CASTOR OIL, HYDROGENATED

(CAS #8001-78-3)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 19, 2024

Expiration Date: November 19, 2029

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GreenScreen® Executive Summary for Castor Oil, Hydrogenated (CAS #8001-78-3)

Castor oil, hydrogenated, also known as hydrogenated castor oil, or HCO, is an extract from the seeds of the *Ricinus communis* plant that has been hydrogenated. It is used in numerous consumer products including cosmetics applied to the skin and on or near the eyes, it is approved for direct and indirect addition to food, and has numerous industrial applications such as impregnating paper and making water-repellant coatings for textiles.

HCO is a solid/powder; as it is plant-derived, it has variable composition, but primarily consists of glyceryl-tri-hydroxystearate. HCO is not a volatile organic compound (VOC).

HCO 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 Health Hazard (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E).

Data gaps (DG) exist for neurotoxicity (Ns and Nr*). As outlined in GreenScreen® Guidance (Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), HCO meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if HCO were assigned a High score for the data gaps Ns or Nr*, it would still be categorized as a Benchmark 2 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include reliance on historical safe use, application of QSAR models for respiratory sensitization, acute and chronic aquatic toxicity, persistence and bioaccumulation, and various *in vitro* tests for genotoxicity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

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

Type I (input data) uncertainties in HCO's NAMs dataset include use of limited or no experimental data for endocrine activity, respiratory sensitization, acute and chronic aquatic toxicity, and bioaccumulation, and no validated test methods to assess respiratory sensitization. HCO's Type II (extrapolation output) uncertainties include reliance on *in vitro* genotoxicity test methods that do not entirely mimic *in vivo* metabolic conditions, use of QSAR models that do not define the applicability domain, the uncertain *in vivo* relevance of high throughput *in vitro* screening assays for endocrine receptor activities, the incomplete coverage for EDSP Tox 21 assays of critical endocrine pathways, and the lack of consideration of non-immunologic mechanisms of respiratory sensitization by OECD Toolbox structural alerts. Some of HCO'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 for HCO

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

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 Castor Oil, Hydrogenated (HCO) (CAS #8001-78-3)

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

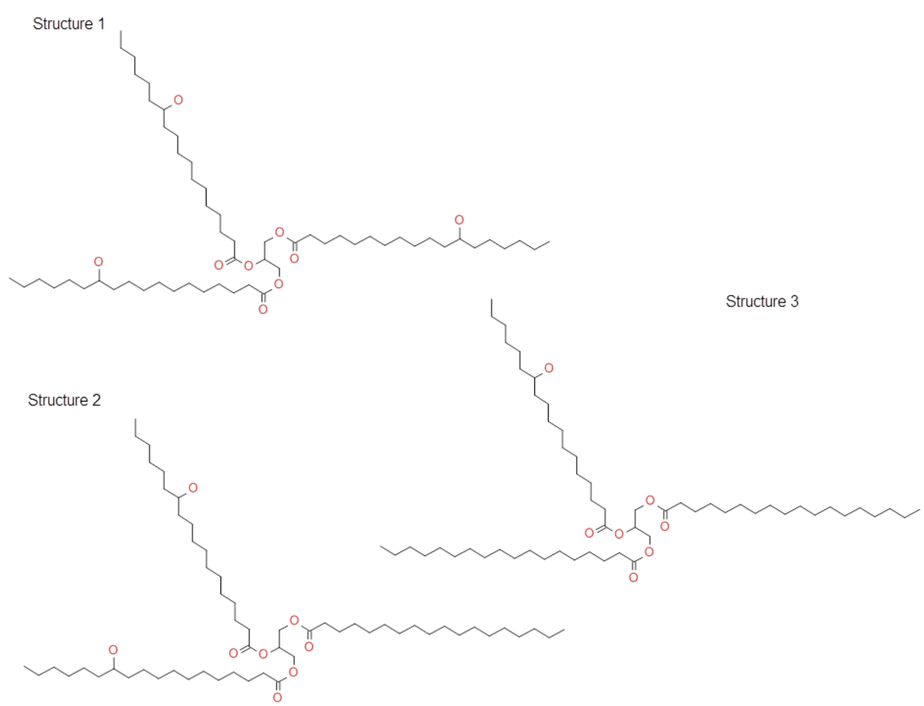
GreenScreen® Assessment (v.1.4) Prepared By:	**Quality Control Performed By:**
Name: Nancy Linde, M.S.	Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist	Title: Senior Toxicologist
Organization: ToxServices LLC	Organization: ToxServices LLC
Date: November 8, 2024	Date: November 19, 2024

Expiration Date: November 19, 2029[2]

Chemical Name: Castor Oil, Hydrogenated (HCO)

CAS Number: 8001-78-3

Chemical Structure(s):



(ECHA, CAS #8001-78-3, 2024).

Also called: Castor Wax; Montane 481, Hydrogenated Jojoba Oil; LC-180, Hydrogenated Castor Oil; HCO (CIR 2007, ECHA, CAS #8001-78-3, 2024).

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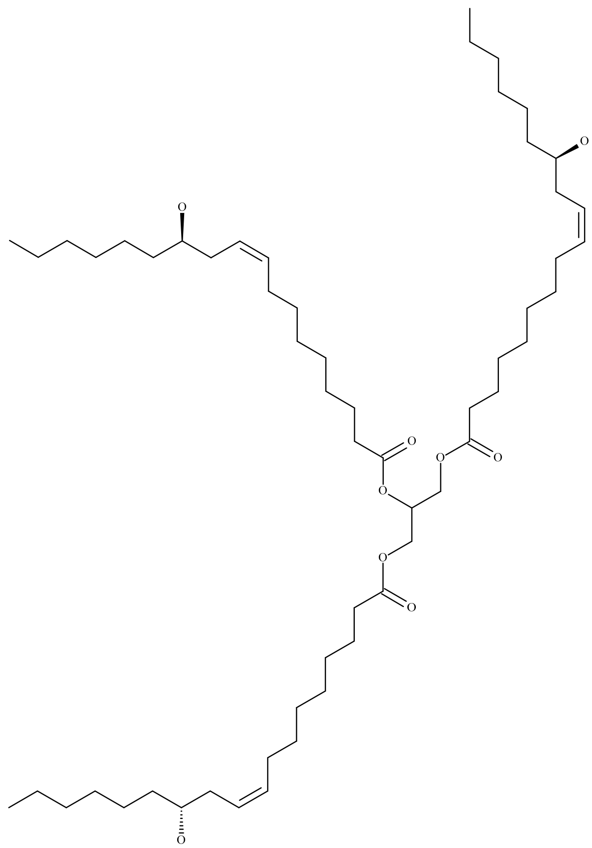
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment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

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Castor oil (CAS #8001-79-4), a mixture of triglycerides obtained from the seeds of *Ricinus communis*, is the precursor of HCO. Castor oil is the main surrogate in this report as as it differs from HCO only in that it has not been hydrogenated. Hydrogenation is not expected to significantly affects its toxicities. As castor oil is a UVCB, similar to HCO, it also has no discrete structure. Castor oil consists of 85-95% esterified ricinoleic acid (U.S. EPA 2011), which makes up approximately 87% of the fatty acid composition of castor oil (HSDB 2010). PubChem (2024) presents the structure for the triglyceride of ricinoleic acid (glyceryl triricinoleate, CAS #2540-54-7) for castor oil (SMILES: CCCCCC[C@@H](O)C/C=C\CCCCCCCC(=O)OCC(OC(=O)CCCCCCC/C=C\C[C@H](O)CCCCCC)COC(=O)CCCCCCC/C=C\C[C@H](O)CCCCCC). Therefore, modeling was performed with the structure of glyceryl triricinoleate, as follows:



Triglyceride of ricinoleic acid (glyceryl triricinoleate), CAS #2540-54-7 (PubChem 2024).

Identify Applications/Functional Uses:
1. Direct and indirect food additive (U.S. FDA 2024).
2. Skin-conditioning agent (CIR 2007)
3. Viscosity increasing agent (CIR 2007)
4. Lubricant (CIR 2007)
5. Mold release agent (CIR 2007)
6. Waterproofing agent (CIR 2007)

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

GreenScreen® Summary Rating for HCO[4,5 6,7]: HCO 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 Health Hazard (reproductive toxicity-R, developmental toxicity-D, and endocrine activity-E).

Data gaps (DG) exist for neurotoxicity (Ns and Nr*). As outlined in GreenScreen® Guidance (Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), HCO meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if HCO were assigned a High score for the data gaps Ns or Nr*, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen® Hazard Summary for HCO

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As HCO is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

HCO is the hydrogenated form of castor oil, which is derived from the seeds of the *Ricinus communis* plant. It consists primarily of glyceryl-tri-hydroxystearate (CAS #139-44-6). Castor oil, and therefore HCO, do not contain significant amounts of ricin because ricin does not partition to the oil (CIR 2007). It is used in chemical synthesis, lacquers and varnishes, metal industry, adhesives, cosmetics, and

[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.

lubricants, water-repellent coatings, candles, shoe polish, carbon paper, ointments, for impregnating paper, wood, cloth, and electrical condensers, and as a pressure mold release agent (EC 2000, CIR 2007). HCO has various approvals as a direct and indirect food additive (U.S. FDA 2024).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2024a). 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 2024b).

HCO is on the SCIL with a half-green circle to indicate that it is expected to be of low concern based on experimental and modeled data, and additional data would strengthen the confidence in the chemical's safer status.

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 2024) 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 HCO can be found in Appendix C.

- HCO is assigned NoGS by Pharos, and therefore a full GreenScreen® is required.
- HCO is not listed on the U.S. DOT list.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for HCO, as indicated in Table 1. No occupational exposure limits (OELs) were identified (Table 2). General personal protective equipment (PPE) recommendations are presented in Table 3, below.

Table 1: GHS H Statements for HCO (CAS #8001-78-3) (ECHA, CAS #8001-78-3, 2024)	
H Statement	**H Statement Details**
No harmonized GHS H statements are reported by the European Chemicals Agency (ECHA). According to its ECHA registration dossier and the majority of notifications provided by companies to ECHA in REACH registrations, no hazards have been classified.	

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for HCO (CAS #8001-78-3)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Safety glasses, nitrile gloves, and P1 respiratory mask.	Sigma-Aldrich Inc. 2024	None	Not applicable

Physicochemical Properties of HCO

HCO is a white to cream waxy solid under standard conditions. Its estimated low vapor pressure indicates a low potential to form a vapor. It is not soluble in water and the estimated log K_{ow} suggests that it is not bioavailable. However, this does not account for metabolism.

Table 3: Physical and Chemical Properties of HCO (CAS #8001-78-3)		
Property	**Value**	**Reference**
Molecular formula	UVCB	PubChem 2024
SMILES Notation	Variable (UVCB); Representative structure: O=C(CCCCCCCCCC(CCCCCC)O)OC(COC(=O)(CCCCCCCCCCC(O)CCCCCC))C(=O)(OCCCCCCCCCCC(O)CCCCCC)	ECHA, CAS #8001-78-3, 2024
Molecular weight	Variable (UVCB)	
Physical state	Solid (powder)	Sigma-Aldrich 2024
Appearance	White to cream waxy solid and tasteless	CIR 2007
Melting point	78 to 90°C	CIR 2007
Boiling point	> 300°C	EC 2000
Vapor pressure	7.96E-29 mmHg at 25°C (estimated based on representative SMILES)	U.S. EPA 2017, Appendix D
Water solubility	Insoluble	CIR 2007
Dissociation constant	Not applicable	
Density/specific gravity	0.98 at 25°C	CIR 2007
Partition coefficient	Log K_{OW} = 18.75 (estimated based on representative SMILES)	U.S. EPA 2017, Appendix D

Toxicokinetics

The following studies suggest HCO is absorbed following oral exposure, distributes to fatty tissues, is metabolized in the citric acid cycle, or used to synthesize sugars and lipids. Thus, they are not excreted unchanged but rather are used for energy and storage.

- CIR 2007
    - HCO and hydroxystearic acid metabolites hydroxypalmitic acid, hydroxymyristic acid, and hydroxylauric acid, were found in abdominal fat and other body lipids at necropsy in a dietary repeated dose toxicity study in rats. Upon cessation of dietary exposure to HCO, there was a rapid decrease in the amount of HCO-derived hydroxy fatty acids.
- ECHA, CAS #8001-78-3, 2024
    - Fatty acid glycerides (mono-, di-, and tri-esters of carboxylic acids with glycerol) have a common metabolic fate that involves stepwise hydrolysis to carboxylic acids and glycerol. They subsequently enter the citric acid cycle, and used to synthesize sugar and lipids.
    - Medium- and long-chain fatty triacylglycerols derived from vegetable oils are generally

degraded to their corresponding fatty acids and glycerol by enzymes present in the saliva and intestinal tract. From the intestines, the medium-chain fatty acids (MCFAs) are absorbed directly into the bloodstream and transported to the liver for fatty acid metabolism, whereas long-chain fatty acids (LCFAs) are incorporated into chylomicrons and enter the lymphatic system. The MCFAs are readily broken down to carbon dioxide and two carbon fragments, while LCFAs are re-esterified to triacyclglycerols and are either metabolized for energy or stored in adipose tissue.

Hazard Classification Summary

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

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

HCO was assigned a score of Low for carcinogenicity based on surrogate data. The surrogate castor oil was not carcinogenic and was not a tumor promotor and was anticarcinogenic in animal studies. Additionally, the surrogate castor oil has widespread use in food and numerous consumer products with no reported association of cancer in humans. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate and negative data are available, and there is no GHS classification (CPA 2018b). The confidence in the score is low as no standard carcinogenicity study is available that has been conducted according to current guidelines (i.e. two-year exposure, 50 animals/sex/dose group, at least 3 doses tested, etc.).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2007
  - *Dermal: <u>Surrogate: Castor oil (CAS #8001-79-4):</u>* A tumor promotion study was performed with mice (10/dose group, strain and sex not specified) administered a single application of 9,10-dimethyl-1,2-bexanthracene in liquid paraffin. Undiluted castor oil was then applied to the skin semi-weekly for 20 weeks. Castor oil treatment did not promote the formation of tumors in this study.
  - *Subcutaneous: <u>Surrogate: Castor oil (CAS #8001-79-4):</u>* A study evaluating the anticancer activity of an extract of castor oil was performed with male Kunming mice and mice bearing S180 ARS ascitic fluid tumor cells. The castor oil was saponified and acidified to obtain a coarse, fatty acid mixture that was subsequently recrystallized and refined to produce the evaluated compound which was emulsified in Tween-80 (polysorbate 80). Additionally, a polyphaser liposome was produced from the castor oil extract. Ascites were isolated from mice inoculated with S180 tumor cells that had been rinsed with physiological brine in order to collect the cancer cells. The mice were injected subcutaneously into the right front axilla. The day following the injection, the mice were randomized into separate groups (8-10/group) and were injected with 200, 300, or 400 mg/kg of a physiological brine solution containing an equal load of Tween-80. For the dilution control and polyphase liposome control groups, injections were administered to the abdominal cavity daily for 7 days, after which the mice were sacrificed. Subcutaneous tumors were isolated and weighed in order to calculate the tumor suppression rate (%). A dose response in the tumor suppression rate was identified for the dilution controls: 30.6% (200 mg/kg dose group), 37% (300 mg/kg dose group), and 53.1% (400 mg/kg dose group). The polyphaser liposome control groups exhibited tumor suppression but not in a dose-response manner: 40.2% (300 mg/kg dose

  - group), 36.4% (the other 300 mg/kg dose group), 55.7% (400 mg/kg dose group), and 58% (the other 400 mg/kg dose group).
  - *Subcutaneous: Surrogate: Castor oil (CAS #8001-79-4):* In a second experiment, the inhibitory action of the anticancer component extracted from castor oil on ARS ascites cancer was evaluated according to a similar procedure. Ascites were isolated from mice inoculated with ARS cancer cells that had been rinsed with physiological brine in order to collect the cancer cells. The physiological brine was diluted and subsequently injected into the abdominal cavity of each mouse. The day after injection, each of nine mice was injected with a polyphase liposome that was produced from castor oil extract at 200 mg/kg/day for 7 days. At the end of the treatment period, the animals were maintained and monitored for survival for an additional 35 days without exposure. The results indicate that the castor oil extract had a strong suppressive effect on the growth of S180 body tumors in mice. Additionally, its suppressive effect on ARS ascites cancer was very strong, with 64% of the ascites tumors in mice being completely cured. The survival of mice injected with the extract was 136% of the control survival rate.
- No other carcinogenicity studies were identified. Based on the wide use of the surrogate castor oil, and no report of association with cancer in humans, the carcinogenicity potential is considered to be low.

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

HCO was assigned a score of Low for mutagenicity/genotoxicity based on measured data for HCO and the surrogate castor oil. HCO was not mutagenic in a bacterial reverse mutation assay. The surrogate castor oil was neither mutagenic nor clastogenic in a series of *in vitro* and *in vivo* assays. 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 measured data on the target chemical and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #8001-78-3, 2024
  - HCO was negative in a bacterial reverse mutation assay in *Salmonella typhimurium* test strains TA98, TA100. TA1535, TA1537, and TA1538 at concentrations up to 5,000 µg/plate, with and without metabolic activation (Klimisch 2, reliable with restrictions).
- EC 2000
  - HCO was not mutagenic in a bacterial reverse mutation assay in *S. typhimurium* (strains not specified) at concentrations up to 1,600 µg/plate, with and without metabolic activation (OECD 471) (no further details provided).
- CIR 2007
  - *In vitro*: *Surrogate: Castor oil (CAS #8001-79-4):* Negative results for mutagenicity were obtained in an Ames test. *Salmonella typhimurium* test strains TA 97, TA 98, TA 100, and TA 1535 were exposed to castor oil (US Pharmacopeia grade) in DMSO at 100-10,000 µg/plate, with and without metabolic activation. The mutation frequency did not increase with treatment in the presence or absence of metabolic activation.
  - *In vitro*: *Surrogate: Castor oil (CAS #8001-79-4):* Negative results for mutagenicity were obtained in a bacterial reverse mutation assay. *S. typhimurium* strains TA97, TA98, TA100, TA102, TA1537 and *Escherichia coli* strain WP2/pKM102 were exposed to castor oil (purity not specified) at 100-5,000 µg/plate with and without metabolic activation.

Cytotoxicity was detected only in strain WP2/pKM102, with and without metabolic activation. No increase in mutation frequency was detected with treatment in the presence or absence of metabolic activation.

- NTP 1992
    - *In vitro*: Surrogate: Castor oil (CAS #8001-79-4): Negative results for genotoxicity were obtained in a sister chromatid exchange assay. Chinese hamster ovary (CHO) cells were exposed to castor oil at 0, 160, 500, 1,600, or 5,000 µg/ml in DMSO, with and without metabolic activation. The treatment was not associated with an increase in sister chromatid exchanges in the presence or absence of metabolic activation.
    - *In vitro*: Surrogate: Castor oil (CAS #8001-79-4): Negative results for clastogenicity were obtained in a chromosome aberration assay. CHO cells were exposed to castor oil at 0, 1,600, 3,000, or 5,000 µg/mL (stated in report as mg/mL but this is likely an error), with and without metabolic activation. The treatment was not associated with an increase in chromosome aberrations in the presence or absence of metabolic activation.
    - *In vivo*: Surrogate: Castor oil (CAS #8001-79-4): A subchronic toxicity study was performed with B6C3F1 mice (10/sex/dose group) provided diets containing castor oil in DMSO at 0, 0.62, 1.25, 2.5, 5.0, or 10% (equivalent to 0, 917, 2,022, 3,800, 7,823, 15,017 mg/kg/day for males and 0, 1,153, 2,282, 5,009, 9,627, and 16,786 mg/kg/day for females, respectively) continuously for 13 weeks. Peripheral blood erythrocytes were isolated from cardiac punctures performed at study termination, and were evaluated for the frequency of micronuclei. Treatment was not associated with an increase in the frequency of micronuclei.

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

HCO was assigned a score of Moderate for reproductive toxicity based on surrogate data. Changes to the number of corpora lutea, number of implantation sites, number of live fetuses, and pre- and post-implantation deaths were detected in female rats administered single doses of the surrogate castor oil on the first day of estrus. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when limited or marginal evidence of reproductive toxicity is available in animals (CPA 2018b). The confidence in the score is Low as only a non-standard reproductive toxicity study was available, and the route of exposure was intramuscular injection, which is not typically relevant for GreenScreen® assessments.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1992
    - *Oral*: Surrogate: Castor oil (CAS #8001-79-4): A subchronic toxicity study was performed with F344/N rats (10/sex/dose group) provided diets containing 0, 0.62, 1.25, 2.5, 5.0, or 10% castor oil (equivalent to 0, 404, 809, 1,583, 3,067, and 5,835 mg/kg/day for males and 0, 401, 797, 1,569, 3,045, and 5,725 mg/kg/day for females, respectively) continuously for 13 weeks. Sperm motility and morphology were evaluated at study termination and vaginal cytology was evaluated for the week preceding sacrifice. Reproductive organ weights and histopathology were also assessed. No effects on sperm parameters, vaginal cytology, or histopathological findings were observed with treatment. *ToxServices identified a reproductive NOAEL of 5,725 mg/kg/day (lowest value for the 10% dose group) based on the lack of reproductive toxicity observed in this study at up to the highest dose tested.*
    - *Oral*: Surrogate: Castor oil (CAS #8001-79-4): A subchronic toxicity study was performed with B6C3F1 mice (10/sex/dose group) provided diets containing 0, 0.62, 1.25, 2.5, 5.0, or 10% castor oil (equivalent to 0, 917, 2,022, 3,800, 7,823, 15,017 mg/kg/day for males and 0,

1,153, 2,282, 5,009, 9,627, and 16,786 mg/kg/day for females, respectively) continuously for 13 weeks. Sperm motility and morphology were evaluated at study termination and vaginal cytology was evaluated for the week preceding sacrifice. Reproductive organ weights and histopathology were also assessed. No adverse effects were noted on male or female reproductive parameters following treatment with castor oil. *ToxServices identified a reproductive NOAEL of 15,017 mg/kg/day (lowest value for 10% dose group) based on the lack of reproductive toxicity observed in this study at up to the highest dose tested.*

- CIR 2007
  - *Oral:* *Surrogate: Castor oil (CAS #8001-79-4):* Pregnant Wistar rats (8/group) were administered oral gavage doses of 2 mL castor oil-containing diet (mixture of 30 mL castor oil and one chicken egg) for a total of four feedings or a control diet. The animals were sacrificed 4 hours after the fourth feeding. Relative to controls, the treatment group animals exhibited a significant increase in the concentration of prostaglandin E_2 (PGE_2) in the intestinal mucosa, placenta, amnion, and amniotic cells.
  - *Intramuscular injection:* *Surrogate: Castor oil (CAS #8001-79-4):* Female Wistar rats (number not specified) were administered single intramuscular injections of 0.2 mL castor oil (equivalent to 193 mg/kg[9]) on the first day after estrus. The animals were evaluated for effects on the estrous cycle including cytology from vaginal smears, phase structure, and frequency of estrus over a 15-day period following the injection. Fertility was also evaluated by mating the females with male rats on the second day after the injection. Pregnant females were sacrificed on day 20 (not specified if gestation day 20 or 20 days after injection). Rats injected with castor oil exhibited a 1.4-fold reduction in the frequency of estrus and a 39.6% increase in the inter-estrous phase. The fertility index (ratio of number of mated females to the total number of females) was 100% for the control and treatment groups, and no reliable difference in the pregnancy index was detected between the two groups. Treated females exhibited a reduced number of corpora lutea in the ovaries, which the study authors identified as a consequence of the suppression of folliculogenesis and ovulation. Consequently, the number of implantation sites in the uteri of treated rats was less than the value for control animals. A decreased number of live fetuses in the uterus and increased incidences of pre- and post-implantation deaths were also observed in treated rats. The study authors concluded that castor oil exhibited anti-implantation and abortive activity in this study.

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

HCO was assigned a score of Moderate for developmental toxicity based on surrogate data. Increased resorption rates and changes to male and female reproductive development occurred in the offspring of female rats administered oral doses of the surrogate castor oil during gestation. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity is available in animals (CPA 2018b). The confidence in the score is low as the critical study had only 5 animals/group, and only tested one dose, where OECD Guideline 414 recommends use of 20 animals/group, and three doses levels[10].

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Salami and Raji 2014, 2015

[9] Castor oil has a specific gravity (g/mL) of up to 0.965 (HSDB 2010). Therefore, the volume of 0.2 mL is equivalent to 0.2 mL * 0.965 g/mL * 1,000 mg/g = 193 mg/kg.

[10] https://www.oecd-ilibrary.org/environment/test-no-414-prenatal-development-toxicity-study_9789264070820-en

  - *Oral: <u>Surrogate: Castor oil (CAS #8001-79-4):</u>* A series of developmental toxicity tests was performed with pregnant female Wistar rats (5/group) administered gavage doses of castor oil (purity not specified) at 0 or 950 mg/kg/day on gestational day (GD) 1-7, 7-14, 14-21, or 1-21. Maternal examinations included evaluation of body weight, serum hormones, clinical biochemistry, and histopathology of the reproductive organs. The F1 and F2 offspring were evaluated for birth weight, morphometric data, anogenital distance (AGD), pubertal age, sperm parameters, hormonal profile, organ weights, and histopathology. No treatment-related effects were detected on maternal body weight. The dams exhibited significant decreases in serum alanine aminotransferase (ALT) activity when exposed on GD 7-14 and 14-21. Significant decreases in serum aspartate aminotransferase (AST) levels were detected in dams exposed on GD 1-7, 7-14, and 1-21. Increased total cholesterol, triglyceraldehyde, and high-density lipoprotein (HDL) levels increased with treatment. Circulating levels of progesterone and estrogen decreased significantly in treated females. No histopathological changes were detected in the ovaries, but an increased incidence of resorption and ballooning of the uterine epithelial tissues was detected following treatment on GD 1-7 and 7-14, respectively. Male pups in the GD 1-7 and 7-14 groups exhibited statistically significantly decreased birth weight/morphometric data. All F1 males in the treatment groups exhibited decreased AGD. Relative to the concurrent controls, F1 females exhibited a decreased pubertal age. At postnatal day 90, treated F1 males exhibited decreased body weights, testis weights, sperm count and motility, and a decreased incidence of normal morphology. Significant decreases in testosterone levels and increased incidences of testicular interstitial edema and epididymal hypospermia were detected in treated F1 males. The only treatment-related effect detected in F2 rats was alterations in pubertal indices (no details provided). ToxServices identified maternal toxicity and developmental toxicity LOAELs of 950 mg/kg/day based on alterations in reproductive hormone levels and increased resorption rates and changes to male and female reproductive development in the offspring, respectively.
- NatMed 2024
  - Castor oil may induce premature labor or miscarriage in pregnant women. The probable mechanism for this effect is the secretion of prostaglandins and/or reflex stimulation of the uterus.

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

HCO was assigned a score of Moderate for endocrine activity based on surrogate data. Changes to anogenital distance and male sexual maturation (changes to testosterone levels and testicular histopathology) were observed in an oral prenatal developmental toxicity study in rats performed with surrogate castor oil. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when evidence of endocrine activity is available, but no associated adverse health effects that would warrant a score of High for carcinogenicity, reproductive toxicity, developmental toxicity, or repeated dose systemic toxicity (CPA 2018b). The confidence in the score is low as there were only 5 animals per exposure group, and only 1 dose was tested, whereas OECD Guideline 414 recommends use of 20 animals/group, and three doses levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Salami and Raji 2014, 2015
  - *Oral: <u>Surrogate: Castor oil (CAS #8001-79-4):</u>* As summarized above in the developmental toxicity section, pregnant Wistar rats administered oral doses of 950 mg/kg/day castor oil on

GD 1-7, 7-14, 14-21, or 1-21 exhibited decreased levels of circulating progesterone and estrogen. All F1 males born to treated females exhibited decreased AGD, a potential sign of feminization of these males. These males also exhibited decreased testosterone levels, changes to testicular histopathology, and sperm parameters. Female F1 offspring exhibited a decreased pubertal age, indicating that they achieved puberty at an earlier date than controls (which is). The study authors concluded that castor oil exhibits endocrine-disrupting capabilities based on these findings. *ToxServices notes that early puberty is the opposite of what would be expected with decreased estrogen levels. Altogether, the study details are insufficient to determine if the effects on the testicular histopathology, sperm parameters, and female puberty onset are related to the observed endocrine activity.*

- U.S. EPA 2024c
  - *Surrogate: Castor oil (CAS #8001-79-4):* Castor oil was active in 1/8 androgen receptor (AR) assays, 0/6 estrogen receptor (ER) assays, 0/8 thyroid receptor assays, and 0/2 steroidogenesis assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century (Appendix D).

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

HCO was assigned a score of Low for acute toxicity based on an oral LD_{50} > 10,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral LD_{50} values are greater than 5,000 mg/kg (CPA 2018b). The confidence in the score is high based on reliable measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2007
  - *Oral:* HCO was evaluated in an acute oral toxicity study in male Wistar rats exposed at 10,000 mg/kg by gastric probe. There were no clinical signs of toxicity and no mortality. Authors assigned the LD_{50} at > 10,000 mg/kg.

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

HCO was assigned a score of Low for systemic toxicity (single dose) based on surrogate data. The surrogate castor oil has subchronic oral NOAELs of 5,725 mg/kg/day for rats, and 15,017 mg/kg/day for mice. From the subchronic toxicity data, ToxServices inferred that no systemic toxicity is observed at single oral doses up to 2,000 mg/kg in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when no toxicity is observed at doses greater than 2,000 mg/kg (CPA 2018b). The confidence in the score is high based on reliable measured data on 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.
- *Oral:* *Surrogate: Castor oil (CAS #8001-79-4):* No acute toxicity data were identified for castor oil. However, subchronic toxicity studies identified oral NOAELs of 5,725 mg/kg/day for rats and

15,017 mg/kg/day for mice, suggesting that no systemic toxicity is elicited following single oral doses up to 2,000 mg/kg.

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

HCO was assigned a score of Low for systemic toxicity (repeated dose) based on limited data for HCO, supplemented with data for surrogate castor oil. HCO has an oral subchronic NOAEL of 796 mg/kg/day in male rats, and 891 mg/kg/day in female rats, however the study has limited reporting. The surrogate castor oil has oral subchronic NOAELs of 5,725 mg/kg/day in rats, and 15,017 mg/kg/day in mice from robust and well-reported studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when subchronic oral toxicity LOAELs are > 100 mg/kg/day (CPA 2018b). The confidence in the score is high based on reliable measured data 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.
- CIR 2007
  - *Oral*: In a 16-week dietary exposure study, groups of 15 male Wistar rats were given diets with different ratios of HCO and corn oil. The HCO consisted of 86.5% 12-hydroxystearic acid, 10.3% nonoxygenated acids, and 3.2% 12-ketostearic acid, and the dietary values for HCO content are based on the 12-hydroxystearic acid content:
    - Group 1 was given HCO at 0.865% + 19% corn oil for 16 weeks;
    - Group 2 was given 0.865% HCO + 19% corn oil for 8 weeks, followed by the control diet of 20% corn oil for 8 weeks;
    - Group 3 was given 8.65% HCO + 10% corn oil for 16 weeks;
    - Group 4 was given 8.65% HCO + 10% corn oil for 8 weeks, followed by the control diet of 20% corn oil for 8 weeks;
    - The control group was given 20% corn oil for 16 weeks.

    At 12 weeks, animals exposed at 8.65% HCO had significantly reduced body weights compared to the 0.865% group and the control group. At 16 weeks, control rats had gained statistically significantly more body weight than those treated with 8.65% HCO for 16 weeks (Group 3), or 8.65% HCO for 8 weeks followed by the control diet for 8 weeks (Group 4). No further adverse effects were reported. *ToxServices assigned a 16-week NOAEL of 0.865% HCO, based on decreased body weight gain at 8.65% HCO. In subchronic studies, male and female Wistar rats consume an average of 0.092 and 0.103 kg-food/kg-bw/day, respectively (TERA undated). Therefore, a NOAEL of 0.865% HCO in the diet is approximately 796 mg/kg/day for males (0.865% = 8,650 mg/kg, and 8,650 mg HCO/kg x 0.092 kg food/kg-bw/day = 796 mg/kg/day), and 891 mg/kg/day for females (8,650 mg HCO/kg x 0.103 kg food/kg-bw/day = 891 mg/kg/day).*
  - It may be noted decreased body weight gain was also the only significant finding in the preliminary feeding study, which used female rats instead of males, and the animals were exposed at HCO in the diet at 8.65 or 17.3%.
- NTP 1992
  - *Oral*: <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> A subchronic toxicity study was performed with F344/N rats (10/sex/dose group) provided diets containing 0, 0.62, 1.25, 2.5, 5.0, or 10% castor oil (equivalent to 0, 404, 809, 1,583, 3,067, and 5,835 mg/kg/day for males and 0, 401, 797, 1,569, 3,045, and 5,725 mg/kg/day for females, respectively) continuously for 13 weeks. Additional groups of 10 rats were included for each dose level for evaluation of clinical chemistry and hematological parameters on days 5 and 21 of the study. These

additional animals were sacrificed after the blood collection on day 21. The animals were evaluated for body weight, clinical chemistry, hematology, organ weights, gross pathology and histopathology. Survival, body weights, and food consumption were not affected by treatment. No biologically significant effects were noted on hematological parameters with treatment. A dose-dependent increased in serum alkaline phosphatase activity was observed on days 5 and 21 and at the end of the study. Total bile acids were increased in males in the two highest dose groups at days 5 and 21 but not at study termination. Absolute and relative liver weights increased in high dose male rats. Gross pathology and histopathological evaluation did not identify treatment-related microscopic alterations in any organs or tissues. *ToxServices identified a NOAEL of 5,725 mg/kg/day (lowest value for the 10% castor oil dose group) based on the lack of histopathological effects following oral doses of castor oil.*

- *Oral*: <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> A subchronic toxicity study was performed with B6C3F1 mice (10/sex/dose group) provided diets containing 0, 0.62, 1.25, 2.5, 5.0, or 10% castor oil (equivalent to 0, 917, 2,022, 3,800, 7,823, 15,017 mg/kg/day for males and 0, 1,153, 2,282, 5,009, 9,627, and 16,786 mg/kg/day for females, respectively) continuously for 13 weeks. Additional groups of 10 mice were included for each dose level for evaluation of clinical chemistry and hematological parameters on days 5 and 21 of the study. These additional animals were sacrificed after the blood collection on day 21. The animals were evaluated for body weight, clinical chemistry, hematology, organ weights, gross pathology and histopathology. Treatment with castor oil did not adversely affect survival or food consumption. Body weights of high dose male mice were consistently lower than controls from week 3 to study termination. Absolute liver weights were increased in males and females of the two highest dose groups and females in the two highest dose groups also exhibited increased absolute kidney weights. Gross pathology and histopathological evaluation did not identify treatment-related microscopic alterations in any organs or tissues. *ToxServices identified a NOAEL of 15,017 mg/kg/day (lowest value for the 10% castor oil dose group) based on the lack of histopathological effects following oral doses of castor oil.*

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): DG
HCO was assigned a Data Gap for neurotoxicity (single dose) based on lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
HCO was assigned a score of Data Gap for neurotoxicity (repeated dose) based on lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
HCO was assigned a score of Low for skin sensitization based on human clinical data for HCO and the surrogate castor oil, combined with a history of safe use in cosmetic products, including baby products, bath products, and makeup at up to 39% concentration. GreenScreen® criteria classify chemicals as a

Low hazard for skin sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is High based on history of safe use at high levels in cosmetics.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2007
  - In a human patch test of 1 to 20 patients either suffering from or suspected of suffering from contact allergy to cosmetic products, there were no reactions to 30% HCO in petrolatum (no further details provided).
  - Three humans with occupational hypersensitivity to castor allergens were evaluated with patch and skin prick tests. Each subject and 7 normal control subjects were exposed to castor bean extract, and four castor wax (HCO) extracts derived from sodium lauryl sulfate (SLS), phosphate buffered saline (PBS), urea-NaCl, or Triton X-100 via a patch test, and the castor bean extract and SLS-HCO extract were also used for a prick test.
    - The prick tests were designed to detect IgE-mediated hypersensitivity at 15 minutes post-application of 1 drop of the potential allergen to the skin. A positive reaction was defined as a wheal and flare reaction with edema at > 5 mm. There were no immediate skin reactions to castor bean extract at concentration up to 1,000 µg/mL, or to SLS-HCO extract up to 22,000 µg/mL.
    - The patch tests were designed to detect cell-mediated hypersensitivity. Each potential allergen, or a paraffin control, was applied under semi-occlusive patch (concentrations not specified) for 24 and 48 hours, and reactions were scored at 24 and 48 hours post-removal. Three patients were sensitive to the castor bean extract and the SLS-HCO extract; however, the level of sensitivity for the SLS-HCO extract was 100-to- 100,000-fold less than that for the castor bean extract. These patients did not react to HCO in different solvents or in a deodorant stick (no further details provided).
  - SLS-HCO extract was evaluated in an *in vitro* direct RAS study using serum from a patient sensitive to castor allergens, a patient sensitive to peanuts, or pooled human serum (control). The patient sensitive to castor allergens had a significant RAS test ratio of 18.87 and 8.04 to the castor bean allergen and SLS-HCO extract, respectively. The patient sensitive to peanuts did not have a significant RAS test to either extract. Authors concluded that SLS-HCO extract contains castor bean allergens, although the SLS-HCO extract can nonspecifically inhibit the RAS assay.
  - Castor Wax (HCO) extract was analyzed for reactivity in a 48-hour passive cutaneous anaphylaxis (PCA) study in mice. The mice were sensitized with a reaginic antibody specific to castor bean extracts, and were challenged 48 hours later by intravenous injection. The antiserum did not react with PBS, urea-NaCl, or Triton X-100 extracts of HCO, but did react with antiserum with the SLS-HCO extract.
  - Based on the above studies, the CIR Expert Panel concluded that allergens are present at low concentrations in HCO. The CIR Expert Panel also concluded that HCO is safe as a cosmetic ingredient in the current practices of use and concentrations (up to 39%).
- CIR 2007
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> Castor oil is not a skin sensitizer in human clinical tests, but patients with occupational dermatoses may react to castor oil.
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> 332 patients (25 males, 307 females; 20 to 70 years old) suspected of having cosmetic contact dermatitis were patch-tested with numerous

cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 hours, and reactions were evaluated 30 minutes, 24 hours, and 4 to 5 days after patch removal. None of the 49 patients patch-tested with castor oil had a positive reaction.
  - *Surrogate: Castor oil (CAS #8001-79-4):* 346 patients (31 males, 315 females; 20 to 70 years old) suspected of having cosmetic dermatitis were patch tested with various cosmetic products and cosmetic ingredients. Patch tests (Finn chambers) were applied to the back for 48 hours, and reactions were evaluated 30 minutes, 24 hours, and 4 to 5 days after patch removal. Of the 76 patients patch-tested with castor oil, one (1.3%) had a positive reaction that was detected only during the second reading 24 hours after patch removal.
- HSDB 2010
  - *Surrogate: Castor oil (CAS #8001-79-4):* Although widely used, castor oil is associated with some reports of allergic contact dermatitis, mostly to cosmetics.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
HCO was assigned a score of Low for respiratory sensitization based on extrapolation from its lack of dermal sensitization potential, according to ECHA's guidance on respiratory sensitization evaluation (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data, no structural alerts, and no GHS classification are available (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 2024
  - The representative structure of HCO in OECD Toolbox for CAS #8001-78-3, with the SMILES of CCCCCCC(O)CCCCCCCCCCOC(=O)C(COC(=O)CCCCCCCCCC(O)CCCCCC)OC(=O)CCCCCCCCCC(O)CCCCCC does not have any structural alerts for respiratory sensitization (Appendix E).
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of HCO according to ECHA's guideline (ECHA 2017), which 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 HCO 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 HCO, and as HCO does not contain any structural alerts for respiratory sensitization (OECD 2024), HCO is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
HCO was assigned a score of Low for skin irritation/corrosivity based on historical safe use in cosmetics in baby products, bath products, makeup, and other products applied directly to the skin and limited surrogate data. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low based on lack of data from an *in vivo* OECD Guideline study, such as No. 404, and non-

guideline studies performed under exacerbated conditions on surrogate castor oil demonstrate some potential for skin irritation, but are insufficient for GHS classification purposes.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2007
  - The CIR Expert Panel also concluded that HCO is safe as a cosmetic ingredient in the current practices of use and concentrations (up to 39%), with no qualifying statements.
  - *Surrogate: Castor oil (CAS #8001-79-4):* The dermal effects of castor oil were evaluated using albino or Long-Evans rats (216 total, sex not specified). Castor oil was swabbed to a large area of dorsal clipped skin daily for **5 days to 2 weeks**. Small areas of the skin were obtained and evaluated microscopically. Castor oil was found to have a mild effect on the epidermis that was mostly confined to the stratum granulosum.
  - *Surrogate: Castor oil (CAS #8001-79-4):* Undiluted castor oil was applied as four drops to one shaved flank of albino guinea pigs (six total, sex not identified) and young pigs (six total, sex not identified) within 30 seconds of each other on **10 successive days**. The other flank served as the control. On day 11 of the study, the animals were sacrificed and a section of skin was excised for microscopic evaluation. Administration of castor oil caused a slight reddening of the skin at the application site. Microscopic evaluation revealed hyperplasia, with an increase in the cell and nuclear density of the basal cell layers, with castor oil treatment. Epidermal widths increased with treatment in both the pigs and guinea pigs.
  - *Surrogate: Castor oil (CAS #8001-79-4):* Undiluted castor oil was applied to the depilated skin of female albino rats (five total) in 0.5 mL volumes daily for **30 days**. Occlusive dressing covered the application site. On study days 10, 20, and 30, two small skin punch biopsies were obtained for microscopic evaluation. Slight erythema and slight edema were observed following castor oil application. On day 10, the microscopic evaluation revealed acanthosis with vacuolization and disorganization of the basal layer, accompanied by an infiltration of mononuclear cells and fibrocytes in the dermis. The epithelial changes increased in severity at day 20 and 30 but the appearance of the infiltrate did not change.
  - *Surrogate: Castor oil (CAS #8001-79-4):* In an open skin irritation test performed for **8 weeks** on rabbit skin, undiluted castor oil and 10% aqueous castor oil were well tolerated.
  - *Surrogate: Castor oil (CAS #8001-79-4):* The skin irritation potential of castor oil was evaluated with albino angora rabbits (six total, sex not specified) administered 100 mg of liquid or semisolid castor oil (undiluted) to two test areas clipped free of hair for **24 hours**. At the end of the exposure period the appearance of the skin was scored. Thirty minutes after scoring of the skin, the test area was clipped and castor oil was reapplied. A third application was applied 48 hours later and the reactions scored then and at 72 hours. Castor oil was found to be severely irritating to the skin of rabbits (score = 3).
  - *Surrogate: Castor oil (CAS #8001-79-4):* Undiluted castor oil was applied at 100 mg to the clipped dorsal skin of male Hartley guinea pigs (six total). The study design was the **same as above** for rabbits. Castor oil was mildly irritating to the skin of guinea pigs.
  - *Surrogate: Castor oil (CAS #8001-79-4):* Undiluted castor oil was applied at 100 mg to the clipped dorsal skin of male Wistar rats (six total). The study design was the **same as above** for rabbits. Castor oil was mildly irritating to the skin of rats.
  - *Surrogate: Castor oil (CAS #8001-79-4):* Undiluted castor oil was applied at 50 mg to the skin of Pitman-Moore miniature swine (six total, sex not specified) for **48 hours**. Castor oil was not irritating to the skin of miniature swine.

- The CIR Expert Panel also concluded that castor oil is safe as a cosmetic ingredient in the present practices of use and concentrations (up to 81%), with no qualifying statements.
- Overall, the results of these dermal irritation studies are not sufficient for classification of castor oil as a dermal irritation per the GHS criteria (UN 2023). ToxServices notes that no studies similar to OECD Guideline 404 were identified. Although the studies performed on surrogate castor oil demonstrated varying degrees of skin irritation, all had exposure conditions much more stringent than those of OECD Test Guideline 404. In particular, OECD Guideline 404 recommends a single application of the test substance for 4 hours on one day only, with scoring immediately after the 4-hour exposure, and at several time points up through 72 hours, and if necessary through day 14 to confirm reversibility of effects (OECD 2015).

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

HCO was assigned a score of Low for eye irritation/corrosivity based on surrogate data. Limited data for the surrogate castor oil demonstrate no-to-minimal irritation, insufficient for GHS classification. Although not reviewed by the United States Food and Drug Administration (U.S. FDA), a variety of homeopathic eye drop and eyelash products have castor oil as a primary ingredient, which supports a history of safe use. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high as it is based on reliable measured data 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.
- EC 2000
  - HCO was slightly irritating to the eyes of rabbits in a Draize test, without rinsing (no further details provided).
  - HCO was not irritating to the eyes of rabbits in a Draize test (no further details provided).
- CIR 2007
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> Undiluted castor oil (0.5 mL) was administered to the eyes of albino rabbits (number not specified) with the eyelids held open for one minute. Reactions were scored 18 and 24 hours after instillation. An injury grade of 1/20 was reported for castor oil.
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> The ocular irritation of castor oil was evaluated on rabbit eyes according to official French methods. Slight congestion of the iris and conjunctiva but no corneal involvement was observed following instillation of undiluted castor oil without ocular rinsing.
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> Castor oil was used as a vehicle control in a rabbit ocular irritation study. Ten drops of castor oil (purity not specified) were applied to the eyes of rabbits (10 eyes/group) daily for 3 weeks. At the end of the 3-week period, the animals were sacrificed and the corneas excised for evaluation via electron microscopy. Intact, normal sections were observed for the castor oil-treated animals and the authors concluded that the castor oil did not damage the rabbit corneal epithelium or endothelium.
- Buyers Guide 2024
  - <u>*Surrogate: Castor oil (CAS #8001-79-4):*</u> A variety of homeopathic products formulated with castor oil are marketed for use on the eyes. Although not FDA reviewed, this information supports a history of safe use.

Ecotoxicity (Ecotox)

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

HCO was assigned a score of Low for acute aquatic toxicity based on a measured LC_{50} in fish of > 10,000 mg/L, and predicted no effects at saturation (NES) in daphnia and algae. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when LC/EC_{50} values are > 100 mg/L, or when NES are expected (CPA 2018b). The confidence in the score is low due to lack of measured data for daphnia and algae.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #8001-78-3, 2024
  - 96 hour LC_{50} (*Danio rerio*): >10,000 mg/L (nominal), semi static conditions (ISO 7436/1-3, non-GLP) (Klimisch 2, reliable with restrictions).
- U.S. EPA 2022
  - HCO belongs to the Esters and Neutral Organics ECOSAR chemical classes. The most conservative predicted acute E/LC_{50} values are 6.8E-13 mg/L in fish (96h), 1.8E-12 mg/L in daphnia (48h), and 1.2E-10 mg/L in green algae (96h); however, predicted log K_{ow} of 18.75 is greater than the log K_{ow} cut-offs of 5, 5, and 6.5 for acute aquatic toxicity in fish, daphnia, and green algae, respectively; therefore, NES are expected (Appendix F).

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

HCO was assigned a score of Low for chronic aquatic toxicity based on predicted NES in fish, daphnids, and algae. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when NES are expected (CPA 2018b). The confidence in the score is low based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2022
  - HCO belongs to the Esters and Neutral Organics ECOSAR chemical classes. The most conservative predicted chronic values (ChVs) are 4.11E-13 mg/L in fish, 1.3E-11 mg/L in daphnia, and 1.8E-10 mg/L in green algae; however, predicted log K_{ow} of 18.75 is greater than the log K_{ow} cut-offs of 8.0 for chronic aquatic toxicity in fish, daphnia, and green algae; therefore, no effects at saturation are expected (Appendix F).

Environmental Fate (Fate)

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

HCO was assigned a score of Very Low for persistence based on measured data indicating it met the pass level in 28 days, modeled data supporting ready biodegradability, and because it is predicted to partition predominantly to sediment. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when a substance partitions mainly to soil, sediment, or water and is readily biodegradable (meet the 10-day window) (CPA 2018b). The confidence in the score is low based on lack of measured data for the 10-day window requirement.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #8001-78-3, 2024

- HCO was evaluated for ultimate biodegradability according to ISO 10708, using a two-phase closed bottle test. The test substance was added to domestic (adaptation not specified) activated sludge at a nominal concentration of 100 mg/L. Biodegradation under aerobic conditions was measured after 28 days based on theoretical oxygen demand (ThOD). Biodegradation at days 7, 14, 21, and 28 was 3, 28, 54, and 65%, respectively. Biodegradation > 60% on day 28 indicates ultimate biodegradability (Klimisch 2, reliable with restrictions).
- EC 2000
  - In a BOD Test for insoluble substances (ISO Draft guideline), HCO was degraded 5% in 28 days by domestic activated sludge, under aerobic conditions using a two-phase closed bottle test (no further details provided).
  - In a BOD Test for insoluble substances (ISO Draft guideline), HCO was degraded 17% in 28 days by domestic activated sludge, under aerobic conditions using a two-phase closed bottle test (no further details provided).
  - In a BOD Test for insoluble substances (ISO Draft guideline), HCO was degraded 51% in 28 days by domestic activated sludge, under aerobic conditions using a two-phase closed bottle test (no further details provided).
  - In a COD Test for insoluble substances (ISO Draft guideline), HCO was degraded 64% in 28 days by domestic activated sludge, under aerobic conditions test (no further details provided).
  - In a BOD Test for insoluble substances (ISO Draft guideline), HCO was degraded 64% in 28 days by domestic activated sludge, under aerobic conditions using a two-phase closed bottle test (no further details provided).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that HCO is expected to be readily biodegradable. Fugacity modeling (EQC default method) predicts 66.7% will partition to sediment with a half-life of 135 days, 29.5% will partition to soil with a half-life of 30 days, and 3.66% will partition to water with a half-life of 15 days (Appendix G).
- Based on the weight of evidence, a score of Very Low was assigned. A two-phase closed bottle test (BODIS test) is specifically designed for poorly water-soluble compounds comparable to an OECD Guideline 301 ready biodegradation test in terms of stringency and pass level (Richterich et al. 1998, SCHER 2005). Therefore, based on the > 60% degradation in 28 days in the BODIS, HCO meets the pass levels of a ready biodegradation study. However, the 10-day window could not be determined due to the lack of reporting/study design limitations. Nevertheless, modeled data indicates that it is expected to be readily biodegradable (hence meeting the 10-day window).

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

HCO was assigned a score of Very Low for bioaccumulation based on an estimated BAF of 0.893. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BAF values ≤ 100 (CPA 2018b). The confidence in the score is low based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017
  - BCFBAF predicts a BAF of 0.893 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration, based on the estimated log K_{ow} of 18.75 (Appendix G).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
HCO was assigned a score of Low for reactivity based on lack of reactive functional groups in the molecular structure. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when GHS reactivity classifications are not needed (CPA 2018b). The confidence in the score was low based on lack of 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.
- CIR 2007
  - HCO is incompatible with strong oxidizing agents.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of HCO. These procedures are listed in the GHS (UN 2023).
  - Based on the structure of its components or moieties, HCO is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix H).
  - Based on the structure of its components or moieties, HCO is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.

Flammability (F) Score (vH, H, M, or L): L
HCO was assigned a score of Low for flammability based on results from a flammable solids test. GreenScreen® criteria classify chemicals as a Low hazard for flammability when GHS classification is not necessary (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:* Not present on any screening lists for this endpoint.
- ECHA, CAS #8001-78-3, 2024
  - HCO did not ignite upon contact with the flame of a Bunsen burner in a non-GLP flammability test conducted according to EU Method A.10 (flammability (solids)) (Klimisch 1, reliable without restriction).
- CIR 2007
  - HCO is combustible.
- EC 2000
  - HCO has a flash point of ~300°C in a closed cup test (EU Method A.9). *ToxServices notes GHS classification for solids requires a time-to-ignition test, therefore, the closed-cup method is informative but not suitable for classification.*

Use of New Approach Methodologies (NAMs)[11] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include reliance on historical safe use, application of QSAR models for respiratory sensitization, acute and chronic aquatic toxicity, persistence and bioaccumulation, and various *in vitro* tests for genotoxicity. NAMs are non-animal alternatives that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020, OECD 2020). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

As shown in Table 4, Type I (input data) uncertainties in HCO's NAMs dataset include limited or no experimental data for endocrine activity, respiratory sensitization, acute and chronic aquatic toxicity, and bioaccumulation, and no validated test methods to assess respiratory sensitization. HCO's Type II (extrapolation output) uncertainties include reliance on *in vitro* genotoxicity test methods that do not entirely mimic *in vivo* metabolic conditions, use of QSAR models that do not define the applicability domain, the uncertain *in vivo* relevance of high throughput *in vitro* screening assays for endocrine receptor activities, the incomplete coverage for EDSP Tox 21 assays of critical endocrine pathways, and the lack of consideration of non-immunologic mechanisms of respiratory sensitization by OECD Toolbox structural alerts. Some of HCO's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** Only limited experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Acute and chronic aquatic toxicity:** Limited experimental data are available. **Bioaccumulation:** No experimental data are available.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12].

[11] 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).

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

	The *in vitro* chromosome aberration assay (based on analogy to OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[13]. The *in vitro* sister chromatid exchange assay (as defined in OECD Guideline 479, a guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[14]. **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. EDSP Tox 21 assays do not cover all critical endocrine pathways. **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* chromosome aberration assay/*in vitro* sister chromatid exchange 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	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox
Skin irritation	N	
Eye irritation	N	

[13] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[14] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: ISO 10708 Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for HCO (CAS #8001-78-3)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

Table 2: Chemical Details

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
									S	R *	S	R *	*	*								
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	HCO	8001-78-3	*L*	L	*M*	*M*	*M*	L	L	L	DG	DG	L	*L*	*L*	L	*L*	*L*	*vL*	*vL*	*L*	L

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
HCO	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
HCO	2

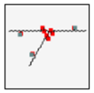
After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

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 HCO (CAS #8001-78-3)

PHAROS Search... Comparisons Common Products Discussions Account



8001-78-3
Castor oil, hydrogenated
ALSO CALLED 1,2,3-PROPANETRIOL TRI(12-HYDROXYSTEARATE), 1,2,3-Propanetriyl tris(12-hydroxyoctadecanoate), 1,3-bi...
View all synonyms (49)

SHARE PROFILE

HAZARDS PROPERTIES FUNCTIONAL USES PROCESS CHEMISTRY RESOURCES

All Hazards View

Show PubMed Results REQUEST ASSESSMENT ADD TO COMPARISON

		Group I Human					Group II and II* Human								Ecotox			Fate		Physical		Mult	Non-GSLT			
	GREENSCREEN®	C	M	R	D	E	AT	ST	ST	N	N	SnS	SnR	IrS	IrE	AA	CA	ATB	P	B	Rx	F	Mult	PBT	GW	O	Other
List Hazard Summary	NoGS	-	-	-	-	-	pC	pC	-	-	-	-	-	pC	pC	-	-	-	-	-	-	-	-	-	-	-	R

Hazard Lists

DOWNLOAD LISTS

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	US EPA - OPP - Registered Pesticides	FIFRA Registered Pesticide	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	

APPENDIX D: U.S. EPA EDSP Results for HCO (CAS #8001-78-3)

EXPORT

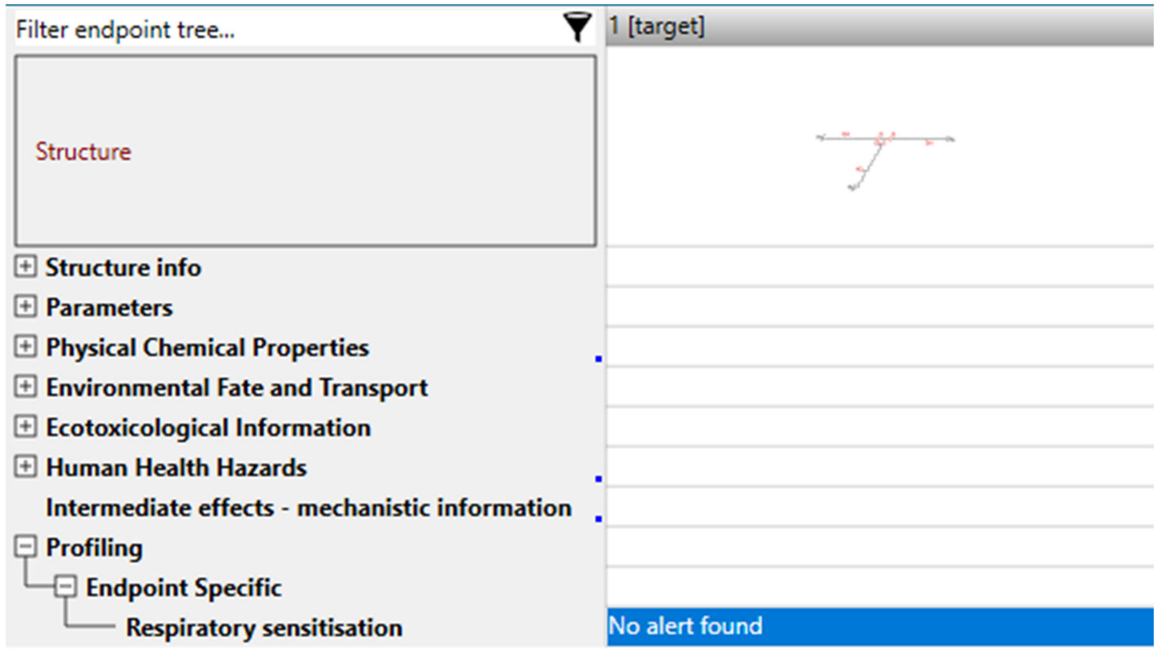
Bioactivity Summary Grid

Filter out non-representative sample (Repr.) results.

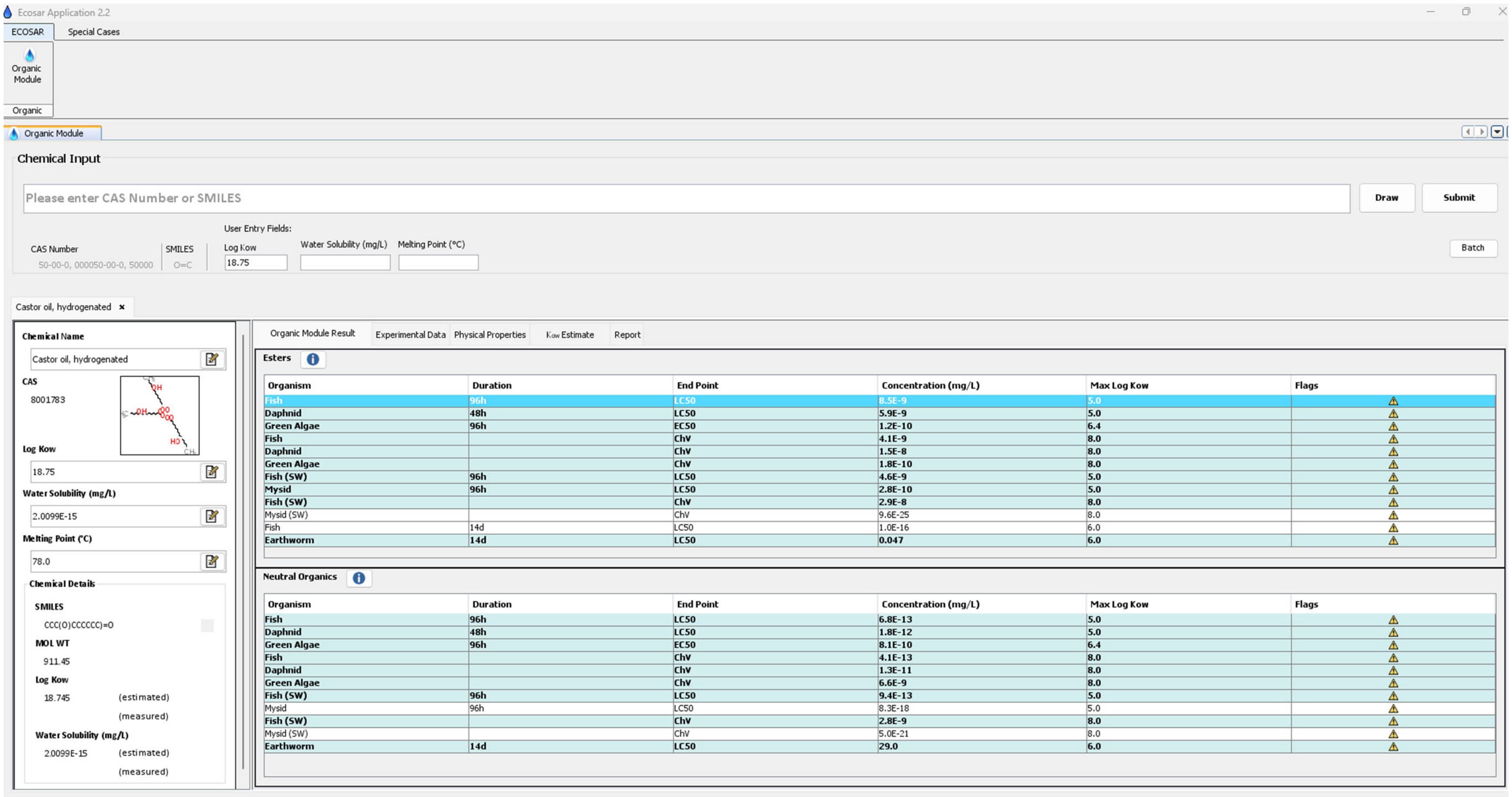
Filter out 'background' from Intended Target Family

Name	Assay Lists	Details	SeqAPASS	Gene Symbol	AOP	Event	Repr. Plot	All Plots	Hit Call	Continuous Hit Call	Top	AC50	logAC50	Cutoff	AC
	(4) EDSP AR,EDSP														
TOX21_AR_LUC_MDAKB2_Ant	EDSP AR		P10275.3	AR	-	-			Inactive	-	2.54	7.80e-3	-2.11	32.13	
TOX21_AR_LUC_MDAKB2_Ant	EDSP AR		P10275.3	AR	-	-			Inactive	0	3.06e-10	45.00	1.65	29.88	
TOX21_AR_LUC_MDAKB2_Ag	EDSP AR		P10275.3	AR	23	25			Inactive	-	3.28	3.11	0.49	20.00	
TOX21_AR_BLA_Agonist_ratio	EDSP AR		P10275.3	AR	23	25			Inactive	0	2.92e-10	40.00	1.60	20.00	
TOX21_AR_BLA_Antagonist_ra	EDSP AR		P10275.3	AR	-	-			Active	0.9895	31.47	2.53	0.40	26.09	
TOX21_ERa_LUC_VM7_Antag	EDSP ER		NP_000116.2	ESR1	-	-			Inactive	0	9.98	45.00	1.65	24.50	
TOX21_ERa_BLA_Antagonist_r	EDSP ER		NP_000116.2	ESR1	-	-			Inactive	0.0003	15.72	2.29	0.36	20.00	
TOX21_ERa_LUC_VM7_Agonis	EDSP ER		NP_000116.2	ESR1	-	-			Inactive	0	5.60e-9	45.00	1.65	20.00	
TOX21_ERa_BLA_Agonist_rati	EDSP ER		NP_000116.2	ESR1	-	-			Inactive	-	0.15	40.00	1.60	20.00	
TOX21_ERa_BLA_Antagonist_v	EDSP ER cytotoxicity burst				263	1771			Inactive	0	3.32	40.00	1.60	38.89	
TOX21_Aromatase_Inhibition	EDSP steroidogenesis		NP_000094.2	CYP19A1	25	36			Inactive	0	2.37	45.00	1.65	26.84	
TOX21_TSHR_HTRF_Agonist_r	EDSP thyroid		P16473.2	TSHR	42 | 54 | 15 9	277			Inactive	-	1.78	5.39e-2	-1.27	27.85	
TOX21_TRHR_HEK293_antago	EDSP thyroid			TRHR	48	389			Inactive	-	1.30e-9	30.00	1.48	20.00	
TOX21_TRHR_HEK293_agonis	EDSP thyroid			TRHR	48	389			Inactive	-	8.20e-12	30.00	1.48	20.00	
TOX21_TSHR_HTRF_Antagoni	EDSP thyroid		P16473.2	TSHR	42 | 54 | 15 9	277			Inactive	-	0.53	45.00	1.65	20.00	
TOX21_TSHR_wt_Agonist_HTF	EDSP thyroid		P16473.2	TSHR	-	-			Inactive	-	1.87	3.73e-4	-3.43	20.00	
TOX21_TR_LUC_GH3_Agonist	EDSP thyroid		NP_003242.1 NP_000452.2	THRA | THR B	-	-			Inactive	-	5.01e-2	45.00	1.65	20.00	
TOX21_TR_LUC_GH3_Antago	EDSP thyroid		NP_003242.1 NP_000452.2	THRA | THR B	-	-			Inactive	0	7.61e-10	45.00	1.65	22.44	
TOX21_TR_LUC_GH3_Antago	EDSP thyroid cytotoxicity burst				-	-			Inactive	0	1.40e-10	45.00	1.65	40.08	
TOX21_AR_LUC_MDAKB2_Ant	cytotoxicity burst EDSP AR				263	1771			Inactive	-	1.39	1.00e-4	-4.00	20.00	
TOX21_AR_LUC_MDAKB2_Ant	cytotoxicity burst EDSP AR				263	1771			Inactive	-	1.32e-10	45.00	1.65	20.00	
TOX21_AR_BLA_Antagonist_v	cytotoxicity burst EDSP AR				263	1771			Inactive	-	1.10	9.02e-4	-3.04	23.06	
TOX21_ERa_LUC_VM7_Antag	cytotoxicity burst EDSP ER				263	1771			Inactive	-	1.43	1.00e-4	-4.00	24.57	
TOX21_Aromatase_Inhibition_	cytotoxicity burst EDSP steroidogenesis				25 | 263	36 | 1771			Inactive	0	2.31	45.00	1.65	27.62	

APPENDIX E: OECD Toolbox Respiratory Sensitization Alerts for a Representative Structure of HCO (CAS #8001-78-3)



APPENDIX F: ECOSAR Modeling Results for HCO (CAS #8001-78-3)



Esters

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	8.5E-9	5.0	⚠
Daphnid	48h	LC50	5.9E-9	5.0	⚠
Green Algae	96h	EC50	1.2E-10	6.4	⚠
Fish		ChV	4.1E-9	8.0	⚠
Daphnid		ChV	1.5E-8	8.0	⚠
Green Algae		ChV	1.8E-10	8.0	⚠
Fish (SW)	96h	LC50	4.6E-9	5.0	⚠
Mysid	96h	LC50	2.8E-10	5.0	⚠
Fish (SW)		ChV	2.9E-8	8.0	⚠
Mysid (SW)		ChV	9.6E-25	8.0	⚠
Fish	14d	LC50	1.0E-16	6.0	⚠
Earthworm	14d	LC50	0.047	6.0	⚠

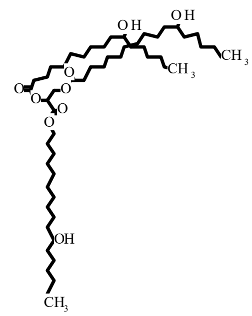
Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	6.8E-13	5.0	⚠
Daphnid	48h	LC50	1.8E-12	5.0	⚠
Green Algae	96h	EC50	8.1E-10	6.4	⚠
Fish		ChV	4.1E-13	8.0	⚠
Daphnid		ChV	1.3E-11	8.0	⚠
Green Algae		ChV	6.6E-9	8.0	⚠
Fish (SW)	96h	LC50	9.4E-13	5.0	⚠
Mysid	96h	LC50	8.3E-18	5.0	⚠
Fish (SW)		ChV	2.8E-9	8.0	⚠
Mysid (SW)		ChV	5.0E-21	8.0	⚠
Earthworm	14d	LC50	29.0	6.0	⚠

APPENDIX G: EPI Suite™ Modeling Results for HCO (CAS #8001-78-3)

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

EPI Suite Results For CAS 8001-78-3



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SMILES :
O=C(CCCCCCCCCC(CCCCCC)O)OC(COC(=O)(CCCCCCCCCCC(O)CCCCCC))C(=O)(OCCCCC
CCCCCC(O)CCCCCC)
CHEM   : Castor oil, hydrogenated
MOL FOR: C55 H106 O9
MOL WT : 911.45
------------------------------ EPI SUMMARY (v4.11) --------------------------
Henry LC (atm-m3/mole) :   ------
Log Kow (octanol-water):   ------
Boiling Point (deg C)  :   ------
Water Solubility (mg/L):   ------
Physical Property Inputs:
Vapor Pressure (mm Hg) :   ------
Melting Point (deg C)  :   ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  18.75

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  893.43  (Adapted Stein & Brown method)
Melting Pt (deg C):  349.84  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  7.96E-029  (Modified Grain method)
VP (Pa, 25 deg C) :  1.06E-026  (Modified Grain method)
Subcooled liquid VP: 4.08E-025 mm Hg (25 deg C, Mod-Grain method)
: 5.44E-023 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  1.294e-016
log Kow used: 18.75 (estimated)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  9.1145e-007 mg/L
```

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method :   2.77E-010  atm-m3/mole  (2.81E-005 Pa-m3/mole)
Group Method:   Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  9.268E+000 atm-m3/mole  (9.391E+005 Pa-m3/mole)
VP:   1E-015 mm Hg (source: MPBPVP)
WS:   1.29E-016 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  18.75  (KowWin est)
Log Kaw used:  -7.946  (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):  26.696
Log Koa (experimental database):  None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :   1.6376
Biowin2 (Non-Linear Model)     :   1.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   2.9805  (weeks       )
Biowin4 (Primary Survey Model) :   4.4152  (hours-days  )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :   1.2295
Biowin6 (MITI Non-Linear Model):   0.9455
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model):  1.0642
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):  5.44E-023 Pa (4.08E-025 mm Hg)
Log Koa (Koawin est  ): 26.696
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  5.51E+016
Octanol/air (Koa) model:  1.22E+014
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  1
Mackay model           :  1
Octanol/air (Koa) model:  1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant =  94.4539 E-12 cm3/molecule-sec
Half-Life =     0.113 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =     1.359 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
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1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc     :  1E+010  L/kg (MCI method)
Log Koc:  11.648       (MCI method)
Koc     :  2.199E+010  L/kg (Kow method)
Log Koc:  10.342       (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C :  1.287E-001  L/mol-sec
Kb Half-Life at pH 8:       62.345  days
Kb Half-Life at pH 7:        1.707  years
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.5817 days (HL = 3.817 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.893)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.893)
log Kow used: 18.75 (estimated)

Volatilization from Water:
Henry LC:  2.77E-010 atm-m3/mole  (estimated by Bond SAR Method)
Half-Life from Model River: 6.381E+006  hours   (2.659E+005 days)
Half-Life from Model Lake : 6.961E+007  hours   (2.901E+006 days)

Removal In Wastewater Treatment:
Total removal:              94.04  percent
Total biodegradation:        0.78  percent
Total sludge adsorption:    93.26  percent
Total to Air:                0.00  percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)
** Note: When the Log Kow is > 7, the model may be underestimating
the mass of material in sediment and overestimating the mass of
material in the water column (biota). Consider using the results
of the default EQC model. **

Mass Amount    Half-Life    Emissions
(percent)         (hr)       (kg/hr)
Air       0.229            2.72         1000
Water     23.3             360          1000
Soil      76.5             720          1000
Sediment  2.45e-005        3.24e+003    0
Persistence Time: 494 hr

Level III Fugacity Model: (MCI Method with Water percents)
Mass Amount    Half-Life    Emissions
(percent)         (hr)       (kg/hr)
Air       0.229            2.72         1000
Water     23.3             360          1000
water     (8.29e-011)
biota     (23.3)
suspended sediment (1.24e-006)
Soil      76.5             720          1000
```

```
Sediment  2.45e-005       3.24e+003    0
Persistence Time: 494 hr
```

```
Level III Fugacity Model: (EQC Default)
Mass Amount    Half-Life    Emissions
(percent)        (hr)        (kg/hr)
Air        0.0883          2.72          1000
Water      3.66            360           1000
water      (9.79e-013)
biota      (0.275)
suspended sediment (3.39)
Soil       29.5            720           1000
Sediment   66.7            3.24e+003     0
Persistence Time: 1.28e+003 hr
```

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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

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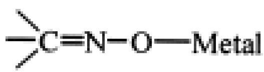
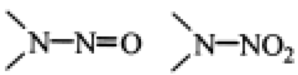
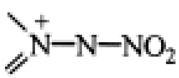
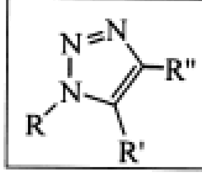
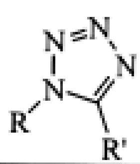
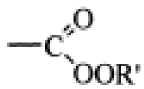
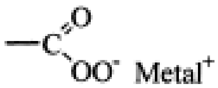
Explosivity – Full List

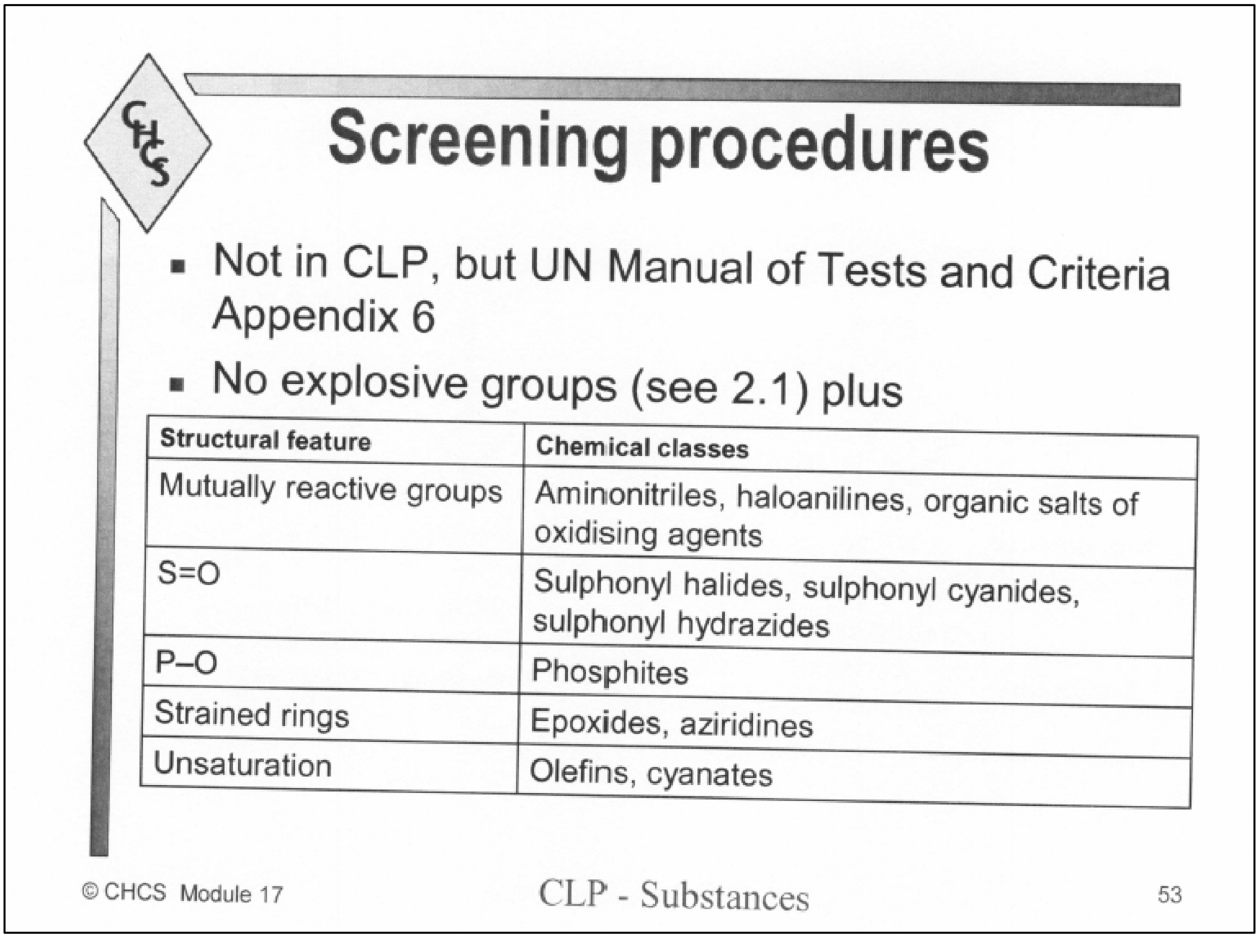
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
(ArN=N)$_2$O, (ArN=N)$_2$S	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
 	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

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

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

Self-Reactive Substances



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

APPENDIX I: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for HCO. This is a new GreenScreen® assessment.

Table 5: Change in GreenScreen® Benchmark™ for HCO			
Date	**GreenScreen® Benchmark™**	**GreenScreen® Version**	**Comment**
November 19, 2024	BM-2	v. 1.4	Original GreenScreen® assessment.

Licensed GreenScreen® Profilers

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