary.
- Based on the structure of its components or moieties, cyclopentanone is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix H).

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

Cyclopentanone was assigned a score of Moderate for flammability based on harmonized EU hazard statement H226 – Flammable liquid and vapour. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when the harmonized EU hazard statement is H3226 (CPA 2018b). The confidence in the score is high based on authoritative A listing, and is supported by data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU – GHS (H-Statements) – H226 – Flammable liquid and vapour
        - Québec CSST – WHMIS 1988 – Class B2 – Flammable liquids
    - *Screening:*
        - GHS – Australia – H226 – Flammable liquid and vapour
        - GHS – Japan – Flammable liquids – Category 3 [H226]
        - GHS – New Zealand – 3.1C – Flammable Liquids: medium hazard
- ECHA 2021a
    - Multiple flash point values are available and range from 26 to 30°C, thus cyclopentanone is a flammable liquid.

## 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 use of *in vitro* data to assess genotoxicity and endocrine activity, and *in silico* modeling to assess skin and respiratory sensitization, chronic aquatic toxicity, environmental partitioning and persistence, and bioaccumulation. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020b, OECD 2020b). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020b):

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

As shown in Table 4, Type I (input data) uncertainties in cyclopentanone's NAMs dataset include limited or lack of experimental data for some endpoints, particularly endocrine activity, skin sensitization, respiratory sensitization, and chronic aquatic toxicity. Cyclopentanone's Type II (extrapolation output) uncertainties include several uses of QSAR models using structural alerts without defined applicability domains (OECD Toolbox and Toxtree), use of *in vitro* data that may not accurately reflect *in vivo* conditions, and assessment of respiratory sensitization without consideration for non-immunologic mechanisms. Some of cyclopentanone's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

| **Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses** | |
|---|---|
| **Uncertainty Analyses (OECD 2020b)** | |
| **Type I Uncertainty: Data/Model Input** | **Endocrine activity:** No *in vivo* data were available.<br>**Skin Sensitization**: Only one animal study was available and had fewer than the recommended number of test animals (OECD 406)<br>**Respiratory sensitization**: No experimental data are available and there are no validated test methods.<br>**Chronic aquatic toxicity:** No experimental data were available for fish and aquatic invertebrate trophic levels. |
| **Type II Uncertainty: Extrapolation Output** | **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[13]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous |

[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).

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

| | | |
|---|---|---|
| | 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]<br>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].<br>**Endocrine activity:** The *in vivo* relevance of EDSP Tox 21 screening assays is unknown due to lack of consideration of metabolism and other toxicokinetic factors.<br>**Skin Sensitization**: The OECD Toolbox and Toxtree only identify structural alerts, and do not define applicability domains.<br>**Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. | |
| **Endpoint** | **NAMs Data Available and Evaluated? (Y/N)** | **Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)** |
| Carcinogenicity | N | |
| Mutagenicity | Y | *In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay |
| Reproductive toxicity | N | |
| Developmental toxicity | N | |
| Endocrine activity | Y | *In vitro* high throughput data: EDSP Tox 21 screening assays |
| Acute mammalian toxicity | N | |
| Single exposure systemic toxicity | N | |
| Repeated exposure systemic toxicity | N | |
| Single exposure neurotoxicity | N | |
| Repeated exposure neurotoxicity | N | |
| Skin sensitization | Y | *In silico* modeling: Toxtree/OECD Toolbox structural alerts |
| Respiratory sensitization | Y | *In silico* modeling: OECD Toolbox structural alerts |
| Skin irritation | N | |
| Eye irritation | N | |

[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

| | | |
|---|---|---|
| Acute aquatic toxicity | N | |
| Chronic aquatic toxicity | Y | *In silico* modeling: ECOSAR |
| Persistence | Y | *In silico* modeling: EPI Suite™<br>Non-animal testing: OECD 301F 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 Cyclopentanone (CAS #120-92-3)

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 | Cyclopentanone | 120-92-3 | M | L | *M* | *M* | DG | *L* | M | *M* | M | *M* | *L* | *L* | H | H | L | *L* | vL | vL | L | M |

**Table 3: Hazard Summary Table**

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

**Table 4**

| Chemical Name | Preliminary GreenScreen® Benchmark Score |
|---|---|
| Cyclopentanone | 2 |

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

**Table 6**

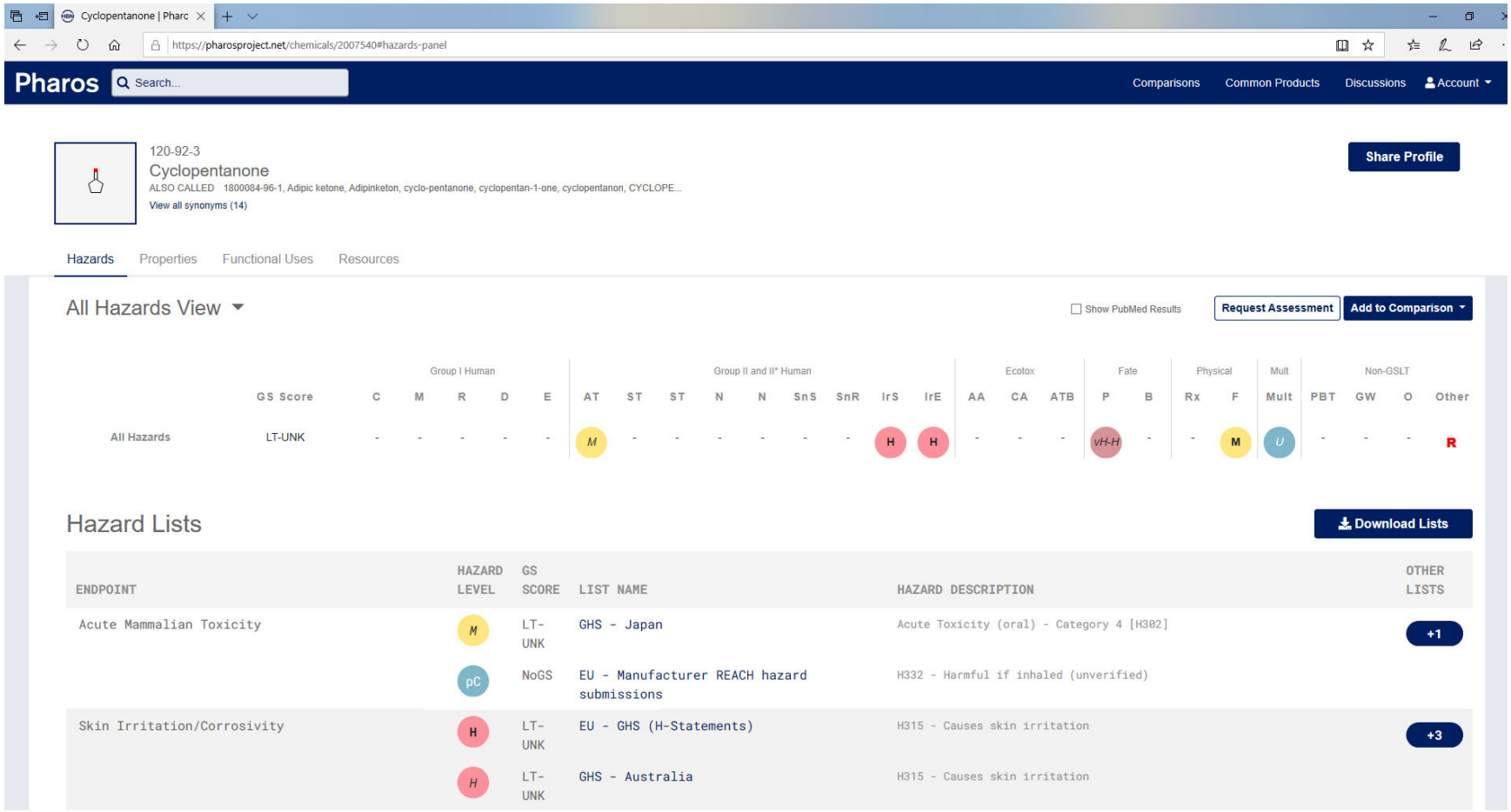
| Chemical Name | Final GreenScreen® Benchmark Score |
|---|---|
| Cyclopentanone | 2 |

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 Cyclopentanone (CAS #120-92-3)




| | | | | | |
|---|---|---|---|---|---|
| | H | LT-UNK | GHS - New Zealand | 6.3A - Irritating to the skin (Cat. 2) | |
| | pC | NoGS | EU - Manufacturer REACH hazard submissions | H315 - Causes skin irritation (unverified) | |
| Eye Irritation/Corrosivity | H | LT-UNK | EU - GHS (H-Statements) | H319 - Causes serious eye irritation | +4 |
| | H | LT-UNK | GHS - Japan | Serious eye damage / eye irritation - Category 2A [H319] | |
| | H | LT-UNK | GHS - Australia | H319 - Causes serious eye irritation | |
| | H | LT-UNK | GHS - New Zealand | 6.4A - Irritating to the eye (Cat. 2A) | |
| | pC | NoGS | EU - Manufacturer REACH hazard submissions | H319 - Causes serious eye irritation (unverified) | |
| Persistence | vH-H | LT-UNK | EC - CEPA DSL | Persistent | |
| Flammability | M | LT-UNK | EU - GHS (H-Statements) | H226 - Flammable liquid and vapour | +5 |
| | M | LT-UNK | GHS - Australia | H226 - Flammable liquid and vapour | |
| | M | LT-UNK | GHS - Japan | Flammable liquids - Category 3 [H226] | |
| | M | LT-UNK | GHS - New Zealand | 3.1C - Flammable Liquids: medium hazard | |
| | vH-M | LT-UNK | Québec CSST - WHMIS 1988 | Class B2 - Flammable liquids | |
| | pC | NoGS | EU - Manufacturer REACH hazard submissions | H226 - Flammable liquid and vapour (unverified) | |
| Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation | U | LT-UNK | German FEA - Substances Hazardous to Waters | Class 1 - Low Hazard to Waters | |

| | | | | |
|---|---|---|---|---|
| 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 |

## Restricted Substance Lists (1)

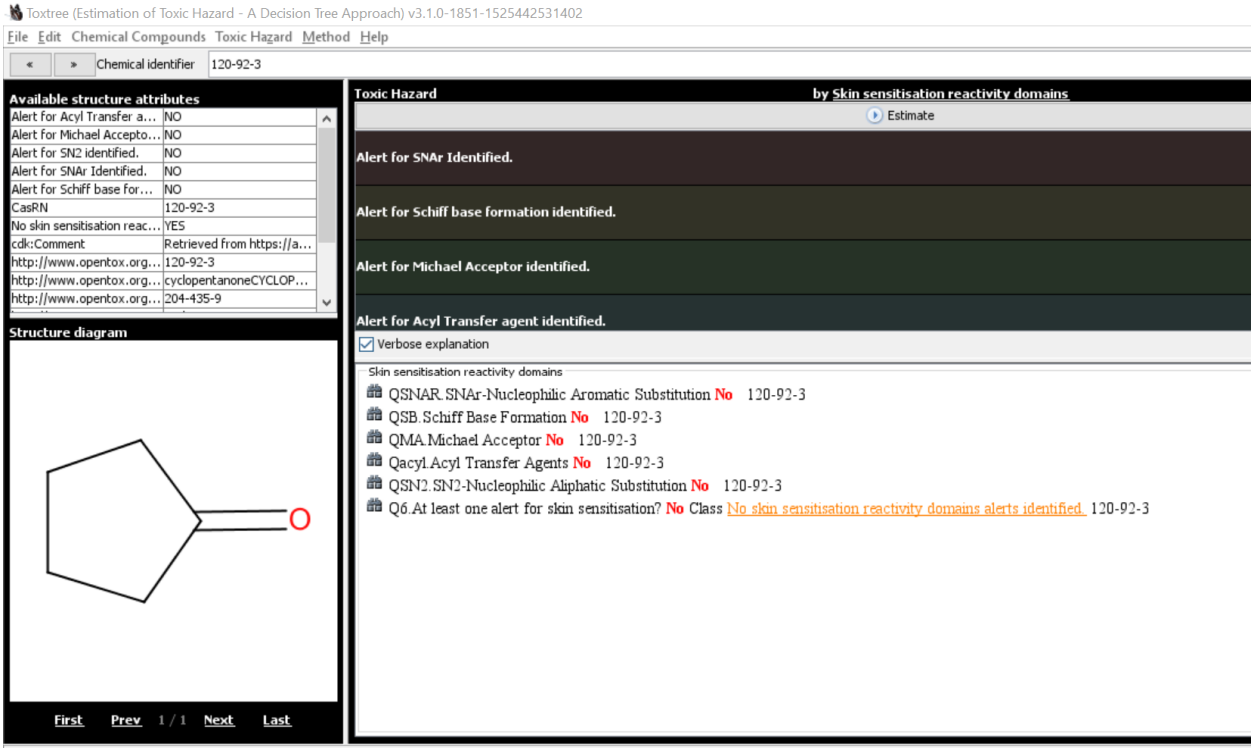
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment

## Discussions

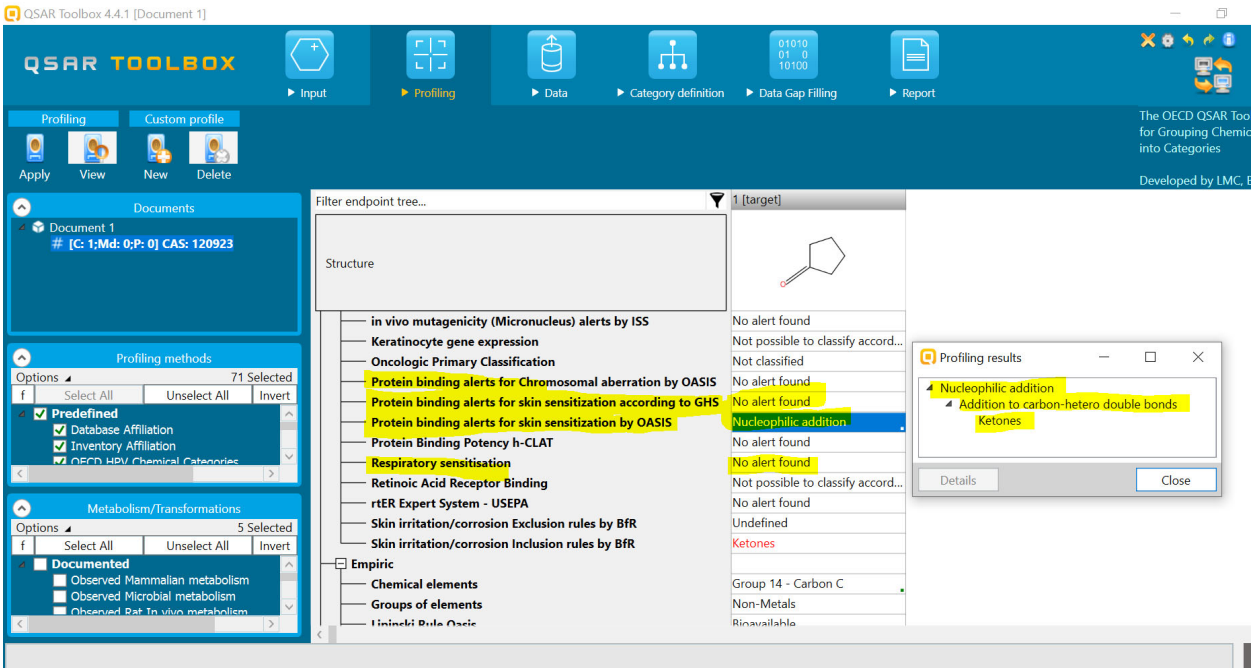
No discussions have been posted yet.

Ask a question about this chemical in the forums >

## APPENDIX D: Toxtree Skin Sensitization Results for Cyclopentanone (CAS #120-92-3)



## APPENDIX E: OECD QSAR Toolbox Structural Alerts for Skin and Respiratory Sensitization of Cyclopentanone (CAS #120-92-3)



## APPENDIX F: ECOSAR Modeling Results for Cyclopentanone (CAS #120-92-3)

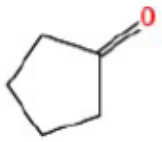
Created on Jun 10, 2021 3:11:44 PM

# Organic Module Report

Results of Organic Module Evaluation

| CAS | Name | SMILES |
|---|---|---|
| 120923 | Cyclopentanone | O=C(CCC1)C1 |

**Structure**




| Details | |
|---|---|
| Mol Wt | 84.12 |
| Selected LogKow | 0.63 |
| Selected Water Solubility (mg/L) | 97490.03 |
| Selected Melting Point (°C) | -51.3 |
| Estimated LogKow | 0.63 |
| Estimated Water Solubility (mg/L) | 97490.03 |
| Measured LogKow | 0.38 |
| Measured Water Solubility (mg/L) | ◆ |
| Measured Melting Point (°C) | -51.3 |

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

**Neutral Organics**

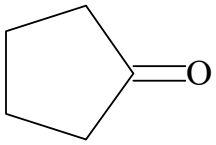
| Organism | Duration | End Point | Concentration (mg/L) | Max Log Kow | Flags |
|---|---|---|---|---|---|
| Fish | 96h | LC50 | 1163 | 5 | |
| Daphnid | 48h | LC50 | 582.15 | 5 | |
| Green Algae | 96h | EC50 | 257.5 | 6.4 | |
| Fish | | ChV | 97.97 | 8 | |
| Daphnid | | ChV | 39.97 | 8 | |
| Green Algae | | ChV | 50.93 | 8 | |
| Fish (SW) | 96h | LC50 | 1452.21 | 5 | |
| Mysid | 96h | LC50 | 2721.27 | 5 | |

1 / 2

## APPENDIX G: EPI Suite™ Modeling Results for Cyclopentanone (CAS #120-92-3)

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

EPI Suite Results For CAS 120-92-3




```
SMILES : O=C(CCC1)C1
CHEM   : Cyclopentanone
MOL FOR: C5 H8 O1
MOL WT : 84.12
------------------------------ EPI SUMMARY (v4.11) --------------------------
Physical Property Inputs:
Log Kow (octanol-water):   0.70
Boiling Point (deg C)  :   -130.00
Melting Point (deg C)  :   -54.00
Vapor Pressure (mm Hg) :   8.35
Water Solubility (mg/L):   301
Henry LC (atm-m3/mole) :   ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  0.63
Log Kow (Exper. database match) =  0.38
Exper. Ref:  DAYLIGHT (2003)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  130.58  (Adapted Stein & Brown method)
Melting Pt (deg C):  -40.55  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  7.52E+004  (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) :  1E+007  (Mean VP of Antoine & Grain methods)
MP  (exp database):  -51.3 deg C
BP  (exp database):  130.5 deg C
VP  (exp database):  1.14E+01 mm Hg (1.52E+003 Pa) at 25 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  4.806e+004
log Kow used: 0.70 (user entered)
melt pt used: -54.00 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  80805 mg/L
```

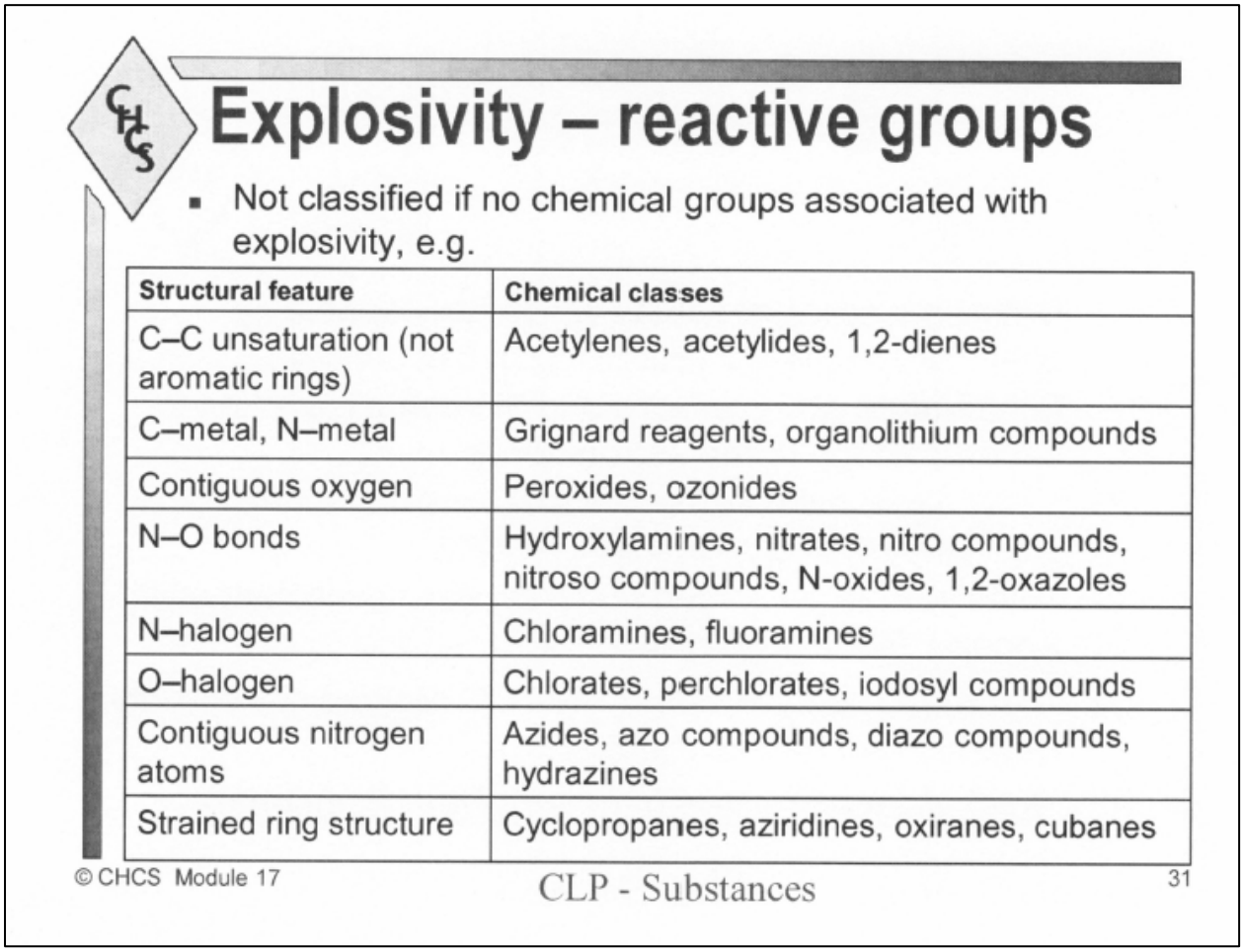
```
ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method :   3.85E-005  atm-m3/mole  (3.90E+000 Pa-m3/mole)
Group Method:   9.09E-006  atm-m3/mole  (9.21E-001 Pa-m3/mole)
Exper Database: 1.00E-05  atm-m3/mole  (1.01E+000 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  3.070E-003 atm-m3/mole  (3.111E+002 Pa-m3/mole)
VP:   8.35 mm Hg (source: User-Entered)
WS:   301 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  0.70  (user entered)
Log Kaw used:  -3.388  (exp database)
Log Koa (KOAWIN v1.10 estimate):  4.088
Log Koa (experimental database):  3.670

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :   0.7143
Biowin2 (Non-Linear Model)     :   0.7960
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   2.9908  (weeks       )
Biowin4 (Primary Survey Model) :   3.7042  (days-weeks  )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :   0.5288
Biowin6 (MITI Non-Linear Model):   0.7208
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.0359
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):  1.11E+003 Pa (8.35 mm Hg)
Log Koa (Exp database): 3.670
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  2.69E-009
Octanol/air (Koa) model:  1.15E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  9.73E-008
Mackay model           :  2.16E-007
Octanol/air (Koa) model:  9.19E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant =   6.8378 E-12 cm3/molecule-sec
Half-Life =     1.564 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =    18.771 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1.56E-007 (Junge-Pankow, Mackay avg)
```

```
9.19E-008 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc    :  9.535  L/kg (MCI method)
Log Koc:  0.979       (MCI method)
Koc    :  32.2  L/kg (Kow method)
Log Koc:  1.508       (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) = -1.3327 days (HL = 0.04648 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.092 (BCF = 1.236)
Log BAF Arnot-Gobas method (upper trophic) = 0.092 (BAF = 1.236)
log Kow used: 0.70 (user entered)

Volatilization from Water:
Henry LC:  1E-005 atm-m3/mole  (Henry experimental database)
Half-Life from Model River:      54.63  hours   (2.276 days)
Half-Life from Model Lake :      672.9  hours   (28.04 days)

Removal In Wastewater Treatment:
Total removal:               2.42  percent
Total biodegradation:        0.09  percent
Total sludge adsorption:     1.77  percent
Total to Air:                0.56  percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       5.45           88.5         1000
Water     38.7           360          1000
Soil      55.7           720          1000
Sediment  0.0865          3.24e+003    0
Persistence Time: 379 hr

Level III Fugacity Model: (MCI Method with Water percents)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       5.45           88.5         1000
Water     38.7           360          1000
water     (38.7)
biota     (9.71e-006)
suspended sediment (0.000554)
Soil      55.7           720          1000
Sediment  0.0865          3.24e+003    0
Persistence Time: 379 hr

Level III Fugacity Model: (EQC Default)
Mass Amount    Half-Life    Emissions
(percent)        (hr)       (kg/hr)
Air       6.02           88.5         1000
Water     44.1           360          1000
```

```
water      (44.1)
biota      (1.11e-005)
suspended sediment (0.000136)
Soil       49.8            720          1000
Sediment   0.0846          3.24e+003    0
Persistence Time: 352 hr
```

## APPENDIX H: Known Structural Alerts for Reactivity

### Explosivity – Abbreviated List



# Explosivity – reactive groups

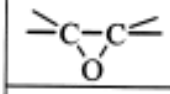
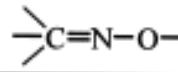
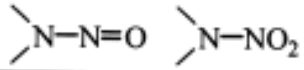
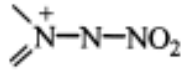
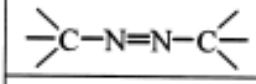
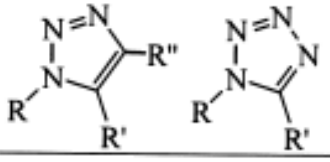
- Not classified if no chemical groups associated with explosivity, e.g.

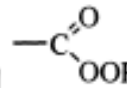
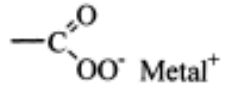
| Structural feature | Chemical classes |
|---|---|
| C–C unsaturation (not aromatic rings) | Acetylenes, acetylides, 1,2-dienes |
| C–metal, N–metal | Grignard reagents, organolithium compounds |
| Contiguous oxygen | Peroxides, ozonides |
| N–O bonds | Hydroxylamines, nitrates, nitro compounds, nitroso 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 |

© CHCS Module 17 CLP - Substances 31

## Explosivity – Full List

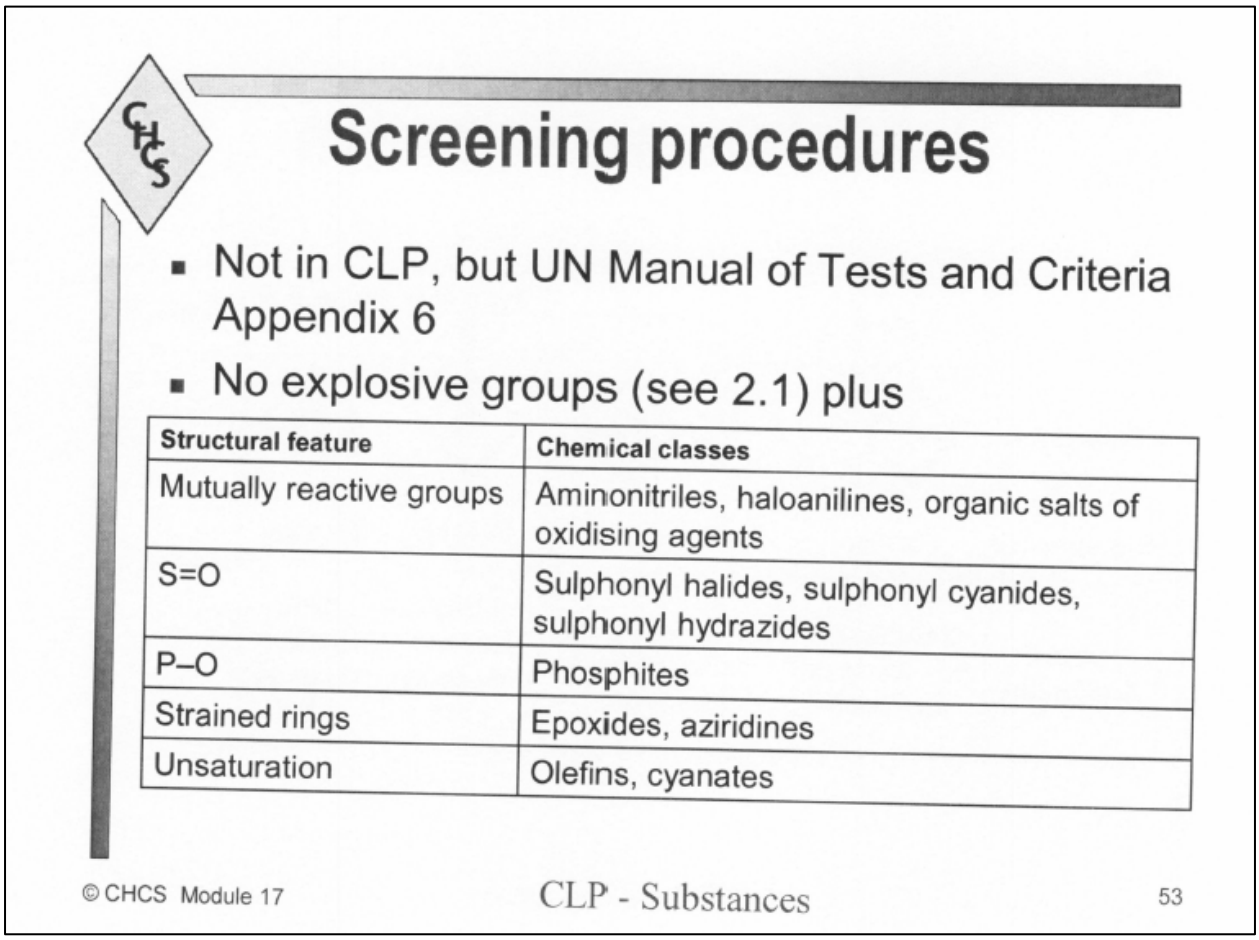
**Table R.7.1-28 Chemical groups associated with explosive properties**

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

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

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

**Self-Reactive Substances**



# Screening procedures

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

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

**Licensed GreenScreen® Profilers**

**Cyclopentanone GreenScreen® Evaluation Prepared by:**

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