COCOAMIDOPROPYL BETAINE

(CAS #61789-40-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: June 7, 2021

Expiration Date: June 7, 2026

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GreenScreen® Executive Summary for Cocamidopropyl Betaine (CAS #61789-40-0)

Cocamidopropyl betaine is a quaternary ammonium compound that functions primarily as a surfactant. It is amphoteric, having both positive and negative charges. Concentrations of cocamidopropyl betaine are expressed as percent activity, referring to the percent solids minus the percent of sodium chloride in the formulation. Cocamidopropyl betaine is a high production volume (HPV) chemical with a reported annual production of 10,000,000 – 50,000,000 lbs. in the United States. It has numerous applications in industrial and personal care products including antistatic, cleansing, foam boosting, hair conditioning, surfactant, and viscosity controlling agent.

Cocamidopropyl betaine is commercially available as ~30% aqueous solutions, which are clear to pale yellow liquid. Cocamidopropyl betaine's molecular weight can vary depending on the length of the fatty alkyl chain, which is inherently variable based on the coconut oil fatty acids starting material (C8-C18), in which the C12 chain dominates. It has good solubility in water. It has no reactive functional groups that would render it explosive, self-reactive, or oxidizing, and it has low concerns for flammability.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
    - Very High Group II Human Toxicity (eye irritation-IrE)
    - Very High Ecotoxicity (acute aquatic toxicity-AA)

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), cocamidopropyl betaine meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if cocamidopropyl betaine were assigned a High score for the data gaps R or E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling using Danish QSAR and Toxtree for carcinogenicity and/or endocrine activity, several *in vitro* assays to evaluate mutagenicity and genotoxicity, *in silico* modeling via OECD QSAR Toolbox to identify structural alerts for respiratory sensitization, one *in vitro* skin irritation assay and one *in vitro* eye irritation assay. 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 cocamidopropyl betaine's NAMs dataset include lack of sufficient *in vivo* data for carcinogenicity and respiratory sensitization, and the lack of GLP status of the two *in vitro* skin/eye irritation assays, which were completed before the test methods were standardized and validated by OECD. Cocamidopropyl betaine's Type II (extrapolation output) uncertainties include lack of a defined applicability domain of Toxtree and OECD Toolbox, limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, lack of consideration of non-immunological mechanisms of respiratory sensitization, and the limitations of single *in vitro* skin/eye irritation assays in definitive GHS classification. Some of

cocamidopropyl betaine's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Cocamidopropyl Betaine

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**	DG	*M*	DG	**M**	**L**	**L**	*M*	DG	*M*	*M*	*H*	*vH*	**vH**	**H**	**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 Cocamidopropyl Betaine (CAS #61789-40-0)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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Date: April 22, 2021; June 1, 2021

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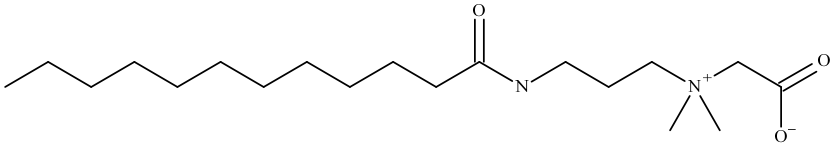
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: April 26, 2021; June 7, 2021

Expiration Date: June 7, 2026[2]

Chemical Name: Cocamidopropyl Betaine

CAS Number: 61789-40-0

Chemical Structure(s):



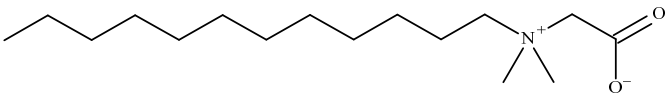
Cocamidopropyl betaine (representative structure) (PubChem 2021). It should be noted the length of the alkyl chain may vary (C8-18) based on variation in the composition of the starting material, coconut oil fatty acids (HERA 2005).

Also called: 2-[3-(dodecanoylamino)propyl-dimethylazaniumyl]acetate (IUPAC); Cocoamidopropylbetaine; Coconut oil, amidopropyl betaine; N-(3-Cocoamidopropyl)-N,N-carboxymethyl betaine; N-(Cocoamidopropyl)-N,N-dimethyl-N-carboxymethyl ammonium, betaine; EINECS 263-058-8; Lauroylamide propylbetaine; Lauramidopropyl betaine; N-Laurylamidopropyl-N,N-dimethylbetaine; Lauroylaminopropyldimethylaminoacetate; 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., hydroxides, inner salts; 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., inner salts; Quaternary ammonium compounds, (carboxymethyl)(3-cocamidopropyl)dimethyl-, hydroxides, inner salts; 1-Propanaminium, 3-amino-N-(carboxymethyl)-N,N-dimethyl-, N-coco acyl derivs., inner salts; N-(Coco alkyl) amido propyl dimethyl betaine (PubChem 2021; ChemIDplus 2021; NICNAS 2020)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
(Carboxylatomethyl)dodecyldimethylammonium (SMILES CCCCCCCCCCCC[N+](C)(C)CC(=O)[O-], CAS #683-10-3) is identified as a surrogate for cocamidopropyl betaine in the REACH dossier (ECHA 2021). Although the maximum common substructure (MCS) Tanimoto coefficient for these compounds is < 0.7 (i.e., the MCS Tanimoto is 0.5357) (ChemMine 2021), which suggests low structural similarity

[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).

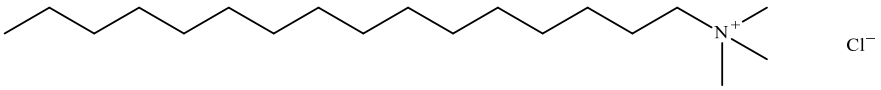
based on the MCS algorithm, ToxServices notes significant similarity based on key functional groups. Specifically, both compounds are zwitterionic, have the dimethylamino carboxylate functional group, and similar alkyl chains. Nevertheless, due to the absence of the amide group in the surrogate and the less than optimal MCS Tanimoto coefficient, ToxServices considered it to be a weak surrogate.



Surrogate: (Carboxylatomethyl)dodecyldimethylammonium (CAS #683-10-3) (PubChem 2021)

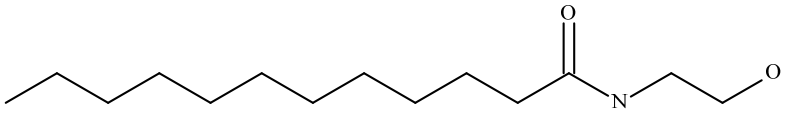
It may be noted three additional surrogates are identified in the REACH dossier for cocamidopropyl betaine (ECHA 2021), however, ToxServices does not consider them sufficiently similar for the assessment of human health endpoints as follows:

- Cetrimonium chloride (SMILES [Cl-].CCCCCCCCCCCCCCCC[N+](C)(C)C-, CAS #112-02-7) and cocamidopropyl betaine both have a quaternary ammonium functional group and similar alkyl chains; however, the surrogate is not zwitterionic, it has a chloride counter ion, it does not have a ketone or aminocarboxy methyl group, and its MCS Tanimoto coefficient is <0.7 (i.e., the MCS Tanimoto coefficient is 0.4516) (ChemMine 2021). Therefore, due to lack of similarity of key functional groups and a low Tanimoto coefficient, ToxServices did not consider cetrimonium chloride a reasonable surrogate and did include data on this compound in this assessment.



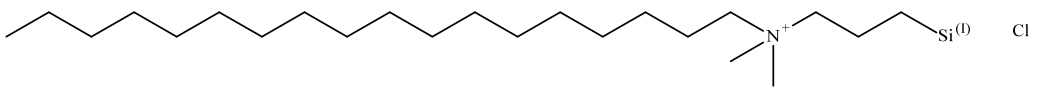
Discounted surrogate: Cetrimonium chloride (CAS #112-02-7) (ChemIDplus 2021)

- Amides, coco, N-(hydroxyethyl) (SMILES CCCCCCCCCCCC(=O)NCCO, CAS #68140-00-1) and cocamidopropyl betaine share similar atoms, and have similar alkyl chains; however, the surrogate does not have a quaternary ammonium functional group, is not zwitterionic, has a terminal alcohol in place of a terminal carboxylate group, and its MCS Tanimoto coefficient is <0.7 (i.e., the MCS Tanimoto coefficient is 0.640) (ChemMine 2021). Therefore, due to lack of similarity of key functional groups and a low Tanimoto coefficient, ToxServices did not consider amides, coco, N-(hydroxyethyl) a reasonable surrogate for human health assessment, and data for this compound are not included in this assessment.



Discounted surrogate: Amides, coco, N-(hydroxyethyl) (CAS #68140-00-1) (PubChem 2021)

- Dimethyloctadecyl[3-(trimethoxysilyl)propyl]ammonium chloride (SMILES CCCCCCCCCCCCCCCCCC[N+](C)(C)CCC[Si] (OC)(OC)OC.[Cl-], CAS #27668-52-6) and cocamidopropyl betaine both have a quaternary ammonium functional group and similar alkyl chains, however, the surrogate has a trimethylsilyl propyl group compared to a dimethylamino carboxyl group, it is not zwitterionic but rather has a chloride counter ion, and its MCS Tanimoto coefficient is <0.7 (i.e., the MCS Tanimoto coefficient is 0.400) (ChemMine 2021). Therefore, due to lack of similarity of key functional groups and a low Tanimoto coefficient, ToxServices did not consider dimethyloctadecyl[3-(trimethoxysilyl)propyl] ammonium chloride a reasonable surrogate for human health assessment, and data for this compound are not included in this assessment.



Discounted surrogate: Dimethyloctadecyl[3-(trimethoxysilyl)propyl]ammonium chloride CAS #27668-52-6) (ChemIDplus 2021)

Identify Applications/Functional Uses: (EC 2021)
1. Antistatic
2. Cleansing agent, surfactant, foam-boosting agent
3. Hair conditioning agent
4. Viscosity controlling agent

Known Impurities[3]:
Known impurities include 3,3-dimethylaminopropylamine (DMAPA) and fatty acid amidopropyl dimethylamine (amidoamine) (CIR 2012). The screen is performed on the theoretical pure substance.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
  - Very High Group II Human Toxicity (eye irritation-IrE)
  - Very High Ecotoxicity (acute aquatic toxicity-AA)

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), cocamidopropyl betaine meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if cocamidopropyl betaine were assigned a High score for the data gaps R or E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Cocamidopropyl Betaine

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**	DG	*M*	DG	**M**	**L**	**L**	*M*	DG	*M*	*M*	*H*	*vH*	**vH**	**H**	**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

[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.

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

Introduction

Cocamidopropyl betaine is a quaternary ammonium compound that functions primarily as a surfactant (EC 2021). It is made from the reaction of coconut fatty acids and 3,3-dimethylaminopropylamine (DMAPA) which yields cocamidopropyl dimethylamine, and then reacted with sodium monochloracetate to derive cocamidopropyl betaine (CIR 2012). Thus, it contains a mixture of coconut oil-derived fatty acids of varying alkyl chain lengths (C8 to C18) connected through amidopropyl linkage to a positively charged, dimethylated nitrogen, and is amphoteric, having both positive and negative charges. Concentrations of cocamidopropyl betaine are expressed as percent activity, referring to the percent solids minus the percent of sodium chloride in the formulation. Cocamidopropyl betaine is a high production volume (HPV) chemical with a reported annual production of 10,000,000 – 50,000,000 lbs. in the United States (PubChem 2021) and 10-100 tons in Europe (ECHA 2021). It has numerous applications in industrial and personal care products, including antistatic, cleansing, foam boosting, hair conditioning, surfactant, and viscosity controlling agent (EC 2021; CIR 2017, U.S. EPA 2010, ECB 2000).

The Cosmetic Ingredient Review (CIR) Expert Panel concluded that cocamidopropyl betaine is safe in the present practices of use and concentration (up to 11% in rinse-off and up to 6% in leave-on products), when formulated to be non-sensitizing, which may be based on a quantitative risk assessment (CIR 2012, 2017).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Cocamidopropyl betaine is listed on the SCIL with a full green circle as a surfactant, meaning it has been verified to be of low concern by U.S. EPA.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S.

DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for cocamidopropyl betaine can be found in Appendix C.

- Cocamidopropyl Betaine is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Cocamidopropyl Betaine is not listed on the U.S. DOT list.
- Cocamidopropyl Betaine is on the following lists for multiple endpoints.
    - German FEA – Substances Hazardous to Waters – Class 1 – Low hazard to Waters
    - GHS – Japan – Hazardous to the aquatic environment (chronic) – Category 2 [H411]
    - EC – CEPA DSL – Inherently Toxic in the Environment (iTE)
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements that are harmonized across the European Union (EU) were identified for cocamidopropyl betaine, however self-assigned hazard statements in its REACH registration dossier are presented below in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2 below. No occupational exposure limits (OEH) were identified.

Table 1: GHS H Statements for Cocamidopropyl Betaine (CAS #61789-40-0) (ECHA 2021)

H Statement	H Statement Details
H315	Causes skin irritation
H319	Causes serious eye irritation
H317	May cause an allergic skin reaction
H412	Harmful to aquatic life with long last effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Cocamidopropyl Betaine (CAS #61789-40-0)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear protective gloves/protective clothing/eye protection/face protection	ECHA 2021	Not applicable	

Physicochemical Properties of Cocamidopropyl Betaine

Cocamidopropyl betaine is a clear to pale yellow liquid that is highly soluble in water. Its molecular weight can vary depending on the length of the fatty alkyl chain, which is inherently variable based on the coconut oil fatty acids starting material. Similarly, the measured values presented below for boiling point, water solubility, and density could vary with additional testing, and may have been performed on commercial preparations, which are ~30% aqueous solutions. Its vapor pressure and log K_{ow} were not identified.

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

Table 3: Physical and Chemical Properties of Cocamidopropyl Betaine (CAS #61789-40-0)		
Property	**Value**	**Reference**
Molecular formula	Variable (e.g., C19H38N2O3)	PubChem 2021
SMILES Notation	CCCCCCCCCCCC(=O)NCCC[N+](C)(C)CC(=O)[O-] (representative)	PubChem 2021
Molecular weight	Variable (e.g., 342-398)	NICNAS 2020
Physical state	Liquid	NICNAS 2020
Appearance	Clear pale yellow liquid with slight fatty odor	NICNAS 2020
Melting point	Not identified	
Boiling point	104.3°C (OECD 103)	ECHA 2021
Vapor pressure	Not identified	
Water solubility	23.676 g/L (OECD 105)	ECHA 2021
Dissociation constant	Not identified	
Density/specific gravity	1.053 g/cm^3 (ASTM 854-02)	ECHA 2021
Partition coefficient	Not identified	
Supplier, Tradename(s)	Not applicable	
Ethoxylated or propoxylated?	No	
# EO Units	None	
# PO Units	None	
EO/PO Ratio	Not applicable	

Toxicokinetics

No specific toxicokinetic information was found for cocamidopropyl betaine, and it is unclear if the amide bond can be hydrolyzed to yield the fatty acids and 3-aminorpopyl betaine (CIR 2012). It has potential to be bioavailable based on its molecular weight distribution and has potential to interact with cellular membranes as it has both polar and non-polar attributes.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Cocamidopropyl betaine was assigned a score of Low for carcinogenicity based on based on a negative dermal carcinogenicity study in mice, supported by negative results with QSAR modeling. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available, and they are not GHS classified (CPA 2018b). The confidence in the score is low as the data are derived from a non-guideline method, with support by QSAR 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.
- CIR 2012
  - An aqueous solution of a non-oxidative hair dye formulation containing 0.09 % cocamidopropyl betaine was examined for carcinogenicity in a non-guideline study (GLP not specified). Male and female Swiss Webster mice (60/sex) were exposed to 0.05 mL test formulation on clipped skin, 3 times per week for 20 months. There were no adverse effects on body weight gains, survival, hematological or urinalysis values, and the incidence of neoplasms in dosed animals was not different from that in the control group.

  - Due to the secondary amide groups in amidopropyl betaine structures and the presence of potential amine impurities, there is concern about formation of carcinogenic N-nitrosation products. Therefore, amidopropyl betaines should not be used in cosmetics formulations that contain N-nitrosating agents.
- DTU 2021 (Appendix D)
  - QSAR modeling with the Danish QSAR database resulted in the following predictions for cocamidopropyl betaine:
    - The Leadscope model predicted the compound to be negative for carcinogenicity with all models, and the compound was in the applicability domain for 6 of the 7 (i.e., FDA RCA Cancer models in female rat, rat, male mouse, female mouse, mouse, and rodent).
    - The E Ultra model predicted the compound to be negative for carcinogenicity with all models, however the compound was outside the applicability domain for all 7.
    - For liver specific cancer in the rat or mouse, results were as follows:
      - Battery – negative, but out of the applicability domain
      - CASE Ultra – inconclusive, and out of the applicability domain
      - Leadscope – negative, and in the applicability domain
      - SciQSAR - negative, but out of the applicability domain
- Toxtree 2018
  - Toxtree predicts cocamidopropyl betaine will not be a genotoxic or nongenotoxic carcinogen using the rulebase by ISS (Appendix E)
- Modeling could not be performed using the OncoLogic program as the compound is not a reasonable fit for any of the current structural classes (U.S. EPA 2021).

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

Cocamidopropyl betaine was assigned a score of Low for mutagenicity/genotoxicity based on lack of mutagenicity in numerous *in vitro* assays and one *in vivo* micronucleus test. Additionally, surrogate data suggest low concerns for chromosomal aberrations based on *in vitro* data. These results meet the criteria for GHS not classified. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high based on reliable 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.
- Henkel KGA 1988, as cited in ECHA 2021 and OECD 2006
  - Cocamidopropyl betaine (30% active ingredient (a.i.)) was evaluated in a GLP-compliant bacterial reverse mutation assay performed according to OECD 471. *Salmonella typhimurium* TA 1538, TA 1535, TA 1537, TA 98, and TA 100 were exposed to the test substance in deionized water, at up to 5,000 µg/plate with and without metabolic activation in Experiment 1, and with metabolic activation at up to 1,024 mg/plate, and without activation at up to 256 mg/plate in Experiment 2. Cytotoxicity was observed at concentrations of 256 µg/plate and above. Results were negative for increased mutations in all strains, at all concentrations, with and without activation, and controls performed as expected (Reliability 4, not assignable according to ECHA dossier; Reliability 1, reliable without restriction according to OECD).
- Jagannath 1988, as cited in ECHA 2021 and OECD 2006

  - Cocamidopropyl betaine (30% a.i.) was evaluated in a bacterial reverse mutation assay performed under GLP according to OECD 471. *Salmonella typhimurium* TA 1535, TA 1537, TA 98, and TA 100 were exposed to the test substance in deionized water, with and without activation at up to 0.300 µL/plate. The highest concentrations were based on cytotoxicity in the range-finding study. Results were negative for increased mutations in all strains, at all concentrations, with and without activation. It is not clear if cytotoxicity was reached in the final test, and results for controls were not specified (Reliability 4, not assignable according to ECHA dossier; Reliability 2, reliable with restrictions according to OECD).
- Huls AG 1995 as cited in OECD 2006
  - Cocamidopropyl betaine (29.6% a.i., 0.7% free amine as impurity) was negative in an Ames assay conducted according to OECD Guideline 471 under GLP in *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 when tested with concentrations of up to 5,000 µg/plate with and without metabolic activation in the plate incorporation test, and up to 1,000 µg/plate (TA1535 and TA1537), and up to 3,000 µg/plate (TA98, TA100) with and without metabolic activation in the preincubation test. Cytotoxicity was observed at 1,000 µg/plate and above in TA1535 and TA1537, and at 5,000 µg/plate in TA98. Positive and negative/vehicle (water) controls were valid (Reliability 1, reliable without restriction).
- Kao Corporation 1992, as cited in OECD 2006
  - Cocamidopropyl betaine (30% a.i.) was negative in an Ames assay conducted according to OECD Guideline 471 under GLP in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 when tested with concentrations of up to 5,000 µg/plate and 500 µg/plate with and without metabolic activation, respectively. Cytotoxicity was observed at 150 µg/plate. Positive and negative/vehicle (water) controls were valid (Reliability 1, reliable without restriction).
- CFTA 1988 as cited in OECD 2006
  - Cocamidopropyl betaine (30% a.i.) was negative in an Ames assay (GLP not reported) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 when tested with concentrations of up to 0.3 µL/plate with and without metabolic activation. No additional details were reported (Reliability 4, not assignable).
- CFTA 1981 as cited in OECD 2006
  - Cocamidopropyl betaine (31% a.i.) was negative in an Ames assay (GLP status not reported) in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 when tested with concentrations of up to 0.4 µL/plate with and without metabolic activation. Cytotoxicity was observed at 318 µg/plate. No additional details were reported (Reliability 4, not assignable).
- CTFA 1982 as cited in ECHA 2021 and OECD 2006
  - Cocamidopropyl betaine (30.9% a.i.) was evaluated in an *in vitro* mammalian cell gene mutation assay (guideline and GLP compliance not specified). L5178Y TK +/- mouse lymphoma cells were exposed at up to 100 µL/mL, with and without metabolic activation. Results were negative for increased mutations compared to the solvent control, with and without activation. No information was provided regarding cytotoxicity, or reason for the top dose. While there was a solvent control, it is not clear if there were positive or untreated negative controls (Reliability 2, reliable with restrictions according to ECHA dossier; Reliability 4, not assignable according to OECD).
- ECHA 2021
  - *Surrogate: (carboxylatomethyl)dodecyldimethylammonium (CAS 683-10-3)*
    (Carboxylatomethyl)didecyldimethylammonium (purity and % active not specified) was

evaluated in an *in vitro* chromosome aberration study in mammalian cells (guideline and GLP compliance not specified). Chinese hamster lung cells (CHL/IU) were exposed to the test substance in physiological saline, with and without activation at up to 200 µg/mL, for 6, 18, or 24 hours. Results were negative for increases in chromosomal aberrations compared to controls for all concentrations and time points, with and without activation. Cytotoxicity was not observed; however, the concentrations were based on results from a range-finding study at which 50% inhibition was observed at 242 µg/mL with activation, 146 µg/mL without activation, and 107 µg/mL in the continuous treatment, and the positive controls performed as expected (Reliability 2, reliable with restrictions).

- Goldschmidt France S.A. 1987 as cited in OECD 2006 and CIR 2012
    - Cocamidopropyl betaine (27% a.i.) was negative in an *in vivo* mouse micronucleus assay conducted under GLP. Male and female OF1 mice (5/sex) were administered 2 doses of 20 or 200 mg/kg via intraperitoneal injection within 24 hours and sacrificed 6 hours later. The highest dose was determined based on irritation observed in a preliminary study. No evidence of clastogenic effects was reported at either dose level (highest tested dose, corresponding to 54 mg active substance/kg) in the bone marrow. Positive and negative controls were valid (Reliability 2, reliable with restrictions).

Reproductive Toxicity (R) Score (H, M, or L): DG
Cocamidopropyl betaine was assigned a score of Data Gap for reproductive toxicity based on insufficient data. While no adverse effects were observed on the reproductive organs in some repeated dose toxicity studies, no robust studies examining the reproductive system and fertility have been identified. Additionally, no data were found to corroborate the GHS rating by Japan.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:*
        - GHS – Japan – Toxic to reproduction – Category 2 [H361]
- ECHA 2021
    - Two repeated dose toxicity studies in rats, summarized below (i.e., the 90-day and 28-day studies), did not identify significant findings based on gross pathology, histopathology, or differences in organ weights in limited evaluations of the reproductive organs. *As these studies were not designed to evaluate reproductive toxicity, and did not examine a sufficient number of reproductive endpoints (e.g., male and female reproductive performance, gonadal function, mating behavior, conception, development of the conceptus, and parturition), ToxServices considered these data to be insufficient to evaluate reproductive toxicity.*
- HERA 2005
    - There is no evidence that cocamidopropyl betaine interferes with reproduction based on organ weights and histopathological examinations of the reproductive organs in a 90-day study.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Cocamidopropyl betaine was assigned a score of Moderate for developmental toxicity based on increased late and total resorptions, decreased viable fetuses, and reduced fetal weights in rats observed at a maternally toxic dose. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity or when they are classified to GHS Category 2 (CPA 2018b). The confidence in the score low as it is unclear if fetotoxicity observed in the rat study is secondary to maternal toxicity.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021 (data in the dossier for surrogate dimethyloctadecyl[3-(trimethoxysilyl)propyl] ammonium chloride (CAS 27668-52-6) was not summarized here as ToxServices does not consider it a reasonable surrogate), HERA 2005.
  - Cocamidopropyl betaine was evaluated in a developmental toxicity study (guideline and GLP compliance not specified). Rats (strain, number, and sex not specified) were exposed to the test substance once daily by gavage (vehicle not specified) at 0, 30, 90, or 300 mg/kg, on gestation days 6-17. Animals were evaluated for cage-side observations, and clinical observations including body weights and food consumption. The ovaries and uterine content were examined at study termination for gravid uterine weight, number of corpora lutea, number of implantations, and numbers of early and late resorptions. No effects were observed based on clinical signs, body weight and weight changes, food consumption, absolute and relative organ weights, histopathology, pre- and post-implantation loss, and early and late resorptions. Authors of the REACH dossier reported the NOAEL at 1,000 mg/kg/day in one part of the study summary, which was not a tested dose, and 300 mg/kg in the executive summary (Reliability 4, not assignable). *ToxServices notes this study as summarized by HERA 2005 reports the NOEL at 300 mg/kg.*
- OECD 2006, HERA 2005
  - Cocamidopropyl betaine was evaluated in a developmental toxicity study conducted according to OECD Guideline 414 (GLP compliance not specified). CD rats (25/dose) were administered 0, 330, 990, or 3,300 mg/kg/day of a 28.9% aqueous solution of cocamidopropyl betaine via gavage. This corresponds to 95, 286, and 950 mg active substance/kg/day. Animals were treated on gestation days 5-19. Treatment with doses of 990 mg/kg/day and greater produced maternal toxicity, stomach ulcers, and thickened stomach mucosa. Increased late and total resorptions, decreased viable fetuses, and reduced fetal weights were measured following treatment with 3,300 mg/kg/day. No external, skeletal, or soft tissue malformations, and no external variations were found. A maternal toxicity NOAEL of 330 mg/kg/day (corresponding to 95 mg active substance/kg/day) and a developmental toxicity NOAEL of 990 mg/kg/day (corresponding to 286 mg active substance/kg/day) were identified.

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

Cocamidopropyl betaine was assigned a score of Data Gap for endocrine activity based on insufficient data. While Danish QSAR predicted it to be negative for estrogen, androgen and thyroid pathways, no *in vivo* data were identified.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2021b
  - Cocamidopropyl betaine has not been evaluated by the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
- DTU 2021
  - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models (see Appendix F).
    - Cocamidopropyl betaine is predicted to be negative for estrogen receptor α binding (full training set, and balanced training set, human *in vitro*) by the model battery

consisting of negative and in domain predictions by Leadscope and SciQSAR models.
- Cocamidopropyl betaine is predicted to be negative for estrogen receptor α activation (human *in vitro*) by the SciQSAR model.
- Cocamidopropyl betaine is predicted to be negative for estrogen receptor activation (CERAPP data *in vitro*) by the Leadscope model.
- Cocamidopropyl betaine is predicted to be negative for androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by Leadscope and SciQSAR models.
- Cocamidopropyl betaine is predicted to be negative for androgen receptor binding, inhibition and activation (CoMPARA data *in vitro*) by the Leadscope model.
- Cocamidopropyl betaine is predicted to be negative for thyroperoxidase (TPO) inhibition (QSAR2, rat *in vitro*) by the Leadscope model.

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): M

Cocamidopropyl betaine was assigned a score of Moderate for acute toxicity based on the lowest reported oral LD_{50} value of 1,473 mg/kg a.i., which corresponds to GHS Category 4 classification (>300 and ≤2,000 mg/kg). Dermal LD_{50} values are > 600 mg/kg and >2,000 mg/kg, which corresponds to GHS Category 5, or not classified. No data were found for inhalation exposure. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when data for the most sensitive route of exposure meets the criteria for GHS Category 4 classification (CPA 2018b). The confidence in the score is high based on high quality data. The Moderate hazard rating is consistent with the GHS classification by Japan, and is more conservative than the classification by GHS New Zealand.

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS – Japan – Acute Toxicity (oral) – Category 4 [H302]
    - GHS – New Zealand – 6.1E (oral) – Acutely Toxic
  - *Screening:* Not present on any screening lists.
- ECHA 2021 (note only studies with Reliability ratings of 1 and 2 are summarized below, and data for surrogate compound dimethyloctadecyl[3-(trimethoxysilyl)propyl]ammonium chloride (CAS 27668-52-6) was excluded as ToxServices does not consider it a suitable surrogate)
  - *Oral:* Cocamidopropyl betaine (31% a.i.) was evaluated for acute oral toxicity according to OECD 401 (GLP compliance not specified). Male and female CD [Crl:COBS CD (SD) BR] rats (5/sex) were orally exposed (route unspecified) to the test substance at 5,000 mg/kg, followed by a 14-day observation period. There were no mortalities during the study period. Authors reported the LD_{50} was > 5,000 mg/kg, equivalent to >1,500 mg/kg a.i. (Reliability 2, reliable with restrictions).
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 14-day observation period. Authors reported the LD_{50} at 7,450 mg/kg (Reliability 2, reliable with restrictions). *ToxServices estimates 7,450 mg/kg, is approximately 2,235 mg/kg a.i. (i.e., 7,450 mg/kg x 30%).*

  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 4,000, 5,000, 6,300, 8,000, or 16,000 mg/kg followed by a 14-day observation period. Authors reported the LD_{50} at 4,900 mg/kg for the test material, equivalent to 1,500 mg/kg a.i. (Reliability 2, reliable with restrictions).
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Sprague-Dawley rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 2,710, 3,680, 5,000, or 6,780 mg/kg, followed by a 15-day observation period. Authors reported the LD_{50} at 4,910 mg/kg (Reliability 2, reliable with restrictions). *ToxServices estimates 4,910 mg/kg, is approximately 1,473 mg/kg a.i. (i.e., 4,910 mg/kg x 30%)*.
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female CFR mice (Carworth strain) (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 6,450 mg/kg, followed by a 7-day observation period. Mortality was 50%, and authors reported the LD_{50} at 6,450 mg/kg (Reliability 2, reliable with restrictions). *ToxServices estimates 6,450 mg/kg, is approximately 1,935 mg/kg a.i. (i.e., 6,450 mg/kg x 30%)*.
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 24-hour observation period. Authors reported the LD_{50} at 8,100 mg/kg (Reliability 2, reliable with restrictions). *ToxServices estimates 8,100 mg/kg, is approximately 2,430 mg/kg a.i. (i.e., 8,100 mg/kg x 30%).*
- CIR 2012
  - *Dermal:* Cocamidopropyl betaine (31% a.i.) was evaluated for acute dermal toxicity (GLP compliance and method not specified). Male and female CD rats (5/sex) were administered 2,000 mg/kg on clipped skin under occlusion for 24 hours. At 24 hours, the skin was rinsed, and observations were recorded daily for 14 days. On day 15, rats were necropsied. There were no mortalities, and no observations indicative of systemic toxicity. There were observations of erythema and sloughing or hyper keratinization, but all effects reversed by day 6. Authors reported a dermal $LD_{50} > 2{,}000$ mg/kg.
  - *Oral:* The oral LD_{50} of full-strength commercial samples of 30% active cocamidopropyl betaine was 4,910 mg/kg in CFR mice, and 7.45 mL/kg in Wistar rats. Several additional studies with 30% solutions provide LD_{50} values $\geqslant$, 4,900 mg/kg in rats. A 35.61% solution provided an LD_{50} value >1,800 mg/kg in male rats, however all females died in this study.
- ECB 2000, CIR 2012, U.S. EPA 2010
  - Cocamidopropyl betaine has very low acute oral (LD_{50} values > 4,900 mg/kg in rats and mice) and dermal (LD_{50} value > 2,000 mg/kg) toxicity.
- OECD 2006
  - The acute toxicity of the cocamidopropyl betaine (30-35.5% aqueous solution) is low as evidenced by acute oral toxicity studies in rats conducted according to OECD Guideline 401 with LD_{50} values generally greater than 5,000 mg/kg (i.e., greater than 1,500 mg active substance/kg) and an acute dermal toxicity study conducted according to OECD Guideline 402 in rats with an LD_{50} value greater than 2,000 mg/kg (i.e., greater than 600 mg active substance/kg).

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

Cocamidopropyl betaine was assigned a score of Low for systemic toxicity (single dose) based on lack of indications of systemic toxicity at sublethal doses in several acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality 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 2021 (note only studies with Reliability ratings of 1 and 2 are summarized here, and data in the dossier for surrogate dimethyloctadecyl[3-(trimethoxysilyl)propyl]ammonium chloride (CAS 27668-52-6) was not summarized here as ToxServices does not consider it a reasonable surrogate).
  - *Oral:* Cocamidopropyl betaine (31% a.i.) was evaluated for acute oral toxicity according to OECD 401 (GLP compliance not specified). Male and female CD [Crl:COBS CD (SD) BR] rats (5/sex) were orally exposed (route unspecified) to the test substance at 5,000 mg/kg, equivalent to ~1,500 mg/kg a.i., followed by a 14-day observation period. There were no mortalities during the study period. Clinical observations included piloerection, diarrhea, and increased salivation in treated rats shortly after dosing, and all effects were reversed by day 4 post-exposure. There were no significant findings at necropsy (Reliability 2, reliable with restrictions).
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 14-day observation period. Authors reported the LD_{50} at 7,450 mg/kg (no details regarding clinical observations or gross pathological findings at necropsy were reported) (Reliability 2, reliable with restrictions).
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 4,000, 5,000, 6,300, 8,000, or 16,000 mg/kg followed by a 14-day observation period. Clinical observations included sluggishness, nasal hemorrhage, diarrhea, and wetness around the posterior, increasing in severity proportionately to dose and observed in all treated animals (no details regarding gross pathological findings at necropsy were reported) (Reliability 2, reliable with restrictions). *ToxServices notes 2,000 mg/kg/day is equivalent to approximately 600 mg/kg a.i..*
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Sprague-Dawley rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 2,710, 3,680, 5,000, or 6,780 mg/kg, followed by a 15-day observation period. Diarrhea was observed in all treatment groups, and decreased motor activity was observed in rats at 2,710 mg/kg and higher. Dried blood around the nose and salivation were observed in 3 to 5 male rats at 5,000 mg/kg. At necropsy, a bloodlike viscous liquid was observed in the intestines. Authors reported the LD_{50} at 4,910 mg/kg (Reliability 2, reliable with restrictions). *ToxServices notes the study summary does not specify which dose groups had observations of bloodlike viscous liquid in the intestines, but it is implied to have occurred at the lethal doses. Accordingly, ToxServices did not assume it to be an indicator of systemic toxicity.*

  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female CFR mice (Carworth strain) (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 6,450 mg/kg, followed by a 7-day observation period. Mortality was 50%, and authors reported the LD_{50} at 6,450 mg/kg (no details were reported for clinical signs, body weights, or gross pathology) (Reliability 2, reliable with restrictions).
  - *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 24-hour observation period. Rats in all dose groups had decreased motor activity, abnormal posture, coordination disturbance, cyanosis, diarrhea, and decreased body temperature beginning approximately 20 minutes after dosing and persisting for 24 hours. Redness of the stomach and intestinal mucous membrane was observed at necropsy. Authors reported the LD_{50} at 8,100 mg/kg (Reliability 2, reliable with restrictions). *ToxServices notes redness of the stomach and intestinal mucous membrane is not necessarily an indicator of systemic toxicity, but may be adaptive in nature, and the doses at which it was observed were not specified.*
- CIR 2012
  - *Dermal:* Cocamidopropyl betaine (31% a.i.) was evaluated for acute dermal toxicity (GLP compliance and method not specified). Male and female CD rats (5/sex) were administered 2,000 mg/kg on clipped skin under occlusion for 24 hours. At 24 hours, the skin was rinsed, and observations were recorded daily for 14 days. On day 15, rats were necropsied. There were no mortalities, and no observations indicative of systemic toxicity. There were observations of erythema and sloughing or hyper keratinization, but all effects reversed by day 6.

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

Cocamidopropyl betaine was assigned a score of Low for systemic toxicity (repeated dose) based on a NOEAL of 250 mg/kg in a 90-day repeated dose oral toxicity study, which exceeds the GHS guidance value of 100 mg/kg for Category 2 classification. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on reliable data. While REACH registration dossier assigned a reliability score of 4 for the critical study because it is cited from secondary sources (i.e., U.S. EPA 2010, HERA 2005 and OECD 2006), ToxServices considered the quality of the study sufficient to warrant a high confidence.

- 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 2021 (note data within the dossier on surrogate amides, coco, N-(hydroxyethyl) (CAS 68140-00-1) was not assessed here as ToxServices does not consider it a suitable surrogate).
  - *Oral:* Cocamidopropyl betaine was evaluated in a repeated dose oral toxicity study according to OECD 407 (GLP-compliance not specified). Male and female Sprague-Dawley rats (10/sex/dose with an additional 5/sex in the control group and high dose groups for assessment of recovery) were exposed to the test substance (purity not specified) by gavage in water, once daily, for 28 days at 0, 250, 500, or 1,000 mg/kg/day. Animals were evaluated for cage side and clinical observations, body weight, ophthalmology, hematology, clinical chemistry, absolute and relative organ weights, gross pathology, and histopathology.

Symptoms of local irritation in the gastrointestinal tract were reported in high dose animals, including head protrusion at the beginning of week 3, and salivation at the beginning of week 4, which persisted through the end of the study. High dose animals also had acanthosis of the mucosa, inflammatory edema of the submucosa and multiple ulcerations. Recovery animals showed complete and regular regeneration of the forestomach mucosa. There was no mortality throughout the study and no additional adverse effects on any of the evaluated endpoints for any of the test groups. Authors reported a NOAEL of 500 mg/kg/day, based on local irritation of the gastrointestinal tract, edema of the forestomach mucosa that disappeared in recovery animals, acanthosis of the mucosa, inflammatory edema of the submucosa, and multiple ulcerations in high dose rats (Reliability 4, not assignable).

  - *Oral:* Cocamidopropyl betaine was evaluated in a repeated dose oral toxicity study according to OECD 408 (GLP-compliance not specified). Male and female Sprague-Dawley rats (10/sex/dose) were exposed to the test substance (purity not specified) by gavage in water, once daily, 5 days/week, for 90 days at 0, 250, 500, or 1,000 mg/kg/day. Animals were evaluated for cage side and clinical observations, hematology, clinical chemistry, urinalysis, gross pathology, and histopathology. There were no significant findings based on clinical signs, mortality, body weight and weight changes, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, or absolute or relative organ weights. Stomach ulcerations at the fundus and cardiac regions were observed in high dose rats. Forestomach gastritis in 6 male and 3 female rats was observed in the high dose groups, and in 2 males and 2 females at 500 mg/kg/day. Authors assigned the NOAEL at 250 mg/kg/day based on stomach ulcerations in both sexes at 500 mg/kg/day and higher (Reliability 4, not assignable).

- CIR 2012
  - In summarizing the 90-day oral toxicity study, the CIR Expert Panel did not consider the observed effects in the stomach and forestomach to be systemic. Additionally, CIR speculates cocamidopropyl betaine is unlikely to penetrate the skin based on its molecular size and water solubility.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *M*
Cocamidopropyl betaine was assigned a score of Moderate for neurotoxicity (single dose)) based on sluggishness at 2,000 mg/kg test substance, approximately 600 mg/kg a.i., and decreased motor activity, abnormal posture, and coordination disturbance at 2,710 mg/kg, approximately 813 mg/kg a.i., in two acute oral toxicity studies in rats. These are considered transient narcotic effects, and meet the criteria for GHS Category 3 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when data support GHS Category 3 classification (CPA 2018b). The confidence in the score is low as the study summaries do not specify if the sluggishness and decreased motor activity were transient at sub-lethal doses, rather ToxServices assumed they were transient. This hazard rating is consistent with GHS Japan's Category 3 classification.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* GHS – Japan – Specific target organs/systemic toxicity following single exposure – Category 3 [H336]
- ECHA 2021 (note only studies with Reliability ratings of 1 and 2 are summarized here, and data in the dossier for surrogate dimethyloctadecyl[3-(trimethoxysilyl)propyl]ammonium chloride (CAS 27668-52-6) was not assessed here as ToxServices does not consider it a reasonable surrogate).

- *Oral:* Cocamidopropyl betaine (31% a.i.) was evaluated for acute oral toxicity according to OECD 401 (GLP compliance not specified). Male and female CD [Crl:COBS CD (SD) BR] rats (5/sex) were orally exposed (route unspecified) to the test substance at 5,000 mg/kg, followed by a 14-day observation period. There were no mortalities during the study period. Clinical observations included piloerection, diarrhea, and increased salivation in treated rats shortly after dosing, and all effects were reversed by day 4 post-exposure. There were no significant findings at necropsy (Reliability 2, reliable with restrictions).
- *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 14-day observation period. Authors reported the LD_{50} at 7,450 mg/kg (no details regarding clinical observations or gross pathological findings at necropsy were reported) (Reliability 2, reliable with restrictions).
- *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 4,000, 5,000, 6,300, 8,000, or 16,000 mg/kg followed by a 14-day observation period. Authors reported the LD_{50} at 4,900 mg/kg for the test material, equivalent to 1,500 mg/kg a.i.. Clinical observations included sluggishness, nasal hemorrhage, diarrhea, and wetness around the posterior, increasing in severity proportionately to dose and observed in all treated animals (no details regarding gross pathological findings at necropsy were reported) (Reliability 2, reliable with restrictions). *ToxServices assumes the sluggishness was transient because it was not discussed in greater detail, and notes 2,000 mg/kg test substance is approximately 600 mg/kg a.i..*
- *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Sprague-Dawley rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 2,000, 2,710, 3,680, 5,000, or 6,780 mg/kg, followed by a 15-day observation period. Diarrhea was observed in all treatment groups, and decreased motor activity was observed in rats at 2,710 mg/kg and higher. Dried blood around the nose and salivation were observed in 3 to 5 male rats at 5,000 mg/kg. At necropsy, a bloodlike viscous liquid was observed in the intestines (Reliability 2, reliable with restrictions). *ToxServices assumes the decreased motor activity was transient because it was not discussed in greater detail, and estimates 2,710 mg/kg, is approximately 813 mg/kg a.i..*
- *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female CFR mice (Carworth strain) (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 6,450 mg/kg, followed by a 7-day observation period. Mortality was 50%, and authors reported the LD_{50} at 6,450 mg/kg (no details were reported for clinical signs, body weights, or gross pathology) (Reliability 2, reliable with restrictions).
- *Oral:* Cocamidopropyl betaine (30% a.i.) was evaluated for acute oral toxicity (GLP compliance and method not specified). Male and female Wistar rats (5/sex/dose) were exposed to the test substance by gavage (vehicle not specified) at 5,000, 6,300, 7,940, or 10,000 mg/kg, followed by a 24-hour observation period. Rats in all dose groups had decreased motor activity, abnormal posture, coordination disturbance, cyanosis, diarrhea, and decreased body temperature beginning approximately 20 minutes after dosing and persisting for 24 hours. Redness of the stomach and intestinal mucous membrane was observed at necropsy. Authors reported the LD_{50} at 8,100 mg/kg (Reliability 2, reliable with restrictions).

- CIR 2012
    - *Dermal* Cocamidopropyl betaine (31% a.i.) was evaluated for acute dermal toxicity (GLP compliance and method not specified). Male and female CD rats (5/sex) were administered 2,000 mg/kg on clipped skin under occlusion for 24 hours. At 24 hours, the skin was rinsed, and observations were recorded daily for 14 days. On day 15, rats were necropsied. There were no mortalities, and no observations indicative of systemic toxicity. There were observations of erythema, and sloughing or hyper keratinization, but all effects reversed by day 6.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
Cocamidopropyl betaine was assigned a score of Data Gap for neurotoxicity (repeated dose) based on lack of 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.
- No data were identified.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *M*
Cocamidopropyl betaine was assigned a score of Moderate for skin sensitization based on weight of evidence. Animal studies are generally negative, although one guinea pig maximization test was ambiguous, and there is one report of a positive LLNA study with limited details. Patch testing in humans suggests weak sensitization potential for dilute substances, but significant sensitization at high concentrations. These data are consistent with GHS Category 1B, low-to-moderate frequency and/or potency. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when data meet the criteria for GHS Category 1B classification (CPA 2018b). The confidence in the score is low due to the mixed results from multiple lines of evidence.

- 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 2021
    - Cocamidopropyl betaine (purity not specified) was evaluated for skin sensitization in a human patch test. Volunteers (n=1,092) were exposed on the skin at 1% in water under occlusion for induction and challenge. Dermal reactions were read on days 2, 3, and 4, or 2, 3, and 6, or 2 and 5, depending on the day of application. At 48 hours, 2 subjects (0.2%) had positive allergic reactions (+++ and ++, respectively), and 166 subjects (5%) had positive skin irritation reactions. Authors concluded the test substance may be considered a potentially weak skin sensitizer (Reliability 2, reliable with restrictions).
    - Cocamidopropyl betaine (purity not specified) was evaluated for skin sensitization in a human patch test. 10 Volunteers were exposed on the skin at 0.1%, 0.3%, or 1.0% under occlusion for induction and challenge. Control subjects had induction exposure only. One control subject had a positive reaction at 1%. In challenged subjects, 5/10 showed clear positive reactions at 1%, typically on day 3, and 3 gave marginal and/or irritant reactions. The observed reactions showed a typical crescendo pattern with no reactions at day 2, but positive reactions on day 3, suggesting a true allergic reaction. Authors concluded the test substance at 1% and above can cause allergic reactions to humans (Reliability 2, reliable with restrictions).
    - Cocamidopropyl betaine (purity not specified) was evaluated in a guinea pig maximization test (GLP compliance not specified). Animals were induced via intradermal injection at 0.1

mL FCA, 0.1 mL test chemical without FCA, and 0.1 mL 0.1% test chemical with FCA (20 animals/group). For the second induction, animals were exposed on the skin under occlusion as 10% aqueous solution for 48 hours. For the challenge, animals were exposed on the skin under occlusion to 10% aqueous solution for 24 hours, and results were evaluated at 48 and 72 hours post-exposure. For the first reading at 72 hours, 2/20 animals exposed to 10% aqueous solution had positive sensitization reactions, 8/20 had signs of erythema, 4/20 had mild intracellular edema that was considered ambiguous, and 14/20 were clearly negative for sensitization. Authors concluded the test substance can be considered sensitizing to the skin (Reliability 2, reliable with restrictions). *Conservatively assuming ambiguous results to be positive, the positivity rate is 6/20 = 30%. According to GHS criteria, ≥ 30% positivity rate at ≤0.1% intradermal induction concentration warrants classification to GHS Category 1A (UN 2019). However, as discussed below by NICNAS (2020), the reliability of this study is questionable.*

  - Cocamidopropyl betaine (purity not specified) was evaluated for skin sensitization in a human patch test. Volunteers (n=210) were exposed on the skin at 1% in water under occlusion for induction and challenge. At 96 hours, 12/210 had positive reactions, and most patients had redness, swelling, and vesicles. Authors noted the possibility of the test chemical being a weak allergen to pre-sensitized humans cannot be ruled out, and the test substance can be considered a weak sensitizer (Reliability 2, reliable with restrictions).
- NICNAS 2020
  - The chemical is not considered to be a skin sensitizer in animals. Four adjuvant tests (two maximization tests according to Magnusson and Kligman, one Draize and one modified Draize test) are available for cocamidopropyl betaine. Three of the studies gave no indication of the chemical's sensitizing potential. The fourth study, a guinea pig maximization test (GPMT) (Magnusson & Kligman; Induction: 0.1 % intracutaneous injection, 10 % patch; Challenge: 10 % patch), gave ambiguous results. These studies were not conducted in full compliance with current OECD test guidelines, and no information on the purity of the test materials was available. A local lymph node assay (LLNA) with cocamidopropyl betaine was positive for sensitization, but no other details were provided.
- CIR 2012
  - Betaines may contain 3,3-dimethylaminopropylamine (DMAPA) and fatty acid amidopropyl dimethylamine (amidoamine) as impurities, which are known sensitizers. The CIR Expert Panel concluded that amidopropyl betaines are safe for use in cosmetics, provided the levels of these sensitizing impurities are minimized and the product is formulated to be non-sensitizing, based on a quantitative risk assessment.
- U.S. EPA 2010
  - Cocamidopropyl betaine is a skin sensitizer in mice based on positive results in a local lymph node assay (LLNA) conducted in 1994. No further details were provided.
- OECD 2006, HERA 2005
  - Negative results were obtained in one maximization test, one Draize test, and one modified Draize test conducted in guinea pigs, and ambiguous results were obtained in one guinea pig maximization test.
- HERA 2005
  - No irritation or sensitization was seen when cocamidopropyl betaine was tested at concentrations up to 3% a.i. in humans.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *M*
Cocamidopropyl betaine was assigned a score of Moderate for respiratory sensitization based on the weight of evidence including AOEC designation as an asthmagen (Rs). While this designation corresponds to either a Moderate or High GreenScreen® hazard rating (CPA 2018b), its listing is based on being sensitizer induced, and as noted above, cocamidopropyl betaine appears to be a weak sensitizer, therefore the Moderate hazard rating is applied. GreenScreen® criteria classify chemicals as a Moderate hazard for respiratory sensitization when they are classified to GHS Category 1B (CPA 2018b). The confidence in the score is low based on lack of respiratory sensitization data.

- Authoritative and Screening Lists
  - *Authoritative:* AOEC – Asthmagens – Asthmagen (Rs) – sensitizer-induced
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020
  - Cocamidopropyl betaine does not contain any structural alerts for respiratory sensitization (Appendix G).
- No data were identified for the target compound to corroborate the AOEC listing. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of cocamidopropyl betaine 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). Cocamidopropyl betaine does not contain any structural alerts, but has concerns for respiratory sensitizer based extrapolation from skin sensitization data. According to the ECHA guidance, the positive skin sensitization results in animals, combined with lack of structural alerts, and lack of evidence of respiratory sensitization, indicate that there is insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Due to the AOEC listing, the positive skin sensitization data, and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Moderate score was assigned.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *H*
Cocamidopropyl betaine was assigned a score of High for skin irritation/corrosivity based on numerous studies indicating moderate irritation, which is consistent with GHS Category 2 classification. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when data support GHS Category 2 classification (CPA 2018b). The confidence in the score is low as none of the studies tested the undiluted substances according to standard protocols that can be directly used to perform definitive GHS classification.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – New Zealand – 6.3A – Irritating to the skin (Cat. 2)
- ECHA 2021 (note only studies with Reliability ratings of 1 and 2 are summarized here)
  - Cocamidopropyl betaine (purity and % active not specified) was evaluated for skin irritation using the plastic occlusion stress test (POST) technique (GLP compliance and method not specified). Eight healthy white male volunteers were exposed at 0.03 mL/cm^2 of 7% test chemical in distilled water, once daily for 3 days on the open skin of the forearm. Irritation

was determined based on skin surface water loss (SSWL) and trans epidermal water loss (TEWL) measured using an evaporimeter. The mean SSWL at 1 minute and 25 minutes was 44.7 and 12.1, respectively. Both values were statistically significant compared to controls. Authors reported the test substance was irritating under the conditions of the test and the test data meet the criteria for GHS Category 2 classification (Klimisch 2, reliable with restrictions). *ToxServices notes the POST technique is not an OECD guideline method, and it is unclear why the notifier classifies the results to GHS Category 2.*

- Cocamidopropyl betaine (purity and % active not specified) was evaluated in a human patch test in which 66 healthy male and female subjects were exposed to the test substance under occlusion at 1% w/v in distilled water for 24 hours. The sum of scores for 22 observations was 4 after 24 hours, using a 4-point scale. The mean score for erythema/edema was 0.17 with a standard deviation of 0.49, at 24 hours. Authors concluded the test substance was irritating to the skin (Reliability 2, reliable with restrictions). *ToxServices notes details of the scoring system were vague and it is unclear how an irritation score of 0.17 corresponds to a conclusion of "irritating."*
- Cocamidopropyl betaine (purity and % active not specified) was evaluated in the EpiDerm™ Epi-100 assay (GLP compliance not specified). Non-transformed human keratinocytes were exposed in triplicate to 100 µL topically applied test material at 0.5% w/v for 1 hour. Post exposure samples were rinsed with phosphate buffered saline, and were placed in fresh medium, and viability was assessed at 24 hours post exposure. Mean tissue viability was 92% (expressed as % untreated), and as this was >20%, authors concluded the test substance was irritating under the conditions of the test (Reliability 2, reliable with restrictions). *ToxServices notes this method is one of the methods cited in OECD 439, and typically cell viability >50% is indicative of a non-irritant. It is unclear if testing was performed in accordance with OECD 439, and it is unclear how the authors derived their conclusion.*
- Cocamidopropyl betaine (10 % a.i.) was evaluated in a human patch test. Volunteers (number and sex not specified) were exposed to the test substance under occlusion for 24 hours. Irritation was scored using the Draize scale. The mean overall irritation score at 24 hours was 1.08. Authors concluded the test substance was irritating to the skin and meets the criteria for GHS Category 2 classification (Reliability 2, reliable with restrictions). *ToxServices notes details of the scoring system were vague and it is unclear how an irritation score of 1.08 corresponds to a conclusion of "irritating."*
- Cocamidopropyl betaine (24% a.i.) was evaluated in a human patch test. Volunteers (24 healthy females aged 18-45 years) were exposed to 40 µL of the test substance under occlusion for 30 minutes, followed by a rinse with tap water. Irritation was scored 24 and 72 hours after patch removal. The Evaporimeter EP1 was used to measure trans epidermal water loss, and the Chroma Meter CR200 was used to evaluate erythema. The mean TransEpidermal Water loss was 1.39 and 1.82 at 24 and 48 hours, respectively, compared to baseline values of 0.57 and 1.03 at 24 and 48 hours, respectively. Results of erythema evaluations were not reported. Authors concluded the test substance was irritating to the skin and meets the criteria for GHS Category 2 classification (Reliability 2, reliable with restrictions). *ToxServices notes that while the results of trans epidermal water loss appear to be significantly higher than controls, it is unclear why the authors assigned GHS Category 2 classification.*

- CIR 2012
  - Based on multiple animal studies, undiluted cocamidopropyl betaine (i.e., 30% active) is irritating to the skin, whereas 50% dilution is not irritating.

  - In a study of cumulative irritation, 0.3mL of 2 soap formulations with 1.9% cocamidopropyl betaine were applied to the skin on the backs of 10 volunteers under occlusion. Daily 23-hour patches were applied for 21 consecutive days. Total irritation scores for each formulation were 588 and 581 (max 630), therefore authors concluded the formulations were irritating. Furthermore, the average irritation times were 1.48 and 1.69 days, respectively, with a median irritation time of 2 days.
  - Cocamidopropyl betaine at 0.06% (based on 1.0% aqueous dilution of a formulation with 6.0% a.i.) was applied to the skin of 19 volunteers as a single insult occlusion patch test. 15 volunteers had no irritation, and 4 had minimal (+) irritation. Authors concluded the test substance was practically nonirritating.
  - Daily application of 0.2 mL of 0.52% cocamidopropyl betaine (based on 85 aqueous dilution of a 6.5% formulation) via occlusive patch to the forearms of 12 volunteers for 5 days resulted in a mean erythema score of 0.48 on a 4-point scale.
- ECB 2000, U.S. EPA 2010, BIBRA 1999, Jacob and Amini 2008, HERA 2005
  - Cocamidopropyl betaine is a moderate skin irritant.
- OECD 2006, HERA 2005
  - In an acute dermal irritation study conducted according to OECD Guideline 404 (semi-occlusive conditions) in rabbits, a 30% aqueous solution of the surrogate cocamidopropyl betaine caused slight dermal irritation that was fully reversible within 8 days. When tested as a moistened spray-dried powder cocamidopropyl betaine (80%) was not irritating to the skin of rabbits in a study conducted according to OECD Guideline 404 (semi-occlusive conditions). Exposure to 25-30% aqueous solutions of cocamidopropyl betaine for 4 hours under occlusive conditions produced dermal irritation in rabbits that was fully reversible within 10 days and exposure to 10% aqueous solutions of cocamidopropyl betaine for 24 hours under occlusive conditions produced moderate dermal irritation in rabbits that was still present at study termination (72 hours).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *vH*
Cocamidopropyl betaine was assigned a score of Very High for eye irritation/corrosivity based on observations of eye irritation in animals exposed at 25-35% concentrations that were not reversible within 21 days of exposure, which meets the criteria for GHS Category 1 classification. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when data support classification to GHS Category 1 (CPA 2018b). The confidence in the score is low due to inconsistent results reported across studies and concentrations. This hazard rating is consistent with the GHS classification of Japan, whereas the Australian and New Zealand classifications align with a less conservative High hazard rating.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening*:
    - GHS – Japan – Serious eye damage / eye irritation – Category 1 [H318]
    - GHS – Australia – H319 – Causes serious eye irritation
    - GHS – New Zealand – 6.4A – Irritating to the eye (Cat. 2a)
- ECHA 2021
  - Cocamidopropyl betaine (purity not specified) was evaluated in an *in vivo* eye irritation study performed in accordance with the Federal Hazardous Substances Act, 16 CFR 1500.42. The test substance was instilled into one eye each of 9 New Zealand White rabbits, with the other eye serving as control, at 0.1 mL of 50.7% w/v dilution in tap water. For 3 rabbits, the eyes were rinsed with tepid tap water after 30 seconds, for a duration of 1

minute. Observations were recorded at 1, 2, 3, 4 and 7 days post instillation, and scoring was assessed using the Draize scale. The mean overall irritation score at 21 days was 0.7 and 14.7 for unwashed and washed eyes, respectively, and did not indicate improvement with rinsing. Authors concluded the test substance was irritating to the eyes under the conditions of the test and the data support GHS Category 2 classification (Reliability 4, not assignable). *ToxServices does not generally prioritize studies with Reliability ratings of 4, however, this is considered the key study in the REACH dossier, is derived from a TSCA Submission, and is reasonably detailed. However, effects persisting to day 21 post exposure, even if minimal, meet the criteria for GHS Category 1 classification (UN 2019).*

- Cocamidopropyl betaine (purity not specified, undiluted) was evaluated in an *in vivo* eye irritation study (GLP compliance and guideline not specified). The test substance was instilled into the eye of rabbits (number not specified) and observations were recorded at 24 hours post exposure (rinsing not specified). The mean overall irritation index at 24 hours was 18 and was considered mildly irritating according to the Draize classification criteria (Reliability 2, reliable with restrictions).
- Cocamidopropyl betaine (purity not specified) was evaluated in an *in vitro* eye irritation study using the EpiOcular™ (OCL-200) model system (GLP compliance not specified). This method uses normal, human-derived epidermal keratinocytes cultured to form a stratified squamous epithelium similar to that found in the human cornea. The cultures were exposed in duplicate to a single administration of 100 µL of 50% test chemical solution for 60 minutes, and incubated for 3 minutes, 30 minutes, or 60 minutes. Following incubation, the samples were rinsed with DPBS and transferred to 24-well plates with 0.3 mL diluted MTT solution/well. The MTT plates were further incubated for 3 hours at 37°C in 5% CO_2. After incubation, tissues were rinsed again with DPBS, and MTT dye was extracted. The ET50 (effective time of exposure to reduce tissue viability to 50%) was < 3 minutes, and authors concluded the test substance is severely irritating to the eyes (Reliability 2, reliable with restrictions).
- Cocamidopropyl betaine (30% aqueous solution) was evaluated in an *in vivo* eye irritation study (GLP compliance and guideline not specified) using the Draize test. The test substance was instilled undiluted into one eye each of 4 rabbits (strain not specified) and observations were recorded from 1 hour to 21 days post exposure (rinsing not specified). Corneal opacity occurred in all 4 rabbits (score = 1) and persisted until day 21. Conjunctival redness was observed in all 4 rabbits (scores 2, 3, 3, and 3 by day 3 or sooner) and was fully reversible for all animals by 7 to 14 days. Authors concluded the test substance was irritating to the eyes under the conditions of the test and the data support GHS Category 2 classification (Reliability 2, reliable with restrictions). *As noted above, effects (including corneal opacity ⩾ 1) persisting to day 21 post exposure meet the criteria for GHS Category 1 classification (UN 2019).*

- CIR 2012
  - Cocamidopropyl betaine produced slight conjunctival irritation at 4.5% active concentration that was very slight if the eyes were rinsed.
- OECD 2006, HERA 2005
  - Cocamidopropyl betaine is irritating to the eyes of rabbits. When cocamidopropyl betaine was tested in OECD Guideline 405 studies conducted in rabbits, concentrations of 25-35% produced eye irritation that was not reversible within 21 days. Aqueous 5-10% solutions of cocamidopropyl betaine produced mild to moderate eye irritation in rabbits that was fully reversible within 7 days (OECD 2006, HERA 2005).

Ecotoxicity (Ecotox)

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

Cocamidopropyl betaine was assigned a score of Very High for acute aquatic toxicity based on several acute toxicity studies providing EC_{50} values <1 mg/L in algae. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when the LC/EC_{50} values for the most sensitive trophic level are <1 mg/L (CPA 2018b). The confidence in the score is high based on reliable data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – Japan – Hazardous to the aquatic environment (acute) – Category 2 [H401]
    - GHS – New Zealand – 9.1A (algal) – Very ecotoxic in the aquatic environment
    - GHS – New Zealand – 9.1D (crustacean) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
    - GHS – New Zealand – 9.1D (fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
- ECHA 2021
  - Cocamidopropyl betaine (29.6% active, purity not specified) was evaluated in an acute toxicity test (guideline and GLP compliance not specified). Zebrafish (*Danio rerio*) were exposed to the test substance for 96 hours under static conditions at nominal concentrations up to 8.0 mg/L. The 96 hr LC_{50} was 2 mg/L (nominal) (Reliability 2, reliable with restrictions).
  - Cocamidopropyl betaine (30% active, purity not specified) was evaluated in an acute toxicity test (guideline and GLP compliance not specified). Carp (*Cyprinius carpio*) were exposed to the test substance for 96 hours under static conditions at nominal concentrations up to 9 mg/L. The 96 hr LC_{50} was 1.9 mg/L (nominal) (Reliability 4, not assignable).
  - Cocamidopropyl betaine (30% active, purity not specified) was evaluated in an acute toxicity test performed according to OECD 203 (GLP compliance not specified). Zebrafish (*D. rerio*) were exposed to the test substance in dechlorinated drinking water for 96 hours under static conditions at nominal concentrations up to 8 mg/L. The 96 hr LC_{50} was 6.7 mg/L (nominal) (Reliability 4, not assignable).
  - Cocamidopropyl betaine (% active and purity not specified) was evaluated in an acute toxicity test performed according to OECD 202 (GLP compliance not specified). *Daphnia magna* were exposed to the test substance for 48 hours in a 50/50 mixture of dechlorinated and distilled water, under static conditions, at nominal concentrations up to 16 mg/L. The 48 hr EC_{50} was 6.4 mg/L (nominal) (Reliability 2, reliable with restrictions).
  - Cocamidopropyl betaine (% active and purity not specified) was evaluated in an acute toxicity test performed according to OECD 202 and EU Method C.2 (GLP compliance not specified). *D. magna* were exposed to the test substance for 48 hours under static conditions, at nominal concentrations up to 100 mg/L. The 48 hr EC_{50} was 21.5 mg/L (nominal) or 21.5 mg/L (measured, 95% confidence limits 16.1-28.1 mg/L) (Reliability 2, reliable with restrictions).
  - Cocamidopropyl betaine (% active and purity not specified) was evaluated in an acute toxicity test (guideline and GLP compliance not specified). *Ulva lactuca* (green seaweed) were exposed to the test substance for 48 hours under static conditions at nominal concentrations up to 40 mg/L. The 48 hr EC_{50} was 30 mg/L (nominal) based on biomass (information on growth rate not specified) (Reliability 2, reliable with restrictions).

ToxServices notes U. lactuca is not one of the preferred species recommended in OECD 201.

- Cocamidopropyl betaine (% active and purity not specified) was evaluated in an acute toxicity test performed according to OECD 201 (GLP compliance not specified). *Desmodesmus subspicatus* were exposed to the test substance for 72 hours under static conditions at nominal concentrations up to 100 mg/L. The 72 hr EC_{50} was 30 mg/L (nominal) based on biomass, and 48 mg/L (nominal) based on growth rate (Reliability 4, not assignable).
- Cocamidopropyl betaine (% active and purity not specified) was evaluated in an acute toxicity test performed according to DIN 34812, Part 9 (GLP compliance not specified). *D. subspicatus* were exposed to the test substance for 96 hours under static conditions at nominal concentrations up to 10 mg/L. The 96 hr EC_{50} was 1.84 mg/L (nominal) based on cell number (Reliability 4, not assignable).

- U.S. EPA Undated
  - A 96 hr LC_{50} of 6.7 mg/L was determined in the fish (Zebra fish) (Reliability 2, reliable with restrictions)
  - A 48 hr EC_{50} of 21.5 mg/L was determined in the aquatic invertebrate (*D. magna*) (Reliability 1, reliable without restriction)
  - A 48 hr EC_{50} of 6.4 mg/L was determined in the aquatic invertebrate (*D. magna*) (Reliability 1, reliable without restriction)
  - A 48 hr EC_{50} of 4.6 mg/L was determined in the aquatic invertebrate (*D. magna*) (Reliability 1, reliable without restriction)
  - A 96 hr EC_{50} of 1.84 mg/L (0.55 mg/L a.i.) was determined in the aquatic plant (*S. subspicatus*) based on growth rate, when tested according to OECD 201 (Reliability 1, reliable without restriction).
  - A 96 hr EC_{50} of 1.84 mg/L (0.55 mg/L a.i.) was determined in the aquatic plant (*S. subspicatus*) based on growth rate, when tested according to DIN 38412, Part 9 (Reliability 1, reliable without restriction).
  - A 72 hr E_bC_{50} of 1.81 mg/L (0.55 mg/L a.i.) was determined in the aquatic plant (*S. subspicatus*) when tested according to OECD 201 (Reliability 2, reliable with restrictions).

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

Cocamidopropyl betaine was assigned a score of High for chronic aquatic toxicity based on chronic exposure EC_{50}/NOEC values in the range 0.1-1 mg/L in fish, daphnia, and algae. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic toxicity values for the most sensitive trophic level are in the range of 0.1-1 mg/L (CPA 2018b). The confidence in the score is high based on reliable data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2021
  - Cocamidopropyl betaine (29.6% active, purity not specified) was evaluated in a chronic toxicity test performed according to OECD 204 (GLP compliance not specified). Rainbow trout (*Oncorhynchus mykiss*) were exposed to the test substance for 28 days under static conditions (concentrations not specified). The 28-day NOEC and LOEC based on mortality were 0.16 and 0.5 mg/L (nominal), respectively (Reliability 4, not assignable).
  - Cocamidopropyl betaine (% active and purity not specified) was evaluated in a 21-day reproduction test performed according to OECD 202 (GLP compliance not specified). *D.*

magna were exposed to the test substance for 21 days under static conditions (concentrations not specified). The 21-day NOEC and LOEC based on reproduction was 0.9 and 3.6 mg/L (nominal), respectively (Reliability 2, reliable with restrictions). *ToxServices notes OECD 202 is an acute toxicity test method, whereas OECD 211 is a 21-day reproduction test.*

- U.S. EPA Undated
    - A 28-day NOEC of 0.16 mg/L was determined in the fish (*O. mykiss*) (Reliability 2, reliable with restrictions).
    - A 21-day NOEC of 0.9 mg/L was determined in the aquatic invertebrate (*D. magna*) (Reliability 2, reliable with restrictions).
    - A 72-hr NOEC of 0.96 mg/L was determined in the aquatic plant (*S. subspicatus*) based on growth rate, when tested according to EU Method C.3 (92/69/EEC) (Reliability 2, reliable with restrictions).

Environmental Fate (Fate)

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

Cocamidopropyl betaine was assigned a score of Very Low for persistence based on biodegradability >60% in 28 days, and meeting the 10-day window in an OECD 301E test. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when ready biodegradability is achieved and the 10-day window is met (CPA 2018b). The confidence in the score is high based on reliable 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 2021 (note ready biodegradability studies in seawater, inherent biodegradability studies, simulation tests, and anaerobic studies are not summarized here, as data are sufficient to establish ready biodegradability based on ready biodegradability tests in freshwater)
    - Cocamidopropyl betaine (purity and % active not specified) was evaluated in a modified Sturm test performed according to Dir 84/449/EEC, C.5 (GLP not specified). The test substance was exposed to unspecified inoculum under aerobic conditions for 20 days at an initial concentration of 20 mg/L. Degradation was reported at 100% in 20 days (no further details provided) (Reliability 4, not assignable).
    - Cocamidopropyl betaine (purity and % active not specified) was evaluated in a closed bottle test performed according to OECD 301D (GLP not specified). The test substance was exposed to domestic sludge under aerobic conditions for 28 days at an initial concentration 2 and 5 mg/L, in two replicates. Biodegradation was measured based on oxygen consumption. Benzoic acid was the reference substance. Biodegradation was reported at 86% by day 28 in one part of the study summary, and as 44, 82, and 93% on days 5, 15, and 28 in the executive summary. Authors concluded the test substance was readily biodegradable (Reliability 4, not assignable). *Based on inconsistent reporting of the biodegradation rates, ToxServices considers this summary not reliable.*
    - Cocamidopropyl betaine (purity and % active not specified) was evaluated in a closed bottle test performed according to OECD 301D (GLP not specified). The test substance was exposed to activated sludge (adaptation not specified) under aerobic conditions for 30 days at an initial concentration of 5 mg/L. Biodegradation was reported at 84% by day 30, and authors concluded the test substance was readily biodegradable (no further details were provided) (Reliability 2, reliable with restrictions).
    - Cocamidopropyl betaine (purity and % active not specified) was evaluated in Modified OECD Screening test performed according to OECD 301E (GLP not specified). The test

substance was exposed to activated sludge (adaptation not specified) under aerobic conditions for 28 days at an initial concentration of 5 or 10 mg/L. Biodegradation was measured as dissolved organic carbon (DOC) removal. When tested at 5 mg/L, the test substance reached 58, 98, 92, and 100% biodegradation at days 7, 14, 21, and 28, respectively. and when tested at 10 mg/L, the test substance reached 58, 90, 85, and 100% biodegradation, respectively. Authors reported that >70% removal was reached within a 10-day window (Reliability 2, reliable with restrictions) (Also described in U.S. EPA (Undated)).

- Cocamidopropyl betaine (purity and % active not specified) was evaluated in a CO_2 evolution test performed according to OECD 301B (GLP not specified). The test substance was exposed to activated sludge (adaptation not specified) under aerobic conditions for 35 days at an initial concentration of 10 and 20 mg/L, in two replicates. Biodegradation was measured as CO_2 evolution, and as DOC removal. Biodegradation based on CO_2 evolution was reported at 71% by day 29 for replicate 1, and 57% by day 29 for replicate 2. Biodegradation based on DOC removal was reported at 88.5% by day 29 for replicate 1, and 81% by day 29 for replicate 2. Authors concluded the test substance was readily biodegradable (Reliability 4, not assignable) (Also described in U.S. EPA (Undated)).

- U.S. EPA Undated
  - After 28 days, 93% biodegradation was achieved in a test performed according to OECD Guideline 301D under GLP. The test substance was identified as "Readily biodegradable"; however, no information regarding the 10-day biodegradation window were provided (Reliability 1, reliable without restriction).
  - After 28 days, 86% biodegradation was achieved in a test performed according to OECD Guideline 301D under GLP. The test substance was identified as "Readily biodegradable"; however, no information regarding the 10-day biodegradation window were provided (Reliability 1, reliable without restriction).

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

Cocamidopropyl betaine was assigned a score of Very Low for bioaccumulation based on conclusions from authoritative bodies such as OECD, HERA and U.S. EPA that the substance is not bioaccumulative. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF or BAF values are less than 100 (CPA 2018b). The confidence in the score is reduced as all authoritative bodies above used modeling to justify the conclusion, and EPI Suite™ modeling may not be appropriate for surfactants.

- 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 2006
  - Using EPI Suite™, OECD estimated that cocamidopropyl betaine is of low bioaccumulation potential. However, OECD also noted that BCF values predicted using the software for surfactants "should be used with care". *ToxServices notes that surfactants are generally outside the applicability domain of EPI Suite™.*
- HERA 2005
  - Cocamidopropyl betaine has a calculated BCF of 71. No additional details were provided.
- U.S. EPA 2010
  - Cocamidopropyl betaine is expected to have low bioaccumulation potential based on an estimated bioaccumulation factor (BAF) of 1.2 by EPI Suite™ modeling.

Physical Hazards (Physical)

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

Cocamidopropyl betaine was assigned a score of Low for reactivity based on lack of reactive functional groups. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is 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.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of cocamidopropyl betaine. These procedures are listed in the GHS (UN 2019).
  - Based on the structure of its components or moieties, cocamidopropyl betaine 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, cocamidopropyl betaine 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

Cocamidopropyl betaine was assigned a score of Low for flammability based on a flash point >93°C, which exceeds the criteria for GHS classification as a flammable liquid. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - The flash point was 95°C when tested with in the closed-cup method at atmospheric pressure (ASTM D93).
  - The test substance is not auto-flammable based on lack of ignition when exposed to air at room temperature of 27°C at 966 hPa.

Use of New Approach Methodologies (NAMs)[9] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling using Danish QSAR and Toxtree for carcinogenicity and/or endocrine activity, several *in vitro* assays to evaluate mutagenicity and genotoxicity, *in silico* modeling via OECD QSAR Toolbox to identify structural alerts for respiratory sensitization, one *in vitro* skin irritation assay and one *in vitro* eye irritation assay. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 2020b, OECD 2020b). The expanded application of NAMs greatly amplifies the need to communicate uncertainties associated with their use. As defined by EFSA (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020b):

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

As shown in Table 4, Type I (input data) uncertainties in cocamidopropyl betaine's NAMs dataset include lack of sufficient *in vivo* data for carcinogenicity and respiratory sensitization, and the lack of GLP status of the two *in vitro* skin/eye irritation assays, which were completed before the test methods were standardized and validated by OECD. Cocamidopropyl betaine's Type II (extrapolation output) uncertainties include lack of a defined applicability domain of Toxtree and OECD Toolbox, limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, lack of consideration of non-immunological mechanisms of respiratory sensitization, and the limitations of single *in vitro* skin/eye irritation assays in definitive GHS classification. Some of cocamidopropyl betaine's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

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

Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity:** Only limited experimental data are available. VEGA tool does not evaluate ionic substances (VEGA 2020) and hence could not be used to model cocamidopropyl betaine. **Respiratory sensitization:** No experimental data or human data are available. While no structural alerts were identified, cocamidopropyl betaine is a skin sensitizer at high concentrations, and is designated as an asthmagen by AOEC. **Skin irritation:** It is not clear if the *in vitro* eye irritation study was conducted under GLP. The *in vitro* test EpiDerm™ Epi-100 assay has not been validated at the time of completion.

[9] 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).

	Eye irritation: It is not clear if the *in vitro* eye irritation study was conducted under GLP, and it does not appear to be conducted following a validated protocol at the time of completion.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity:** Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). **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[10]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[11] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[12]. **Endocrine activity:** The *in vivo* relevance of *in silico* receptor binding/activity predictions is unclear. **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. **Skin irritation:** The EpiDerm™ Epi-200 assay (validated as part of OECD Guidelines 439 and 431) can be used in combination with other *in vitro* or *in vivo* assays to classify chemicals under GHS Category 1 or 2. However, a single assay is insufficient for definitive GHS classification[13]. The relevance of the EpiDerm™ Epi-100 assay (used in this assessment) to GHS classification is unknown. **Eye irritation:** The EpiOcular™ OCL-200 test (validated as part of OECD Guideline 492) does not differentiate between GHS Category 1 and GHS Category 2A[14].

[10] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[11] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[12] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[13] https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1619460682&id=id&accname=guest&checksum=7CFF0EC6304B8D738E2B127343475952
https://www.oecd-ilibrary.org/docserver/9789264264618-en.pdf?expires=1619460971&id=id&accname=guest&checksum=1E59E2811F7C7DBB1818855ACC553703
[14] https://www.oecd-ilibrary.org/docserver/9789264242548-en.pdf?expires=1619460127&id=id&accname=guest&checksum=5BC04C0CCBABAFB736F3F001B11AF05C

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	Y	*In silico* modeling: Danish QSAR/Toxtree
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	Danish QSAR
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	Y	*In vitro* skin irritation assay using the EpiDerm™ model
Eye irritation	Y	EpiOcular™ (OCL-200) model system
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	N	
Bioaccumulation	N	

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Cocamidopropyl Betaine (CAS #61789-40-0)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	Cocamidopropyl betaine	**61789-40-0**	*L*	**L**	DG	*M*	DG	**M**	**L**	**L**	*M*	DG	*M*	*M*	*H*	*vH*	**vH**	**H**	**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	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Cocamidopropyl betaine	2

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

Table 6

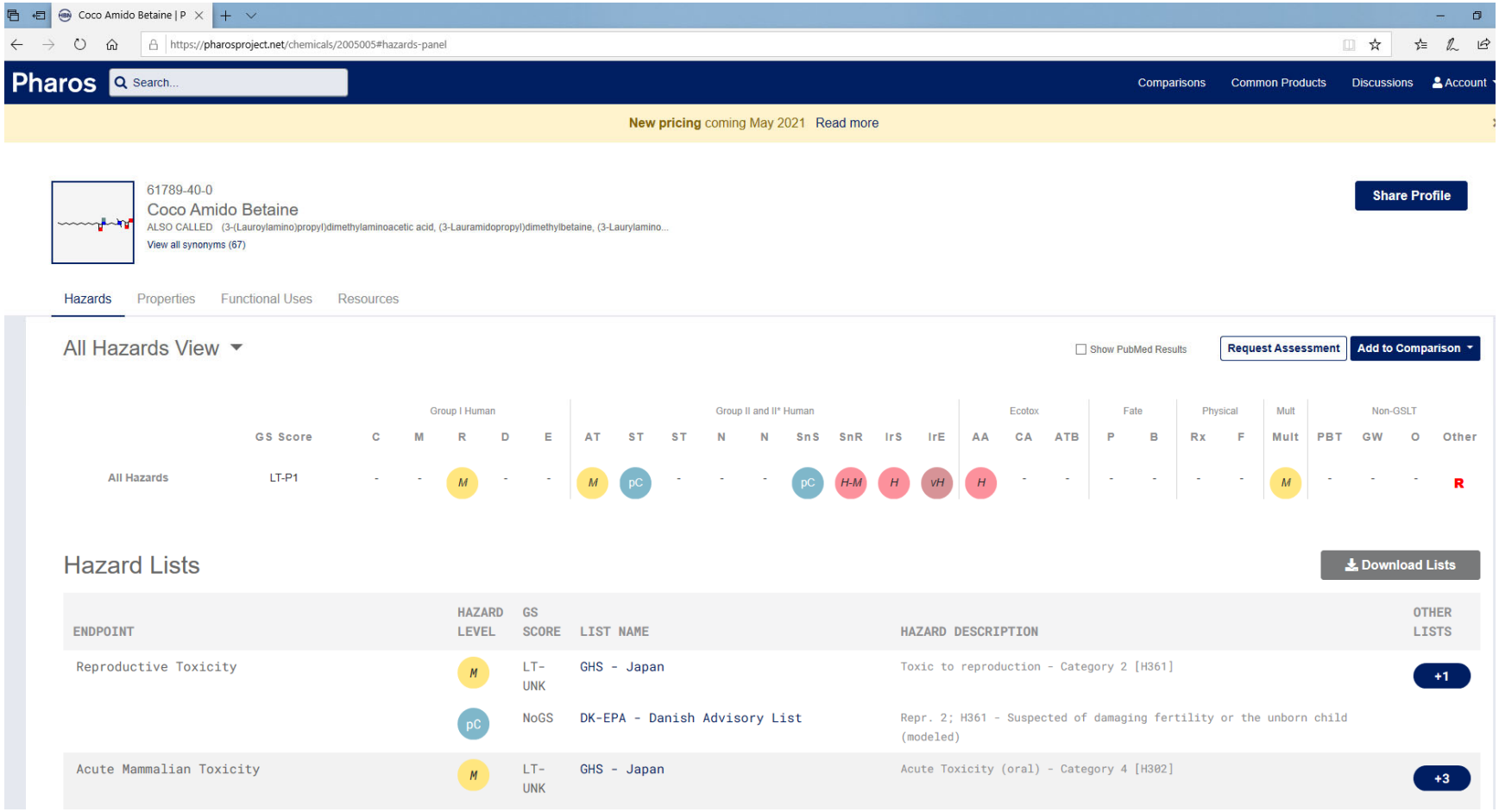
Chemical Name	Final GreenScreen® Benchmark Score
Cocamidopropyl betaine	2

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

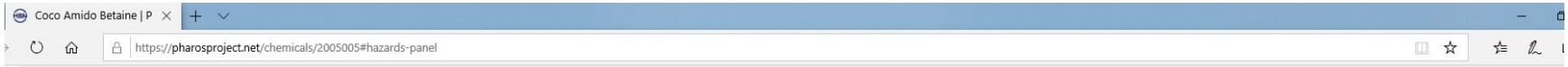
Table 5: Data Gap Assessment Table

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 Cocamidopropyl Betaine (CAS #61789-40-0)



	L	LT-UNK	GHS - New Zealand	6.1E (oral) - Acutely toxic	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H302 - Harmful if swallowed (unverified)	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H312 - Harmful in contact with skin (unverified)	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified)	
Skin Sensitization	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified)	
Respiratory Sensitization	H-M	LT-UNK	AOEC - Asthmagens	Asthmagen (Rs) - sensitizer-induced *	
Skin Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	6.3A - Irritating to the skin (Cat. 2)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Eye Irritation/Corrosivity	vH	LT-UNK	GHS - Japan	Serious eye damage / eye irritation - Category 1 [H318]	+4
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation	
	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified)	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified)	
Acute Aquatic Toxicity	H	LT-UNK	GHS - Japan	Hazardous to the aquatic environment (acute) - Category 2 [H401]	+1



	pC	NoGS	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified)
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-P1	GHS - New Zealand	9.1A (algal) - Very ecotoxic in the aquatic environment +4
	U	LT-UNK	GHS - New Zealand	9.1D (crustacean) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
	U	LT-UNK	GHS - New Zealand	9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H411 - Toxic to aquatic life with long lasting effects (unverified)
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified)
T & P and/or B [(Chronic Aquatic Toxicity and sometimes Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-P1	GHS - Japan	Hazardous to the aquatic environment (chronic) - Category 2 [H411]
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	M	LT-UNK	GHS - Japan	Specific target organs/systemic toxicity following single exposure - Category 3 [H335 or H336]
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)

Restricted Substance Lists (1)

- Credo Beauty's Restricted Substance List: Restricted Chemicals - see Credo for potential source/use restrictions ✱

Positive Lists (3)

- Cosmetic Ingredient Review (CIR): Safe with Qualifications
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients
- US EPA - DfE SCIL: Green Circle - Verified Low Concern

APPENDIX D: Danish QSAR Carcinogenicity Modeling Results

Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

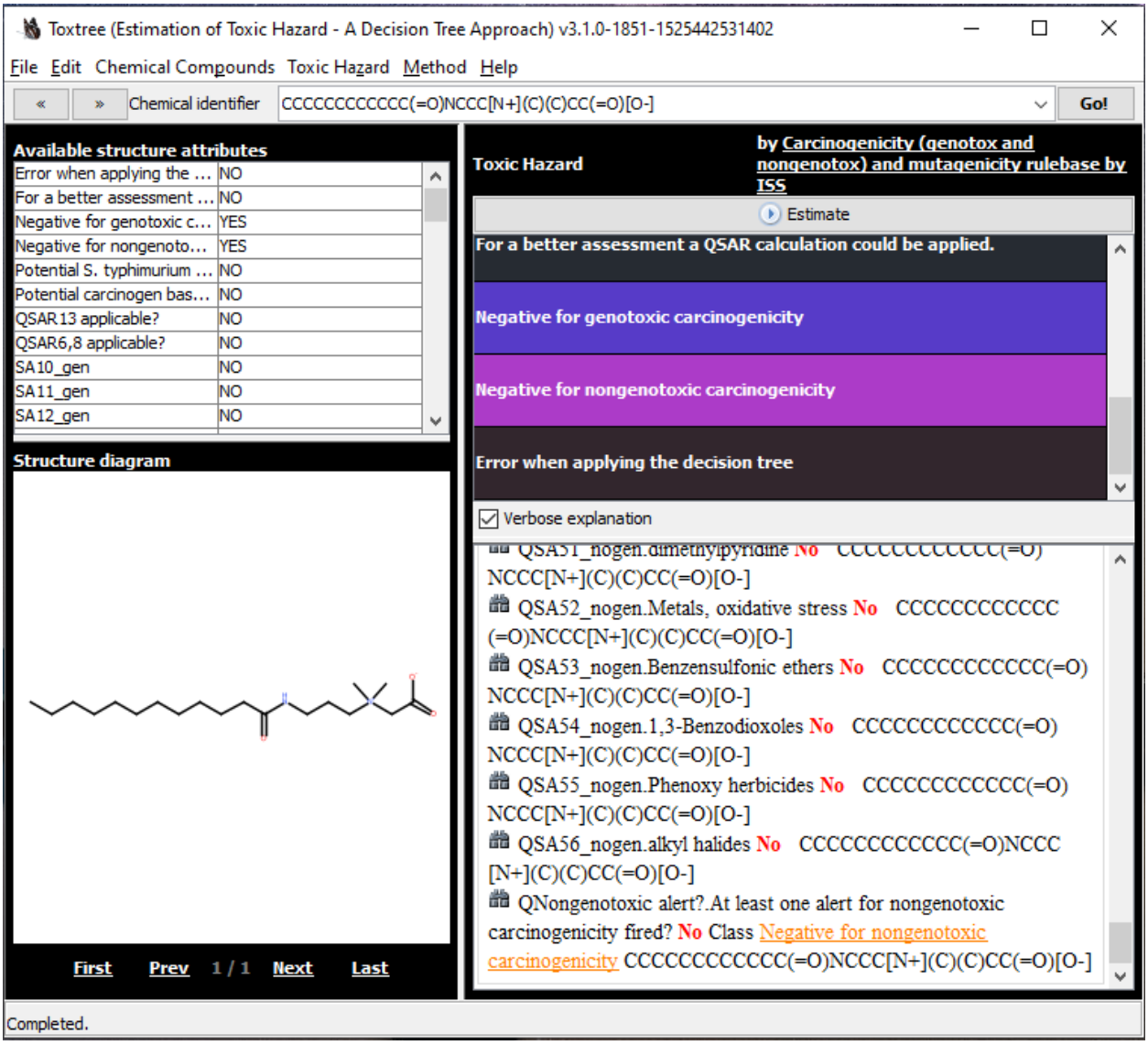
Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	(N/A)
Oncologic Primary Classification, alerts in:	
- parent only	(N/A)

OECD QSAR Toolbox v.4.2 profilers

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

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

APPENDIX E: Toxtree Carcinogenicity Results for Cocamidopropyl Betaine (CAS #61789-40-0)



APPENDIX F: Danish QSAR Endocrine Activity Modeling Results

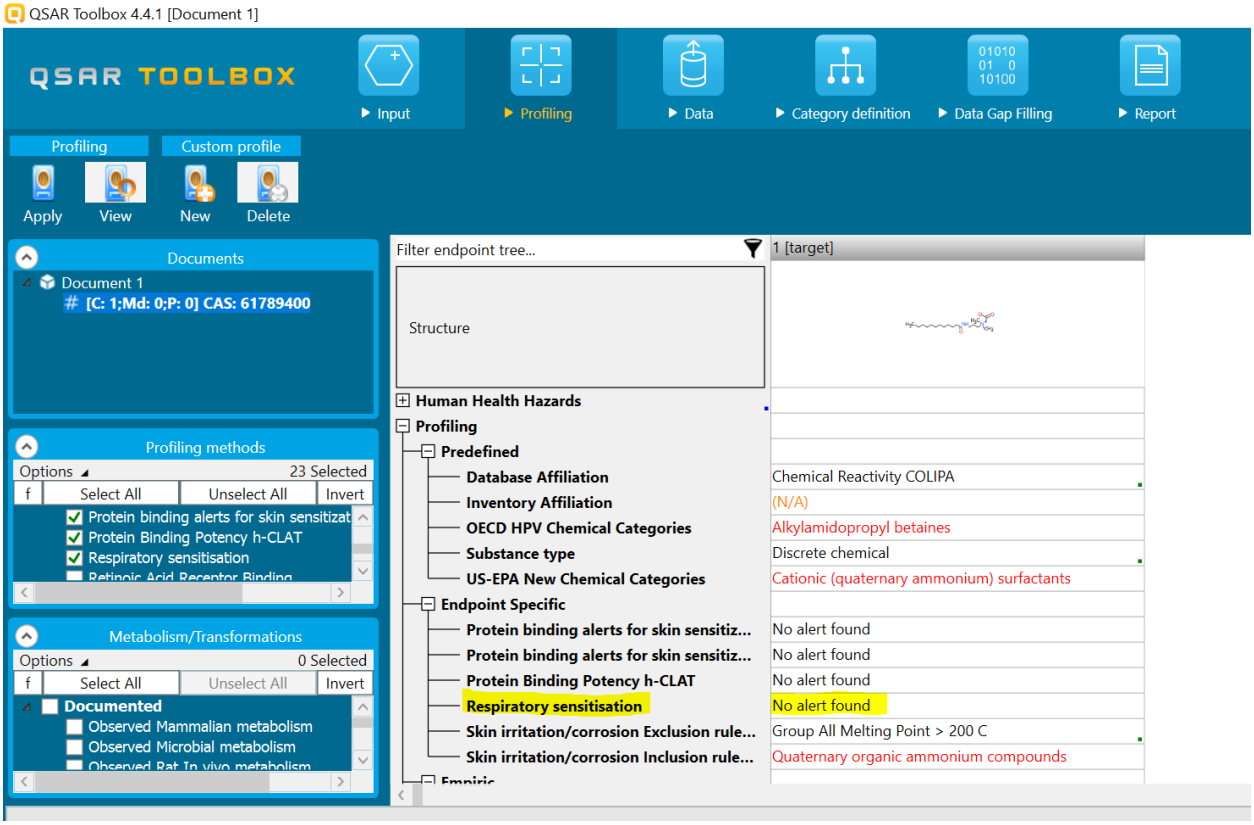
Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	INC_OUT	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			34756.8	2876.403	
- µM			159955.8	13237.62	
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			0.9099964	106.5	
- µM			4.187935	490.1286	
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation –		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Random final model (Human *in vitro*)					
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	INC_OUT	NEG_IN	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
DTU-developed models					

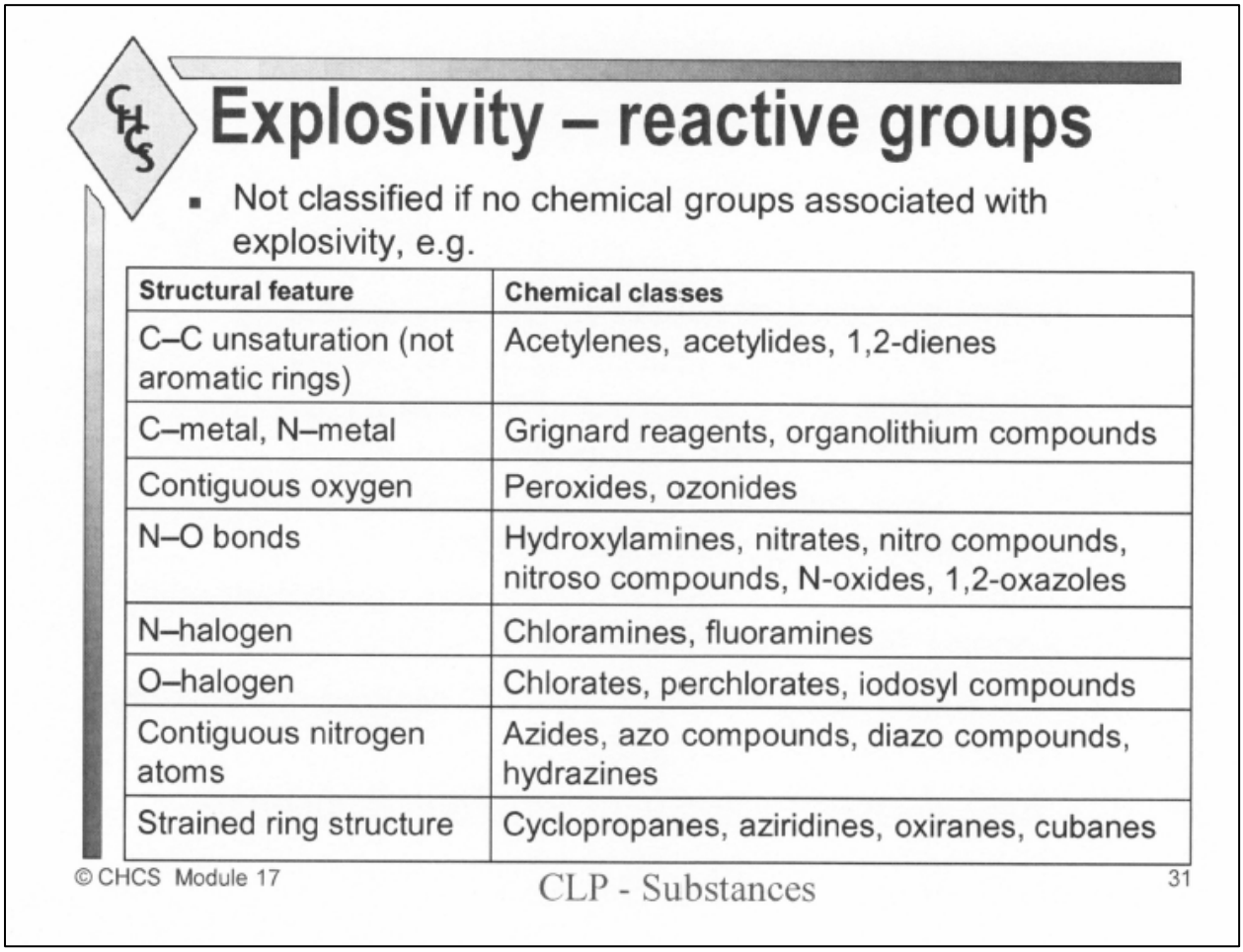
Estrogen Receptor Binding, alerts in:	
- parent only	N/A
- metabolites from *in vivo* Rat metabolism simulator only	
- metabolites from Rat liver S9 metabolism simulator only	
rtER Expert System - USEPA, alerts in:	
├ parent only	N/A
- metabolites from *in vivo* Rat metabolism simulator only	
- metabolites from Rat liver S9 metabolism simulator only	
OECD QSAR Toolbox v.4.2 profilers	
Profiler predictions are supporting information to be used together with the relevant QSAR predictions	

APPENDIX G: OECD QSAR Respiratory Sensitization Modeling Results



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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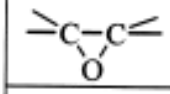
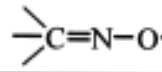
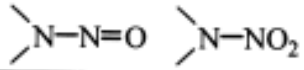
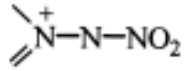
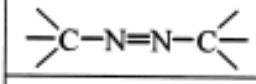
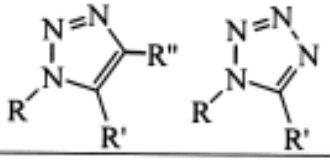
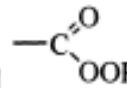
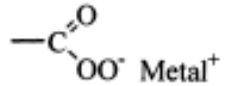
Explosivity – Full List

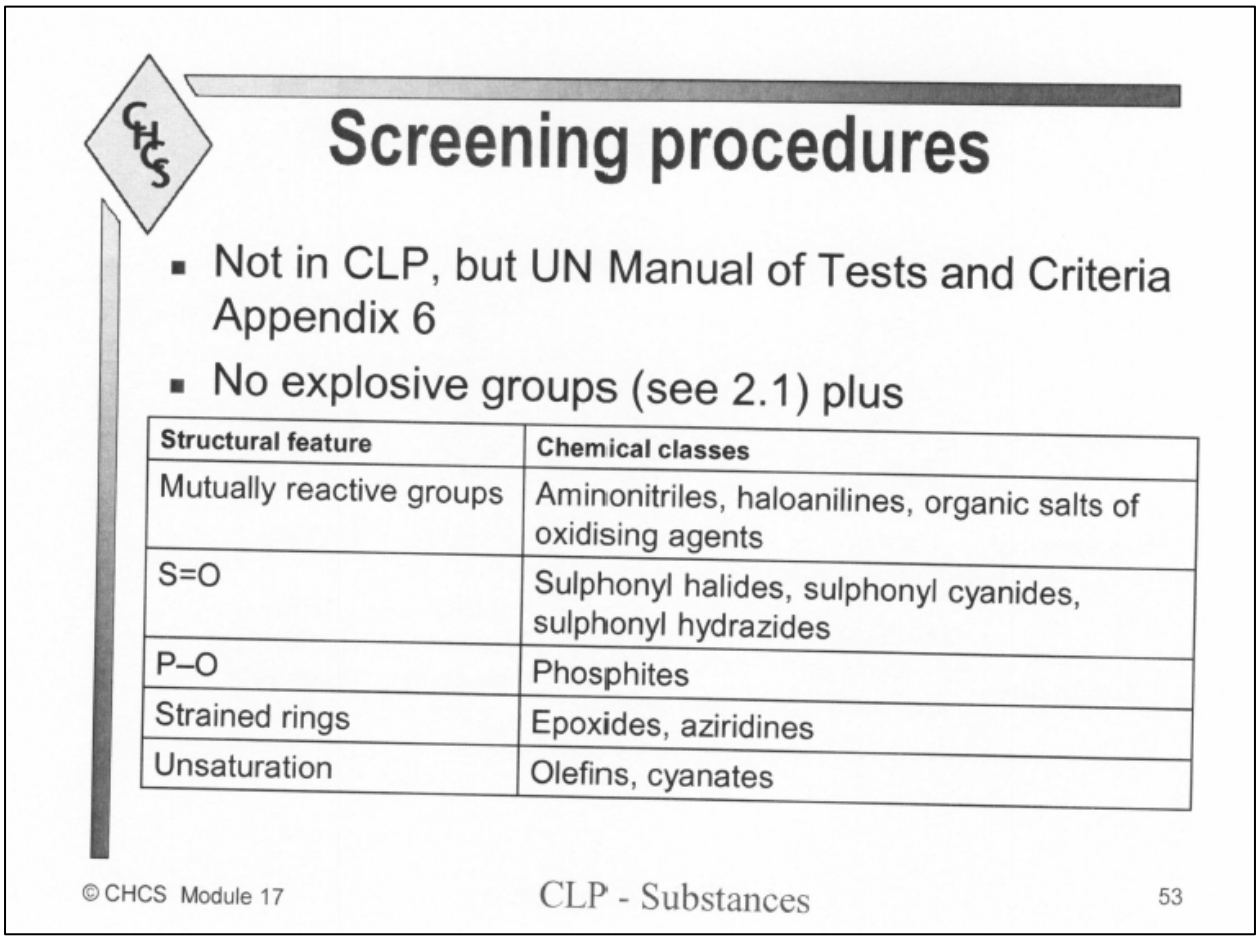
Table R.7.1-28 Chemical groups associated with explosive properties

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
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. NCl_3, $RNCl_2$	N-Halogen Compounds

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

Self-Reactive Substances



Licensed GreenScreen® Profilers

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