AMIDES, COCO, N-[3-(DIMETHYLAMINO)PROPYL],N-OXIDES / COCAMIDOPROPYLAMINE OXIDE

(CAS #68155-09-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

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Assessment Date: June 7, 2021

Expiration Date: June 7, 2026

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GreenScreen® Executive Summary for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides, commonly known as cocamidopropylamine oxide, is a tertiary amine oxide which contains fatty acids from coconut oil. It is the reaction product of coco amidopropyl dimethyl amine and aqueous hydroperoxide.

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is a solid at room temperature but is marketed as an aqueous solution with a water content of 30% or 35%. It is used mainly in cosmetic formulations as a cleansing, foam boosting, and hair conditioning agent, as a hydrotrope, and as a surfactant. Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is highly water soluble, non-reactive and non-flammable.

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard scores:

- Benchmark 2f
    - Very High Group II Human Toxicity (eye irritation-IrE)
    - Very High Ecotoxicity (acute aquatic toxicity – AA)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity and *in silico* modeling for respiratory sensitization. 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 amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide' NAMs dataset include the absence of experimental data and established test methods for respiratory sensitization. Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide' Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, and the OECD Toolbox only identifying structural alerts without defining applicability domains. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries, and ECHA's decision framework and guidance to evaluate respiratory sensitization.

GreenScreen® Hazard Summary Table for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
L	**L**	*L*	*L*	DG	**M**	*M*	**L**	**M**	**L**	**L**	*L*	*H*	**vH**	**vH**	*H*	**L**	**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 Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)

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 28, 2021; May 31, 2021

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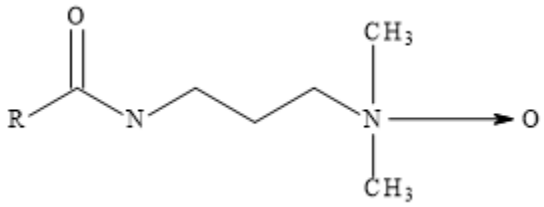
Date: April 28, 2021, June 7, 2021

Expiration Date: June 7, 2026[2]

Chemical Name: Amides, coco, N-[3-(dimethylamino)propyl],N-oxides / Cocamidopropylamine oxide

CAS Number: 68155-09-9

Chemical Structure(s): Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is a UVCB (Unknown or Variable composition, Complex reaction products or of Biological materials) substance (ECHA 2021a,b). It is produced by reacting hydrogenated coconut oil with dimethylaminopropylamine (DMAPA), which is further reacted with a food grade hydrogen peroxide (ECHA 2021a, CIR 2008). A representative structure is shown below (CIR 2008, ECHA 2021a).

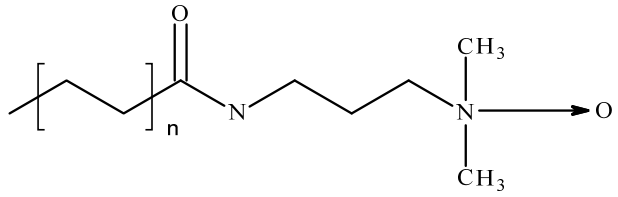


R- represents coconut oil fatty acid alkyl chains with lengths of C8-C18 (CIR 2008);
R- represents C8-C18 even numbered, and C18 unsaturated (ECHA 2021a)

Also called: Reaction product of coco amidopropyl dimethyl amine and aqueous hydroperoxide (ECHA 2021a). Coco amides, N-(3-(dimethylamino)propyl), N-oxide; N-(3-(Dimethylamino) propyl)coco amides-N-oxide; 3-(N,N-Dimethylamino)propyl cocoamido amine oxide; 3-Cocoamidopropyl dimethylamine oxide; Cocamidopropyldimethylamine oxide; Cocoamido-3-propyldimethylamine oxide; N,N-Dimethyl-N-(3-(coconut oil alkyl)amidopropyl)amine oxide; N,N-Dimethyl-N-(3-cocamidopropyl)amine oxide; N-(3-(Dimethylamino)propyl) coco amides N-oxides; N-(Cocoamidopropyl)-N,N-dimethylamine, oxide (ChemIDplus 2021).

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

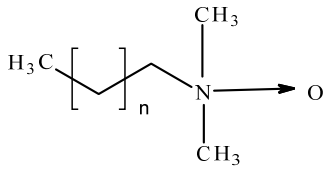
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (CAS #68155-09-9) has a relatively complete toxicological dataset. It lacks data for carcinogenicity and endocrine activity endpoints. ToxServices identified two REACH registration dossiers for the chemical name cocamidopropylamine oxide (CAS #68155-09-9), and the difference in the dossiers is the EC number of the registered substances (268-938-5, associated exclusively with CAS #68155-09-9; or 939-581-9, associated with CAS #1471314-81-4 and 68155-09-9) (ECHA 20201a,b). In both dossiers, the registered substances are UVCB substances with the same representative structure (see below) and physicochemical properties. However, the official name associated with EC #939-581-9 is 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide. This suggests that the substance associated with EC #939-581-9 has a slightly different alkyl chain composition, containing even numbered alkyl chains in the range of C12 and C18, while the substance associated with EC #268-938-5 contains alkyl chains from C8-18 (fatty acid composition of coconut oil, although European Chemicals Agency (ECHA) (2021a) suggests that the alkyl chains are also even numbered). Nevertheless, the studies described in both dossiers are mostly identical. Therefore, ToxServices considered the substance associated with EC #939-581-9 a strong surrogate. When the studies are different from the two dossiers, ToxServices described them separately in this assessment.



n = 5 - 8

Representative structure for 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide (CAS #1471314-81-4/68155-09-9, EC #939-581-9) (ECHA 20201b)

The REACH dossier for 3-C12-18-(even numbered)-alkylamido-N,N-dimethylpropan-1-amino oxide (EC #939-581-9) identified amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS #308062-28-4) as a read-across chemical for the chronic aquatic toxicity endpoint. ToxServices also used this chemical as a surrogate for the carcinogenicity endpoint. Both the surrogate and the target chemical are surfactants containing a dimethylamine oxide group linked to C10 to C18 linear alkyl chains (even numbered). They have similar physicochemical properties (low vapor pressure and high solubility in water). The surrogate, however, lacks an amide group and a propyl chain. Accordingly, ToxServices considered the substance a weak surrogate. As a result, scores based exclusively on analog data are reported with low confidence.



n = 10 or 12

Surrogate: amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS #308062-28-4) (representative structure, ECHA 2021c)

Identify Applications/Functional Uses: (Pharos 2021, CIR 2008)
1. Cleansing agent
2. Foaming boosting agent
3. Surfactant
4. Hair conditioning agent
5. Hydrotrope

Known Impurities[3]:
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide may contain the following impurities: free amidoamine at ≤ 3,000 ppm and free DMAPA at ≤ 5 ppm. Commercial products made with amine oxides may contain "unreacted amine and various other products originating from different stages of synthesis" (CIR 2008). These impurities are not specifically/separately assessed in this screen.

GreenScreen® Summary Rating for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide[4,5 6,7]: Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard scores:

- Benchmark 2f
  - Very High Group II Human Toxicity (eye irritation-IrE)
  - Very High Ecotoxicity (acute aquatic toxicity – AA)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide

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

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

repeated exposures. Group II* Human Health endpoints are indicated by an * after the name of the hazard endpoint or after "repeat" for repeated exposure sub-endpoints. Please see Appendix A for a glossary of hazard acronyms.

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is rapidly biodegradable (see persistence section below), and therefore it is not expected to have relevant transformation products.

Introduction

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is a tertiary amine oxide which is derived from fatty acids from coconut oil. It is the reaction product of coco amidopropyl dimethyl amine and aqueous hydroperoxide (CIR 2008). Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is used mainly in cosmetic formulations as a cleansing, foam boosting, and hair conditioning agent, as a hydrotrope, and as a surfactant (CIR 2008).

ToxServices assessed amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide 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 (SCIL)

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is listed on the SCIL as an acceptable surfactant with a full green circle.

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 amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide can be found in Appendix C.

- Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is not listed on the U.S. DOT list.
- Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is on the following list for multiple endpoints.

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

    - German FEA - Substances Hazardous to Waters - Class 2 - Hazard to Waters.
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is associated with several Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements as shown in Table 1, identified by the authors of its REACH registration dossiers (ECHA 2021a,b). General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9) (ECHA2021a,b, Pharos 2021)

H Statement	H Statement Details
H318	Causes serious eye damage
H315	Causes skin irritation.
H302	Harmful if swallowed.
H400	Very toxic to aquatic life
H412	Harmful to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear respiratory protection if ventilation is inadequate. Wear suitable chemical resistant safety gloves such as nitrile rubber gloves. Wear safety glasses with side-shields.	ECHA 2021a,b	None identified.	N/A

Physicochemical Properties of Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is a white solid at room temperature and is generally marketed as aqueous formulations (water content 30 or 35%). Its measured vapor pressure of 0.034 mmHg and 0.45 mmHg indicate that some of its lighter components may form a vapor under standard conditions. Inhalation exposure to dust or aerosol particles is also possible. The calculated log K_{ow} value of 1.27 indicates that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is more soluble in the organic fraction than in water.

Table 3: Physical and Chemical Properties of Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)

Property	Value	Reference
Molecular formula	$RCONH(CH_2)_3N(CH_3)_2O$ where R CO = C8-C18, even numbered, C18 unsaturated (representative structure)	ECHA 2021a,b

Table 3: Physical and Chemical Properties of Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)		
Property	**Value**	**Reference**
SMILES Notation	CCCCCCCCCCCC(=O)NCCCN(O)(C)C (for R = C11, representative structure)	U.S. EPA 2017
Molecular weight	Approximately 240 g/mol	ECHA 2021a,b
Physical state	Solid	ECHA 2021a,b
Appearance	White	ECHA 2021a,b
Melting point	14°C - 87°C 84.9 - 96.4°C (EU Method A.1)	ECHA 2021a ECHA 2021b
Boiling point	126.5 - 151°C (decomposition) (EU Method A.2)	ECHA 2021a,b
Vapor pressure	≤ 4.5 hPa (equivalent to 0.034 mm Hg) at 20°C (EU Method A.4) 60 Pa (equivalent to 0.45 mm Hg) at 20°C (EU Method A.4)	ECHA 2021a ECHA 2021b
Water solubility	430 g/L (OECD Guideline 105) 1.05 g/L (estimated using the critical micelles concentration (CMC) approach, EU Method A.6	ECHA 2021a ECHA 2021b
Dissociation constant	No data identified	
Density/specific gravity	0.908 - 1.045 at 20°C (OECD Guideline 109, relative density)	ECHA 2021a,b
Partition coefficient	Log K_{ow} = 2.11 at 23°C and pH >= 7.1 - <= 7.2 (OECD Guideline 107) Log K_{ow} = 1.27 at 20°C (calculated from the solubilities of the test substance in water and 1-octanol)	ECHA 2021a ECHA 2021b

Toxicokinetics

No experimental toxicokinetic data are available for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide. Authors of its REACH registration dossiers made predictions using information on its physicochemical properties.

- Absorption
  - ECHA 2021a,b
    - *Oral*: Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is expected to be highly absorbed following oral exposure. It is assumed to be easily soluble in gastrointestinal (GI) fluids and favorable for absorption by passive diffusion. In addition, absorption may be enhanced because of damage to cell membranes as the test substance is a surfactant. Absorption in the stomach is not considered likely and it is assumed that most of the test substance is absorbed in the intestine. Based on data from acute and repeated dose toxicity studies, signs of toxicity (clinical signs and death) indicating that it is

orally bioavailable. As no measured absorption fraction is available, an oral bioavailability fraction of 100% is assumed.

- *Inhalation*: Based on the vapor pressure of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide, it is not expected to be significantly volatile. However, finely divided powder or dust may enter the respiratory tract. Therefore, absorption by inhalation is expected. However, the extent of the inhalation uptake is expected to be limited by the rate at which it dissolves into aqueous fluids (mucus) and then partitions into blood. In addition, it is likely to be swallowed with the mucus or may pass across the respiratory epithelium via aqueous membrane pores. No data experimental animal data, epidemiological data or human accidental exposure data are available. As no measured absorption fraction is available, an inhalation bioavailability fraction of 100% is assumed.
- *Dermal*: The water solubility, surface tension, and the log K_{ow} value for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide suggest some dermal absorption potential. In addition, the low vapor pressure would also favor dermal absorption. The test substance is assumed to have a dermal absorption fraction of 40%.

- Distribution
  - ECHA 2021a,b
    - Based on the results from the *in vivo* toxicity studies along with its relatively high water solubility, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is expected to distribute throughout the body as effects were observed in various organs, such as liver and kidney. In addition, the log K_{ow} value, the molecular weight and the water solubility of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide indicate potential for distribution into cells. With the log K_{ow} value < 4, it is assumed that the test substance has no accumulation potential.
- Metabolism
  - ECHA 2021a,b
    - The chemical structure of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is similar to that of coconut oil with the presence of unsaturated hydrogen bonds which may undergo electrophilic addition and be transformed into an alcohol. The reactive N-oxide group in amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is expected to be metabolized ultimately to an aldehyde via numerous metabolic steps (enzymatic transformation by liver microsomal cytochrome P-450, reduction to $-N(CH_3)_2$ (tertiary amine), followed by three-step oxidation). The resulting aldehyde may interact directly with proteins. Protein interaction is assumed to arise at higher concentrations of the test substance or after long term exposure since the transformation to aldehyde requires numerous metabolic steps. The amide group maybe hydrolyzed by amidohydrolases and transform into primary amines and a carboxylic acid group.
- Excretion
  - ECHA 2021a,b
    - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is expected to be mainly excreted via urine based on its low molecular weight

(< 300 g/mol), good water solubility, and ionization of the molecule at the pH of urine. In addition, exfoliation is also likely to occur.

- In summary, oral absorption of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is assumed to be highly likely as well as absorption by inhalation when the test substance is present as a finely divided powder or dust. Assumed absorption for the dermal route is 40%. Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide is expected to distribute throughout the body, and be metabolized to aldehydes that interact with proteins, to primary amines, and to carboxylic acids. The main excretion pathway is expected to be via urine.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for carcinogenicity based on negative results in two carcinogenicity studies performed with a surrogate. 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 it is based on experimental data on a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021c
  - *Oral: Surrogate: Amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS #308062-28-4):* In a GLP-compliant carcinogenicity study similar to OECD Guideline 451, Charles River CD rats (60/sex/dose) were administered the test substance (purity not reported) in the diet at doses of 0.01, 0.1, and 0.2% for two years. No neoplastic or non-neoplastic treatment related effects were identified. There was no evidence of carcinogenicity at any dose and authors identified a NOAEL of 0.2% for systemic toxicity effects, which is equivalent to 90 mg/kg/day for the pure test substance. The chemical was concluded to be non-carcinogenic in this study (Klimisch 1, reliable without restriction).
  - *Dermal: Surrogate: Amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS #308062-28-4):* In a non-GLP carcinogenicity study similar to OECD Guideline 451, ICR Swiss mice (74/sex/dose) received dermal applications of 0.1 ml of an aqueous solution of the test substance at 0.05%, 0.13%, and 0.26% (active ingredient) on the dorsal skin, 3 times/week, for 2 years. No skin carcinogenicity was observed in the study. The NOEL for dermal carcinogenicity was determined to be the highest dose of 0.26%, which is equivalent to 3.98 mg/kg/day as calculated by the study authors (Klimisch 2, reliable with restrictions).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* assays for mutagenicity and clastogenicity. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both gene mutation and chromosomal aberration, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data of good quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2008, ECHA 2021a,b
  - *In vitro:* Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471. *Salmonella typhimurium* tester strains TA 1535, TA 1537, TA 98 and TA 100, and *Escherichia coli* WP_2 *uvr* A were exposed to amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (purity reported as 79% in ECHA 2021a,b and as 81% in CIR 2008) at concentrations up to 5,000 µg/plate with and without metabolic activation. Cytotoxicity was seen at 200 and 500 µg/plate without and with metabolic activation, respectively. No increase in the mutation frequency was observed in the presence or absence of metabolic activation. The vehicle and positive controls were valid (Klimisch 1, reliable without restriction).
  - *In vitro:* Negative results for clastogenicity were obtained in a GLP-compliant chromosome aberration test conducted according to OECD Guideline 473. Human lymphocytes were exposed to the test material (purity reported as 79% in ECHA 2021a,b and as 81% in CIR 2008) at concentrations ranging from 9.77 to 312.5 µg/mL, with and without metabolic activation. No increase in the frequency of chromosome aberrations was observed with treatment in the presence or absence of metabolic activation. The vehicle, untreated negative and positive controls were valid (Klimisch 1, reliable without restriction).
- ECHA 2021a,b
  - *In vitro*: Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (30% purity) was negative for mutagenicity in a GLP-compliant *in vitro* mammalian cell mutagenicity assay that was conducted according to OECD Guideline 476. Mouse lymphoma L5178Y cells were exposed to the test material at 1.25-75 µg/ml, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation. The vehicle and positive controls were valid (Klimisch 1, reliable without restriction).

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for reproductive toxicity based on a lack of reproductive toxicity in a reproduction/developmental toxicity screening test in rats. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on data from a reproduction toxicity screening test that may not have examined all relevant endpoints.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a,b
  - *Oral*: In a GLP-compliant reproduction/developmental toxicity screening test conducted according to OECD Guideline 421, male and female Wistar rats (10/sex/dose) were administered amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (31.8% purity) in water daily by gavage at doses of 15, 40, or 100 mg/kg/day active ingredient. Male rats were exposed for 42 days and toxicity phase females were exposed for 42-47 days. The parental animals were evaluated for clinical signs of toxicity, body weight, food consumption, testes and epididymis weights, ovarian and uterine content, reproductive

indices (gestation length and fertility indices), gross pathology, and histopathology. Offspring were evaluated for survival, mean litter size, sex ratio, body weight, and external and internal abnormalities. There were no treatment related effects on any of the reproductive parameters measured. Authors assigned a NOAEL of 100 mg/kg/day for reproductive toxicity, which was the highest dose tested (Klimisch 1, reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for developmental toxicity based on the absence of adverse developmental effects in a reproduction/developmental toxicity screening test in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on data from a developmental toxicity screening test that may not have examined all relevant endpoints.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a,b
  - *Oral*: In the previously described GLP-compliant reproduction/developmental toxicity screening test conducted according to OECD Guideline 421, male and female Wistar rats (10/sex/dose) were administered amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (31.8% purity) in water daily by gavage at doses of 15, 40, or 100 mg/kg/day active ingredient. Male rats were exposed for 42 days and toxicity phase females were exposed for 42-47 days. There were no treatment-related effects on number of live and dead pups, sex ratio, body weight, or external macroscopic examination. Authors assigned a NOAEL of 100 mg/kg/day for developmental toxicity, which was the highest dose tested (Klimisch 1, reliable without restriction).

Endocrine Activity (E) Score (H, M, or L): DG
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Data Gap for endocrine activity due to lack of data for this endpoint.

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

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>
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
Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Moderate for acute toxicity based on oral LD_{50} values of > 500 to 1,000 mg/kg in male/female rats. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when the most conservative oral LD_{50} values are >300 – 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS - New Zealand - 6.1E (oral) - Acutely toxic
- CIR 2008, ECHA 2021a,b
  - *Oral*: LD_{50} = 500 - 1,000 mg/kg for active ingredient amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide in female Sprague-Dawley rats (OECD Guideline 423 and GLP-compliant) (Klimisch 1, reliable without restriction). In the CIR 2008, the oral LD_{50} was reported to be between 178 and 1,772 mg/kg of active ingredient amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide for the same study.
  - *Dermal*: LD_{50} > 2,000 mg/kg for active ingredient amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide in male/female Sprague-Dawley rats (purity 81%, OECD Guideline 402 and GLP-compliant) (Klimisch 1, reliable without restriction).
- ECHA 2021b
  - *Oral*: LD_{50} = 2,184 mg/kg active ingredient in male/female rat (purity 35%, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions).
  - *Oral*: LD_{50} = > 1,750 mg/kg in male rats and < 1,750 mg/kg in female rats for active ingredient (purity 35%, similar OECD Guideline 401) (Klimisch 2, reliable with restrictions).
  - *Oral*: LD_{50} = 1,500 and 2,250 mg/kg active ingredient in male rats (purity 30%, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Moderate was assigned. The majority of the reported oral LD_{50} values from high quality studies for the active ingredient amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide are within the GreenScreen® Guidance values for a Moderate score (>300 – 2,000 mg/kg). The CIR panel reported the oral LD_{50} value to be between 178 and 1,772 mg/kg from the same study described in the REACH dossiers. The lower value (178 mg/kg) is within the GreenScreen® Guidance values for a High score (> 50 to 300 mg/kg). However, there were no deaths noted at a dose level of 178 mg/kg; the dose was reported to be 218 mg/kg in REACH dossiers. Therefore, the LD_{50}, which is the dose of the chemical that causes the death of 50% in the treated groups, is unlikely to be 178 mg/kg. Accordingly, ToxServices relied on the oral LD_{50} values of > 500 to 1,000 mg/kg reported by the REACH dossiers and assigned a score of Moderate.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Moderate for single dose systemic toxicity/organ effects based on signs of respiratory irritation after a single oral exposure, classifying it to GHS Category 3 (respiratory irritant). GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified as GHS Category 3 specific target organ toxicants following single exposures for respiratory tract irritation (CPA 2018b). The confidence in the score is reduced as it is based on effects observed in an oral study and no acute inhalation studies are available.

- 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 2008, ECHA 2021a,b
    - *Oral:* In a GLP-compliant acute oral toxicity assay conducted according to OECD Guideline 423, Sprague-Dawley rats (3 females in high dose and 3/sex/low dose) received single doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (92% purity) in water at 218 and 2,174 mg/kg via gavage, equivalent to 200 and 2,000 mg/kg for active ingredient as calculated by the authors of REACH dossiers. The CIR panel calculated the values as 178 and 1,772 mg/kg for the active substance based on 81% purity of the test substance[9]. *ToxServices compared the study records from different sources and concluded that the actual purity of the test substance is 92%*[10]. Animals were observed for 14 days post dosing. Two females at the high dose (2,000 mg/kg) were found dead one or two days after dosing. In addition, treated females at the high dose exhibited clinical signs of toxicity such as hunched posture, diarrhea and increased salivation with incidents of pallor of the extremities, emaciation, lethargy, pilo-erection, decreased respiratory rate, labored respiration, red/brown staining around snout and tiptoe gait. These signs disappeared in the surviving female five days after dosing. Necropsy results of animals that died during the study (treated with 2,000 mg/kg) were hemorrhagic lungs, dark liver, dark kidneys, hemorrhagic gastric mucosa, sloughing and/or hemorrhage of the non-glandular epithelium of the stomach and hemorrhagic small and large intestines. Gross pathologic examination of the animals survived showed no abnormal findings and weight gain was normal in all animals. No deaths or clinical signs of toxicity were seen in animals treated with 200 mg/kg. They appeared normal throughout the study. The authors of REACH dossier identified an oral LD_{50} of ≥ 500 – 1,000 mg/kg in females for active amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (Klimisch 1, reliable without restriction). *Based on signs of respiratory irritation (labored breathing and decreased respiratory rate) which might result from accidental inhalation/aspiration of the test substance during dosing, and the high irritation properties of the test substance (see details in skin and eye irritation sections below), ToxServices classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide as a Category 3 specific target organ toxicant following single exposure for respiratory irritation under GHS criteria (UN 2019). ToxServices did not use the gross pathological findings to classify for systemic toxicity single dose, as these were not seen in surviving animals.*
    - *Dermal:* In a GLP-compliant dermal acute toxicity study conducted according to OECD Guideline 402, Sprague-Dawley rats (5/sex/dose) were administered amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (92% purity) dermally at a single dose of 2,174 mg/kg onto clipped intact for 24 hours under semi-occlusive condition. Animals were observed for 14 days post dosing. One female died. No other mortalities or clinical signs of toxicity occurred during the study. Body weight development was normal, and there were no treatment related gross pathology abnormalities. Authors identified a dermal LD_{50} of > 2,174 mg/kg, equivalent to 2,000 mg/kg active amides, coco, N-[3-

[9] Dose of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide = (Dose of the test material in the study * purity of the test material) / 100 = (2,174 * 81%) / 100% = 1,760 mg/kg.

[10] Both REACH dossiers provided specific details on test material used for the study unlike CIR. According to the dossiers, the test substance has a batch number of 876 TK, is a white off paste and its purity was reported in one dossier (ECHA 20201a) as approximately of 81% while in the other dossier as 92% (ECHA 2021b). The calculated doses for the active ingredient in this study as well as in other *in vivo* studies were the same in both dossiers indicating that the actual purity of the test substance is 92%. In the acute dermal toxicity study reported in one of the REACH dossiers (ECHA 2021a), the purity for the test substance with batch number of 876 TK was reported as approximately of 81% with a specific value of 92%. This supports that the actual purity of the test substance is 92%.

(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (Klimisch 1, reliable without restriction).

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for systemic toxicity (repeated dose) based on an oral LOAEL of 150 mg/kg/day established from a 90-day study supported with an estimated effective dose (ED) value of 126.66 mg/kg/day, which may be treated as a NOAEL. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate negative data are available and they are not GHS classified based on animal studies identifying oral LOAEL values > 100 mg/kg/day in 90-day studies (CPA 2018b). The confidence in the score is high as it is based on measured data of good quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2008, ECHA 2021a,b
  - *Oral*: In a GLP-compliant short term repeated dose toxicity study conducted according to OECD Guideline 407, Sprague-Dawley rats (5/sex/dose) were administered oral doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (92 % purity) in water at 15, 150, or 1,000 mg/kg/day active ingredient via gavage for 28 days. The animals were evaluated for clinical signs of toxicity, food and water consumption, body weight gain, hematology, clinical chemistry, organ weight, gross pathology, and histopathology. Animals at the high dose exhibited clinical signs of toxicity such as hunched posture and sensory reactivity. In addition, reduced food consumption, increase of water consumption and reduced bodyweight gain were measured in treated animals at this dose (1,000 mg/kg/day). Further, treatment caused significant effects in clinical chemistry and hematological parameters in animals at dose levels of 1,000 and 150 mg/kg/day. These included elevations in plasma aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), bilirubin (only at 1,000 mg/kg/day), significant elevation in neutrophil numbers, and slightly elevated prothrombin time. Both groups also had a statistically significant increase in spleen weight and treatment-related microscopic changes in liver (centrilobular hepatocyte enlargement and hepatic pigment (probably hemosiderin) accumulation), spleen (extramedullary hemopoiesis and pigment accumulation), kidneys (pigment (probably hemosiderin) accumulation in the tubular epithelium), urinary bladder (transitional cell epithelial lining hyperplasia, high dose only) and stomach (acanthosis, hyperkeratosis, subepithelial inflammatory cell infiltrates, high dose only). Based on these effects (unspecified), authors assigned the no observed effect level (NOEL) of 15 mg/kg/day for systemic toxicity and classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide to GHS Category 2 (Klimisch 1, reliable without restriction). *The GHS guideline values of 10 and 100 mg/kg/day are multiplied by 3 to 30 and 300 mg/kg/day to account for the 28-day exposure period instead of the 90-day duration. The LOAEL of 150 mg/kg/day is within the duration adjusted GHS value for Category 2 and therefore amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is classified to GHS Category 2. However, the NOEL of 15 mg/kg/day is below the cut off value of 30 mg/kg/day indicating that the possibility cannot be ruled out that the compound is classified to GHS Category 1. As no data were available at the 30 mg/kg/day,*

the confidence in the GHS Category 2 classification for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is low.

- ECHA 2021b
    - *Oral*: In a GLP-compliant subchronic repeated dose toxicity study conducted according to OECD Guideline 408, Sprague-Dawley rats (10/sex/dose) were administered oral doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35.6% purity) in water at 50, 150, or 500 mg/kg/day active ingredient via gavage for 90 days. The animals were evaluated for clinical signs of toxicity, food and water consumption, body weight gain, hematology, clinical chemistry, organ weight, gross pathology, and histopathology. Treatment caused death in one male at the high dose (500 mg/kg/day). In addition, treated animals at this dose exhibited clinical signs of toxicity such as salivation, staining around the mouth and noisy breathing. This was attributed to irritating property of the test material and taste aversion. Changes in the hematology parameters were measured at the high dose and included a decrease in red cell mass showing regeneration with borderline magnitude (between 7% and 19%) to be considered adverse, and a decrease in red blood cell mass of more than 30% which was considered adverse. Microscopic examination of animals at the high dose revealed adverse findings in the (fore)stomach (squamous cell hyperplasia) and urinary bladder (transitional cell hyperplasia) which was considered a result of the irritating properties of the test article. Forestomach squamous cell hyperplasia was also noted in a single male at 150 mg/kg/day and as this finding matched those recorded at 500 mg/kg/day, it was considered adverse. There were no treatment related adverse effects at 50 mg/kg/day. Minor changes in the red blood cell parameters were measured in males at this dose but as the magnitude of change was much lower than animals treated at 500 mg/kg/day, study authors considered them treatment-related but not adverse. Based on the changes in the (fore)stomach, urinary bladder and red blood cell parameters at 500 mg/kg/day and the changes in the (fore)stomach at 150 mg/kg/day, study authors assigned a NOAEL of 50 mg/kg/day for systemic toxicity (Klimisch 1, reliable without restriction). *The LOAEL of 150 mg/kg/day is above the GHS Guidance cut-off value of 100 mg/kg/day for Category 2. Therefore, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not classified per GHS. However, the NOAEL of 50 mg/kg/day is within the guidance values of 10 to 100 mg/kg/day for Category 2 indicating that the possibility cannot be ruled out that the compound is classified to GHS Category 2.*
- Based on the weight of evidence from the above studies, authors of the REACH dossier did not classify amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide for systemic toxicity repeated dose per EU-GHS. Two reliable studies are available for this endpoint: a 28-day oral repeated dose toxicity study and a 90-day oral repeated dose toxicity study. Although the 28-day repeated oral dose toxicity study leads to GHS Category 2 classification, this study is less robust compared to the 90-day repeated oral dose toxicity study as the duration of exposure is shorter and fewer animals are used per group. In addition, the spacing between doses in the 28-day study of 10-fold (compared to 2-3 fold in the 90-day study) also increases the uncertainty about the derived NO(A)EL. Therefore, the oral 90-day NOAEL value is considered more reliable than the 28-day NOEL value and ToxServices selected the 90-day repeated oral dose toxicity study as the key study for the GSH classification. According to the authors, the lowest dose at which significant/severe effects are observed in the 90-day repeated dose study was 150 mg/kg/day (LOAEL); which is above the GHS Guidance cut-off value of 100 mg/kg/day for Category 2 in a 90-day study. But the NOAEL of 50 mg/kg/day is below the Guidance value. Therefore, the first dose at which significant/serious adverse effects are observed (Effective Dose, ED) should be derived by interpolation, as recommended in the EU-GHS Guidance. On the basis of the observed

results and the interpolation, authors of REACH dossier estimated the ED to be 126.66 mg/kg/day, which is above the GHS Guidance cut-off value of 100 mg/kg/day for Category 2 for a 90-day study. Thus, and according to the criteria of the GHS (including EU-GHS), the substance does not need to be classified for systemic toxicity repeated dose. In addition, the changes observed in the stomach can be considered as an adaptive response to the repeated gavage with a corrosive substance.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Moderate for neurotoxicity (single dose) based on transient narcotic effects seen in acute oral toxicity studies classifying it to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified to GHS Category 3 for narcotic effects (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2008, ECHA 2021a,b
  - *Oral:* In the previously described GLP-compliant acute oral toxicity assay conducted according to OECD Guideline 423, Sprague-Dawley rats (3 females in high dose and 3/sex/low dose) received single doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (92% purity) in water at 218 and 2,174 mg/kg via gavage, equivalent to 200 and 2,000 mg/kg for active test substance as calculated by the authors of REACH dossiers. Animals were observed for 14 days post dosing. Two females at the high dose (2,000 mg/kg) were found dead one or two days after dosing. Clinical signs of neurotoxicity were observed in both the animals found dead and the surviving animals and these included hunched posture, lethargy and pilo-erection. Recovery from these symptoms in the surviving animals occurred 5 days after dosing (Klimisch 1, reliable without restriction). *These observations of reversible lethargy are consistent with transient narcotic effects that warrant a GHS Category 3 classification. Accordingly, ToxServices classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide as GHS Category 3 for narcotic effects.*
- ECHA 2021b
  - *Oral:* In an acute oral toxicity assay similar to OECD Guideline 401, male and female Wistar rats (5/sex/dose) received single doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35% purity) at dosage levels of 3.98, 5.00, 6.30 and 7.94 ml/kg via gavage. Animals were observed for 14 days post dosing. Mortalities were observed in animals from 5.00 mL/kg dose groups and above. All animals at all levels exhibited clinical signs of neurotoxicity such as decreased motor activity, coordination disturbance, abnormal body posture, abnormal gait, and piloerection beginning approximately 20 minutes after dosing. Further, at the two highest dose levels animals showed decreased grip- and limb tone. These symptoms partly persisted for 24 hours and disappeared after 48 hours (Klimisch 2, reliable with restrictions). *These observations are also consistent with transient narcotic effects that warrant a GHS Category 3 classification. Accordingly, ToxServices classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide as GHS Category 3 for narcotic effects.*

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of effects on neurological endpoints in a 90-day oral repeated dose toxicity study at doses up to 500 mg/kg/day, greater than the GHS Guidance value for classification. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate negative data are available and they are not GHS classified based on a lack of effects on neurological endpoints at the guidance value of 100 mg/kg/day for a 90-day oral study (CPA 2018b). Although the NOAEL from the 28-day study is below the duration adjusted GHS Category 2 cut-off value, the more robust 90-day study provided sufficient information to conclude that adverse effects do not occur at the GHS Category 2 threshold. Therefore, the confidence in the score is high as it is based on the more robust study (90-day) of good quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2008, ECHA 2021a,b
  - *Oral*: In the previously described GLP-compliant short term repeated dose toxicity study conducted according to OECD Guideline 407, Sprague-Dawley rats (5/sex/dose) were administered oral doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (92% purity) in water at 15, 150, or 1,000 mg/kg/day active ingredient via gavage for 28 days. Animals were evaluated for a functional observation battery (FOB), motor activity (MA), sensory reactivity and grip length. Treatment caused clinical signs of neurotoxicity such as hunched posture and sensory reactivity in animals at the high dose (1,000 mg/kg/day). There were no treatment-related changes in the functional performance parameters measured. Males treated with 1,000 mg/kg/day showed an enhanced startle reflex compared with controls. The percentage peak response was statistically significantly elevated and the percentage average response and RMS response were also higher than controls, although the differences did not achieve statistical significance. Based on this as well as the clinical signs, ToxServices identified a neurotoxicity NOAEL of 150 mg/kg/day (Klimisch 1, reliable without restriction). *The GHS guideline values of 10 and 100 mg/kg/day are multiplied by 3 to 30 and 300 mg/kg/day to account for the 28-day exposure period instead of the 90-day duration. The LOAEL of 1,000 mg/kg/day is above the duration adjusted GHS cut off value of 300 mg/kg/day for Category 2 and therefore amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not classified per GHS for neurotoxicity repeated dose. However, the NOEAL of 150 mg/kg/day is within the duration adjusted GHS cut off values for Category 2. Therefore, there is insufficient information to conclude that adverse effects do not occur at 300 mg/kg/day.*
- ECHA 2021b
  - *Oral*: In the previously described GLP-compliant subchronic repeated dose toxicity study conducted according to OECD Guideline 408, Sprague-Dawley rats (10/sex/dose) were administered oral doses of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35.6% purity) in water at 50, 150, or 500 mg/kg/day active ingredient via gavage for 90 days. Animals were evaluated for a functional observation battery (FOB), motor activity (MA), sensory reactivity and grip length. There were no clinical signs of neurotoxicity and no effect on functional observational battery tests or locomotor activity. ToxServices assigned a neurotoxicity NOAEL of 500 mg/kg/day, which was the highest dose tested (Klimisch 1, reliable without restriction). *The NOAEL of 500 mg/kg/day is above the GHS Guidance cut-off value of 100 mg/kg/day for Category 2.*

Therefore, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not classified per GHS for neurotoxicity repeated dose.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for skin sensitization based on ToxServices not classifying it per GHS based on results from guinea pig maximization tests. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on experimental data of good quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - In a GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406, male and female Pirbright-Hartley guinea pigs (n = 20) were epicutaneously (occlusive) and intradermally induced with a dilution of 50% and 2.5% of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide, respectively. After 14 days, the animals were epicutaneously challenged using a solution of 5% test material under occlusive conditions and evaluated at 24 and 48 hours post challenge. Treatment caused positive reactions in 12 animals at 24 hours after challenge (20%) and in 13 animals at 48 hours after challenge (15%). The authors concluded that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is mildly sensitizing under the conditions of the assay with the effects observed not significant enough in triggering a GHS classification (Klimisch 1, reliable without restriction). *According to GHS criteria, the positive response of 20% is not sufficient to classify amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide to skin sensitization Category 1B, which requires ≥ 30% positive response at > 1% intradermal induction dose in a Guinea pig maximization test.*
  - In a non-Guideline repeat-insult patch test study reported in CIR 2008 with no information on GLP compliance, a facial wash (1% raw material which contained 35% to 36.5% of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide) was used with 199 human subjects. During the induction phase, three subjects exhibited positive reactions (faint, minimal erythema). During the challenge phase, 24 subjects exhibited positive reactions and 6 subjects had a score of 1 for erythema. Authors concluded that the test material did not induce contact dermal sensitization in human subjects (Klimisch 2, reliable with restrictions).
  - In another non-Guideline repeat-insult patch test study reported in CIR 2008 with no information on GLP compliance, a facial wash (1% raw material which contained 35% to 36.5% of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide) was used with 189 human subjects. The test material (0.2 ml) was dispensed onto the semi occlusive webril/adhesive patch, and placed on the left side of the back. The patch was removed 24 hours after application, and the procedure was repeated after a 24 hours nonapplication period (48 hours on the weekends) for a total of nine induction patches. The test site was observed for any signs of reaction and evaluated at the time a new patch was reapplied. During these observations, two ± reactions (faint, minimal erythema) were noted at the first reading. The subjects were given a 2-week period of non-treatment, which was followed by the challenge dose. The challenge patch was applied to the right side of the

back for 24 hours. The site was observed for a reaction immediately after removal and again 48, 72, and 96 hours after application. During this phase, only one positive reaction was noted at 48 hours after application. Authors concluded that the test substance did not induce dermal sensitization (Klimisch 2, reliable with restrictions).

- In a modified Draize assay reported in CIR 2008 using a test product containing 7.5% amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide, 0.025 g of the test material was applied to the scapular area of the back of 110 human subjects under occlusive patches. A total of 10 applications were made in the induction phase. The patches were removed 48 hours after application and the test sites were rinsed and evaluated. New patches were then applied. Twelve days after removal of the last patch, a challenge patch with the same dose used during induction was applied to a previously untested site. The challenge patch was removed 48 hours after application, and the site was evaluated 48 and 96 hours after application. During the induction phase of the study, 1 + reactions (erythema throughout the entire patch area) were observed in 53 subjects and 2+ reactions (erythema and edema) were observed in three subjects. These reactions were considered typical of mild irritation. Two of the subjects had positive reactions at the 48 and 96-hours challenge readings. Authors concluded that "no evidence of sensitization" to 7.5% of the test substance was observed (Klimisch 2, reliable with restrictions).

- ECHA 2021b
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (79% purity) was not sensitizing to the skin in a GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406. Male Pirbright-Hartley guinea pigs (n = 20) were intradermally induced with a dilution of 0.1% and topically induced with 75% of test material. After 14 days, the animals were epicutaneously challenged using a solution of 2% and 5% test material under occlusive conditions and evaluated at 24 and 48 hours post challenge. No positive reactions were observed (Klimisch 1, reliable without restriction).
- CIR 2008
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide at a concentration of 81.5% was not sensitizing when tested in a Magnusson and Kligman maximization test in which albino guinea pigs (n = 20) were given intradermal injections of the test substance (0.1% w/w in distilled water) followed by application with a topical solution (75% w/w in distilled water). Animals were then challenged with a topical solution (5% and 2% w/w in distilled water). No positive reactions were seen.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides /Cocamidopropylamine oxide was assigned a score of Low for respiratory sensitization based on the lack of skin sensitization potential and absence of structural alerts according to the guidance from ECHA regarding assessment of respiratory sensitization potential. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not classifiable under GHS in the presence of adequate data (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020a
  - Based on its default structure as recognized by the U.S. EPI Suite™ (U.S. EPA 2017) which corresponds to its building blocks (N-(3-(dimethylamino)propyl)-, N-oxide moiety linked to

dodecanamide (C11)), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide does not contain any structural alerts for respiratory sensitization (Appendix D).

- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not expected to be sensitizing to the skin based on surrogate data (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide, and as the building blocks for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide do not contain any structural alerts for respiratory sensitization (OECD 2020a), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not expected to be a respiratory sensitizer.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of High for skin irritation/corrosivity based on the weight of evidence from dermal irritation studies in rabbits, classifying it to GHS Category 2. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are classified to GHS Category 2 (CPA 2018b). The confidence in the score is reduced as no data are identified for the 100% active substance.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS - New Zealand - 6.3B - Mildly irritating to the skin
- ECHA 2021a
  - In a dermal irritation assay conducted according to an acceptable guideline, 0.5 ml of 25% amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide was dermally administered to the shaved skin of five leinrusse Chbb:HM/Fa rabbits (sex not reported) for 4 hours under occlusive conditions. Animals were monitored for 14 days. The scores for edema and erythema reactions were assigned based on the Draize system. The primary dermal irritation index was 2.87 out of 8. Mean values for edema and erythema for animal 1, animal 2, animal 3, animal 4, and animal 5 were 0.6 and 1.3, 1.0 and 1.6, 0.6 and 2.0, 1.6 and 3.0, 1.0 and 1.3, respectively. Based on this, authors concluded that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is mildly irritating to the skin and is classified to GHS Category 3 (Klimisch 1, reliable without restriction).
- ECHA 2021a,b[11]
  - In a GLP-compliant dermal irritation assay conducted according to OECD Guideline 404, 0.5 mL of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (approximately 79 or 92% purity) was dermally administered to the clipped skin of three New Zealand White rabbits (sex not reported) for 4 hours under semi-occlusive conditions. Animals were monitored for 14 days. The erythema scores at 24, 48, and 72 hours were 0 for animal 1, 2 for animals 2 and 3 with effects being fully reversible within 7

[11] Study No. 2 in ECHA 2021b.

days. The edema scores at 24, 48, and 72 hours were 0 for animal 1, 1 for animal 2 and 2 for animal 3, with effects being fully reversible within 7 days. Authors concluded that the test substance is not classified for irritation according to EU -GHS. However, according to DSD classification criteria, the test material should be classified as skin irritant (Klimisch 1, reliable without restriction). *According to GHS Criteria, chemicals that are Category 3 (Mild irritant) should have a mean value between 1.5 and 2.3 for erythema/edema in at least 2 of 3 tested animals at 24, 48 and 72 hours or, if reactions are delayed, on 3 consecutive days after the onset of skin reactions. As the erythema scores at 24, 48, and 72 hours were > 1.5 (score of 2) in at least two animals, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is classified to GHS Category 3.*

  - Although the available skin irritation studies classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides /cocamidopropylamine oxide at most to GHS Category 3 for skin irritation (mildly irritating, as shown above), authors of REACH dossiers classified it to Category 2 (irritating to the skin) as a conservative approach. This is because only dilutions of the test substance were tested in the above studies with mixed results observed. Authors of REACH dossier also stated as the substance is normally produced as a 35% solution and none of the studies show a skin irritant effect that warrant Category 2 classification at lower concentrations. Therefore, a specific concentration limit (SCL) of 35% is established for non - skin classification.

- CIR 2008
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide solution was not a primary dermal irritant when tested at 5.0% using six Albino rabbits. An amount of 0.5 mL of the test material was applied to an abraded and an intact skin for 24 hours under occlusive condition. The primary irritation score was 1.41, indicating the potential for mild irritation.
  - In a dermal irritation test, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (81.5% purity) was applied to the intact skin of three New Zealand white rabbits for 4 hours under semi-occlusive condition. Treatment caused well-defined erythema, slight edema, loss of skin elasticity and flexibility, crust formation, and slight desquamation. The test material was classified as a moderate irritant to rabbit skin according to the Draize classification scheme. *Based on the qualitative description, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is at worst a GHS Category 2 irritant.*
- Based on the weight of evidence, a score of High was assigned. The available dermal irritation studies indicated that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is irritating to the skin with its irritation potential/GHS classification (Category 2 or 3) being dependent on the concentration. As no data are available on the neat chemical (100% active ingredient), ToxServices relied on the conservative GHS Category 2 classification, and assigned a score of High.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Very High for eye irritation/corrosivity based on being severely irritating to the rabbit eye with effects being irreversible in experimental tests, classifying it to GHS Category 1. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when they are classified to GHS Category 1 (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS - New Zealand - 6.4A - Irritating to the eye (Cat. 2A).
- ECHA 2021a
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide at concentration of 25% was severely irritating to the eye of four rabbits in an ocular irritation test conducted according to OECD Guideline 405. An amount of 0.1 mL of the test substance (25% active ingredient) was instilled into the conjunctival sac of the left eye of rabbits and animals were observed for 1, 6, 24, 48, and 72 hours and 7, 10, 14, 17, and 21 days after instillation. Treatment caused severe corneal and conjunctival reactions which persisted for 21 days in three test animals. Further, one treated animal showed irreversible corneal damage after 21 days. Reactions to the iris were not observed (Klimisch 2, reliable with restrictions).
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide at a concentration higher than 0.05% was considered irritating to the eye when tested in a Hen's Egg Test – Chorioallantoic Membrane (HET-CAM) assay. Chorioallantoic membrane of hen's eggs was exposed to concentrations of 0.01, 0.05, 0.1, 0.5, 1, 5, and 10% of the test substance in water. An amount of 300 µl was applied on each egg. The observation period was 300 seconds and the membranes were evaluated according to a point scheme; no reaction (0 points), slight reaction (1 point), moderate reaction (2 points), and strong reaction (3 points). Results demonstrate that the test substance induced irritating reactions at a concentration higher than 0.05% (Klimisch 2, reliable with restrictions).
  - In a mucous membrane irritation test, 0.1 ml of a diluted solution containing 15% amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide in water was applied into the conjunctival sac of five male New Zealand White rabbits for an uninterrupted duration (no washing). Observation time points were after 2, 6, 24, 48, 72, and 96 hours, and after 8, 12, 16, and 21 days. Treatment caused slight to moderate irritations to conjunctiva, cornea and iris with overall irritation scores between 17.0 and 43.0 as means from 24/48/72 h. The effects to iris, conjunctiva, and cornea in at least one animal were irreversible, thus authors classified the test substance as seriously eye damaging (Klimisch 2, reliable with restrictions).
  - Based on the above results, authors of REACH dossier classified amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide to GHS Category 1 for eye irritation with a hazard statement of H318: Causes serious eye damage.
- ECHA 2021b (Only the study designated as the key study (study No. 9) by the registration dossier is described in this report as it is sufficient to assign a GreenScreen® score in combination with the results from the studies described above and in the CIR assessment)
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide at concentration of 30% was severely irritating to the eye of one New Zealand White rabbit in a GLP-compliant ocular irritation test conducted according to OECD Guideline 405. An amount of 0.1 mL of the test substance (30% active ingredient) was instilled into the conjunctival sac of the left eye of the rabbit and the animal was observed for 24, 48, 72 hours and 21 days after instillation. Treatment caused severe corneal and conjunctival reactions which persisted for 21 days. The 24/48/72 hours mean values were 2/4 for cornea, 0.33/2 for iris, 2.67/3 for conjunctivae (hyperemia) and 4/4/ for conjunctivae edema, with effects not being reversible within 21 days. Based on that authors considered the test substance to be severe irritating to the eye and classified it to GHS Category 1 (irreversible effects on the eye) (Klimisch 1, reliable without restriction).
- CIR 2008

- Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide at 81.5% concentration was severely irritating to the eye of New Zealand white rabbits. A single application (amount unknown) of the material caused opalescent corneal opacity, iridial inflammation, and severe conjunctival irritation in one treated animal. Effects were reversible after 14 days.

Ecotoxicity (Ecotox)

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Very High for acute aquatic toxicity based on a 96-hour LC_{50} of 0.64 mg/L in fish and a 72-hour EC_{50} of 0.705 mg/L in algae. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when the most conservative acute aquatic toxicity value is ≤ 1 mg/L (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for all three trophic levels for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment (iTE) (based on an aquatic toxicity value (iT) of 0.4 mg/L (OECD 2021).
- ECHA 2021a
  - 96-hour LC_{50} (*Leuciscus idus*, fish) = 5.9 mg/L (purity not reported, OECD Guideline 203, GLP not specified) (Klimisch 2, reliable with restrictions).
  - 48-hour EC_{50} (*Daphnia magna*, invertebrate) for mobility = 46 mg/L (purity not reported, non GLP, OECD Guideline 202) (Klimisch 2, reliable with restrictions).
  - 72-hour EC_{50} (algae, species not specified) > 500 mg/L for growth rate (purity not reported, OECD Guideline 201, GLP not specified) (Klimisch 2, reliable with restrictions).
- ECHA 2021b
  - 96-hour LC_{50} (*Oncorhynchus mykiss,* fish) = 1.81 mg/L for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35.8% purity); equivalent to 0.64 mg/L active ingredient (GLP-compliant, OECD Guideline 203) (Klimisch 1, reliable without restriction).
  - 96-hour LC_{50} (*Danio rerio*, fish) mortality = 5.9 mg/L for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35% purity); equivalent to 2.06 mg/L active ingredient (GLP-compliant, OECD Guideline 203) (Klimisch 1, reliable without restriction).
  - 48-hour EC_{50} (*D. magna*, invertebrate) mobility = 55.5 mg/L for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35.8% purity); equivalent to 19.9 mg/L active ingredient (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction).
  - 48-hour EC_{50} (*D. magna*, invertebrate) mobility = 46 mg/L for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35% purity); equivalent to 16 mg/L active ingredient (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction).
  - 72-hour EC_{50} (*Pseudokirchneriella subcapitata*, algae) growth rate = 1.97 mg/L for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (35.8% purity); equivalent to 0.705 mg/L active ingredient (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).

- 72-hour EC_{50} (*P. subcapitata*, algae) = 341 mg/L for growth rate, and 132 mg/L for biomass, for amides, coco, N-[3-(dimethylamino)propyl], N-oxides /cocamidopropylamine oxide (30% purity); equivalent to 119.5 mg/L (growth rate) active ingredient (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of High for chronic aquatic toxicity based on an experimental NOEC (72-hour) value of 0.303 mg/L in algae and NOEC value of 0.42 mg/L in fish (302-day) for a surrogate. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when the chronic aquatic toxicity values are > 0.1 to 1 mg/L (CPA 2018b). The confidence in the score is reduced as no measured data are available for aquatic invertebrates, although it does not appear to be the most sensitive trophic level (fish and algae) in acute aquatic toxicity studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021b
  - 72-hour NOEC (*P. subcapitata*, algae) growth rate = 0.303 mg/L active ingredient (35.5% purity, GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - 72-hour NOEC (*P. subcapitata*, algae) growth rate = 5.6 mg/L active ingredient (35% purity, GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - *Surrogate: Amines, C12-14 (even numbered)-alkyldimethyl, N-oxides (CAS #308062-28-4):* 302-day NOEC (*Pimephales promelas*, fish) = 0.42 mg /L active ingredient for reduced fry survival, reduced egg hatch, and occluded eyes (purity not reported, non GLP, EPA OPPTS 850.1500) (Klimisch 1, reliable without restriction).

Environmental Fate (Fate)

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for persistence based on meeting the GHS rapid degradation criteria. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they meet the rapid degradation criteria under GHS, and they primarily partition to soil, water or sediment (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide degraded by 93% after 28 days in a GLP-compliant ready biodegradability test conducted according to OECD Guideline 301A (DOC Die Away Test) in which non-adapted activated sludge was exposed to an aqueous solution of the test substance (purity not reported) for 28 days. Authors concluded that that the test substance was readily biodegradable. No further details were provided (Klimisch 2, reliable with restrictions).
- ECHA 2021b
  - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (35% purity; 45 mg/L starting concentration) was biodegradable but failed the 10-day window in a GLP-compliant test conducted according to OECD Guideline 301 B (Ready

Biodegradability: CO_2 Evolution Test) using non-adapted activated sludge inoculum. After 29 days, the substance reached 68-71% biodegradation (Klimisch 1, reliable without restriction).
    - In another GLP-compliant test conducted according to OECD Guideline 301 B (Ready Biodegradability: CO_2 Evolution Test) using activated sludge inoculum, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (purity not reported; 17 mg/L starting concentration) was readily biodegradable, achieving a degradation rate of 79% by the end of exposure period (28 days) (Klimisch 1, reliable without restriction).
    - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (purity not reported; 24.6 and 25.4 mg/L starting concentrations) achieved 66% biodegradation in 28 days (based on DOC removal) in a ready biodegradation test that was conducted according to OECD Guideline 301E (Ready biodegradability: Modified OECD Screening Test) using predominantly domestic sewage inoculum. Authors concluded that the substance is not readily biodegradable as the pass level (70%) was not reached within the test period (biodegradation after 28 d: 67%) (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Low was assigned. Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was readily biodegradable but not within the 10 day window in three ready biodegradability tests conducted according to OECD Guidelines (301 B and A) and in compliance with GLP. In these studies, the degradation rate achieved at the end of the exposure period was greater than the pass level (70%). This indicates that it meets the GHS criteria for "rapid degradability", which corresponds to a score of Low. Although one study (OECD Guideline 301E) reported that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine is not readily biodegradable, OECD Guidance states that positive results in ready biodegradability tests can be considered valid despite negative results in other tests, provided the scientific quality and test conditions are adequate (OECD 2001). As the three positive studies were well conducted and reported, ToxServices considered amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide to be readily biodegradable and hence meet the GHS criteria for rapid degradability. Due to its surface-active properties, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is outside the applicability domain of the EPI Suite™ and therefore modeling could not be performed to determine environmental distribution. However, the high water solubility and low vapor pressure indicates that amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is unlikely to partition mainly to the air.

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Very Low for bioaccumulation based on measured log K_{ow} values of 2.11 and 1.27. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCFs/BAFs are ≤100 and log K_{ow} values are ≤ 4 (CPA 2018b). The confidence in the score is high as it is based on log K_{ow} value obtained from an acceptable method 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.
- ECHA 2021a
    - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide has a measured log K_{ow} value of 2.11 at 23°C and pH between 7.1 and 7.2 obtained from a GLP-compliant test conducted according to OECD Guideline 107 (Shake Flask Method) (Klimisch 1, reliable without restriction).

- ECHA 2021b
    - Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide (100% purity) has a log K_{ow} value of 1.27 calculated from its solubility in water) and octanol. The solubility of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide in octanol was determined as 19.6 g/L and its solubility in water was determined as 1.05 g/L, which was estimated using the CMC (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, a score of Very low was assigned. The log K_{ow} values for amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide obtained from a shake flask method or calculated based on its water and octanol solubilities are below the GreenScreen® Guidance value for a Very Low score. According to ECHA Guidance on regulatory compliant K_{ow} determination for surfactants (ECHA 2017), the calculated K_{ow} value based on the octanol and water solubilities is considered the most reliable method for surfactants while shake flask method is the least suitable experimental method. Accordingly, as the calculated value of log K_{ow} is available, the confidence in the score is high.

Physical Hazards (Physical)

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for reactivity based on NFPA reactivity rating of 0 supported by lack of structural alerts for explosivity. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening list (CPA 2018b). The confidence in the score is low due to 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 amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide. These procedures are listed in the GHS (UN 2019).
    - Based on the structure of its building blocks (amine oxide group, amide group and long aliphatic chain), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix E).
    - Based on the structure of its building blocks, amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide 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.
- MakingCosmetics 2015
    - A safety data sheet for an aqueous solution of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (32%) has a reactivity rating of 0 from the NFPA which corresponds to "Normally stable, even under fire exposure conditions, and is not reactive with water".[12]

[12] https://www.fm.colostate.edu/files/forms/safety/CH-23.NFPA.ratings.pdf

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

Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / Cocamidopropylamine oxide was assigned a score of Low for flammability based on negative results in a flammability test supported by NFPA flammability rating of 0. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - In a GLP-complaint flammability test conducted according to UN Manual of Tests and Criteria: Test N.1 (Test method for readily combustible solids), amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide was not a flammable solid. The test item could not be ignited with a flame in a preliminary test. The performance of the main test was therefore not necessary (Klimisch 1, reliable without restriction).
- MakingCosmetics 2015
  - A safety data sheet for an aqueous solution of amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide (32%) has a flammability rating of 0 from the NFPA which corresponds correspond to "Materials that will not burn". [13]

[13] https://www.fm.colostate.edu/files/forms/safety/CH-23.NFPA.ratings.pdf

Use of New Approach Methodologies (NAMs)[14] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity, and *in silico* modeling for respiratory sensitization. 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 amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide' NAMs dataset include the absence of experimental data and established test methods for respiratory sensitization. Amides, coco, N-[3-(dimethylamino)propyl], N-oxides / cocamidopropylamine oxide' Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, and the OECD Toolbox only identifying structural alerts without defining applicability domains. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries, and ECHA's decision framework and guidance to evaluate respiratory sensitization.

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

Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Genotoxicity:** No Type I uncertainty is identified on using the *in vitro* genotoxicity as they are considered relevant (appropriate for the evaluation of the corresponding hazards as recommended in the OECD Guideline), reliable (they have Klimisch scoring of 2 or 1) and adequate (validated methods). **Respiratory sensitization**: No experimental data or human data are available. In addition, there are no formally recognized and validated animal or *in vitro* tests
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (OECD 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[15]. The mammalian cell gene mutation assay (OECD 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo*

[14] 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).

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

	metabolism[16]. 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[17]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Therefore, there is uncertainty on using the OECD QSAR toolbox (*in silico* method) for respiratory sensitization when no structural alert is identified. This is because lack of alert might not necessary be due to effect but rather due to the lack of knowledge as there may be other (non-immunological) mechanisms not included in the examination of structural alerts. In addition, there is still uncertainty regarding the exact underlying mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	N	
Bioaccumulation	N	

[16] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[17] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

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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 Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)

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	Cocamidopropylamine Oxide	68155-09-9	L	L	*L*	*L*	DG	M	*M*	L	M	L	L	*L*	*H*	vH	vH	*H*	L	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	No	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Cocamidopropylamine Oxide	2

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

Table 6

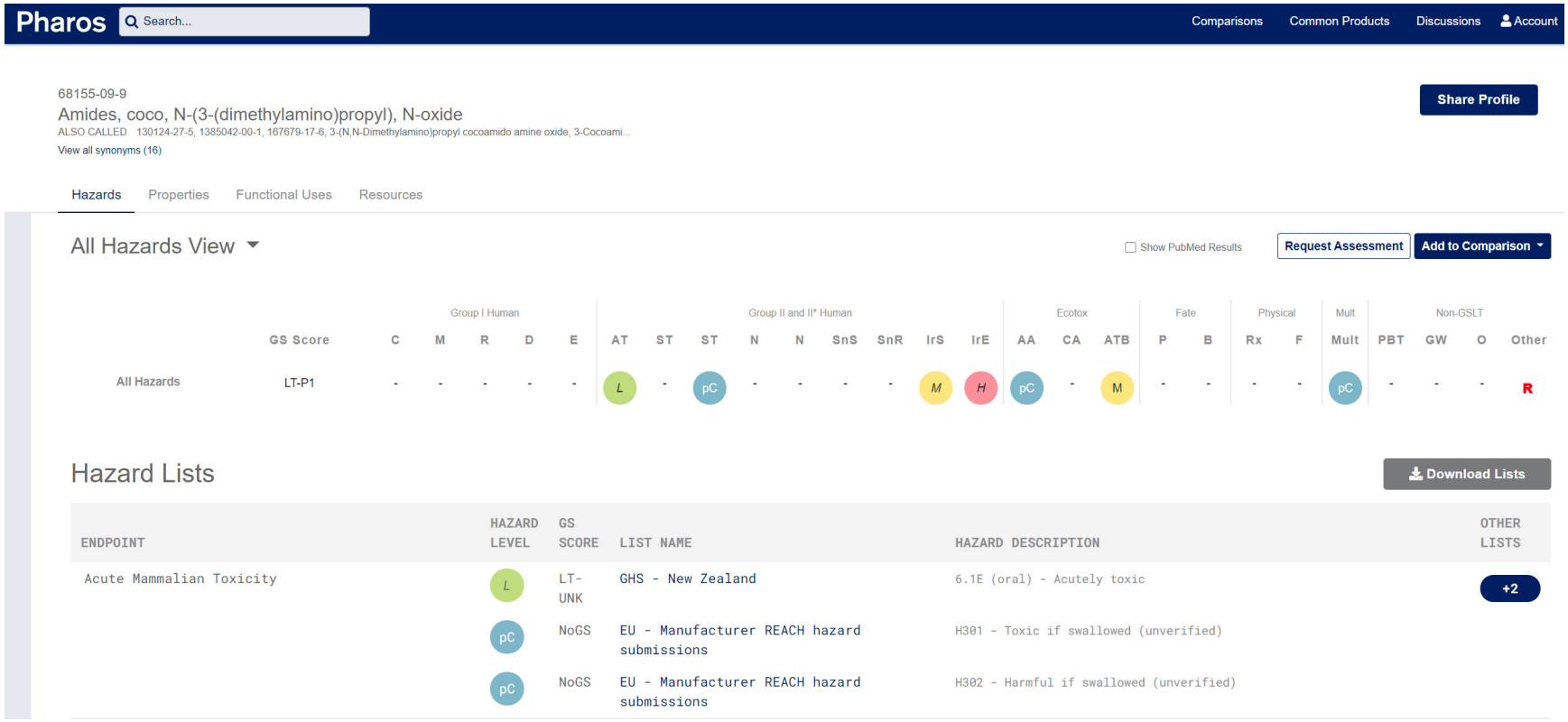
Chemical Name	Final GreenScreen® Benchmark Score
Cocamidopropylamine Oxide	2

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 Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)



Systemic Toxicity/Organ Effects incl. immunotoxicity-Repeated Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H373 - May cause damage to organs through prolonged or repeated exposure (unverified)	
Skin Irritation/Corrosivity	M	LT-UNK	GHS - New Zealand	6.3B - Mildly irritating to the skin	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified)	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	+2
	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	pC	NoGS	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified)	
Terrestrial Ecotoxicity	M	NoGS	GHS - New Zealand	9.3C - Harmful to terrestrial vertebrates	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified)	+1
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H411 - Toxic to aquatic life with long lasting effects (unverified)	

Restricted Substance Lists (1)

- Cosmetic Ingredient Review (CIR): Multiple Findings

Positive Lists (2)

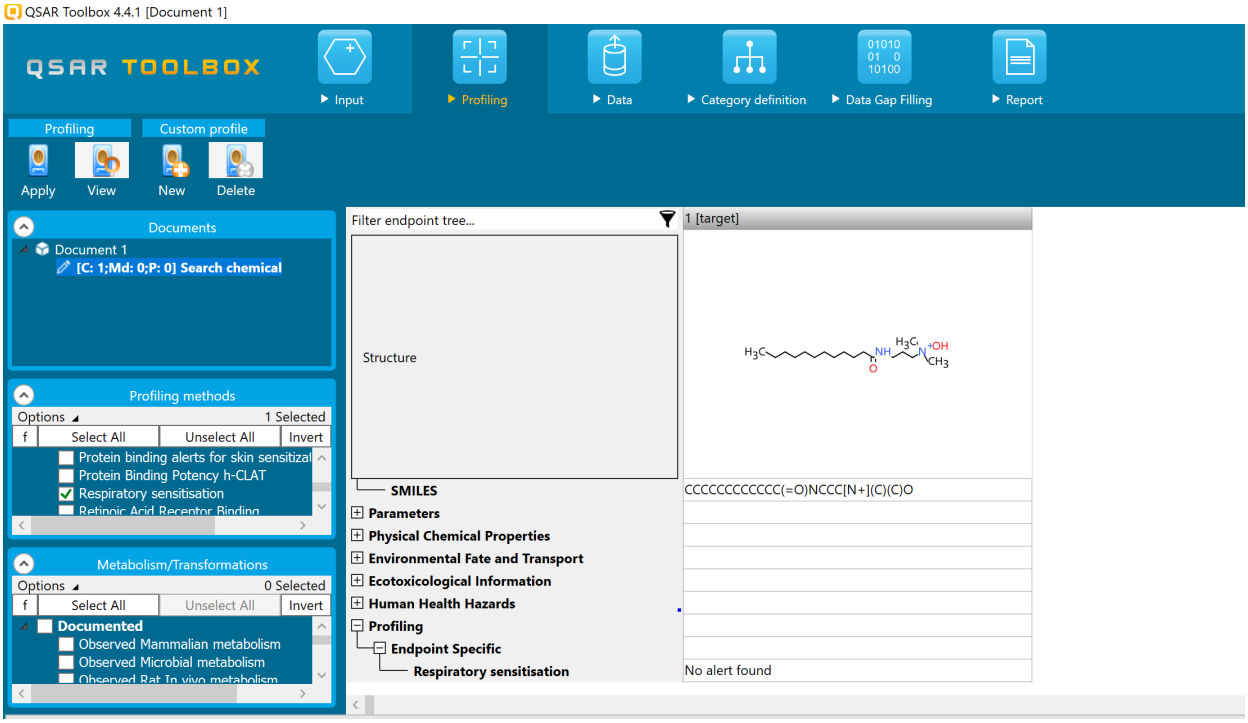
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients
- US EPA - DfE SCIL: Green Circle - Verified Low Concern

Discussions

No discussions have been posted yet.

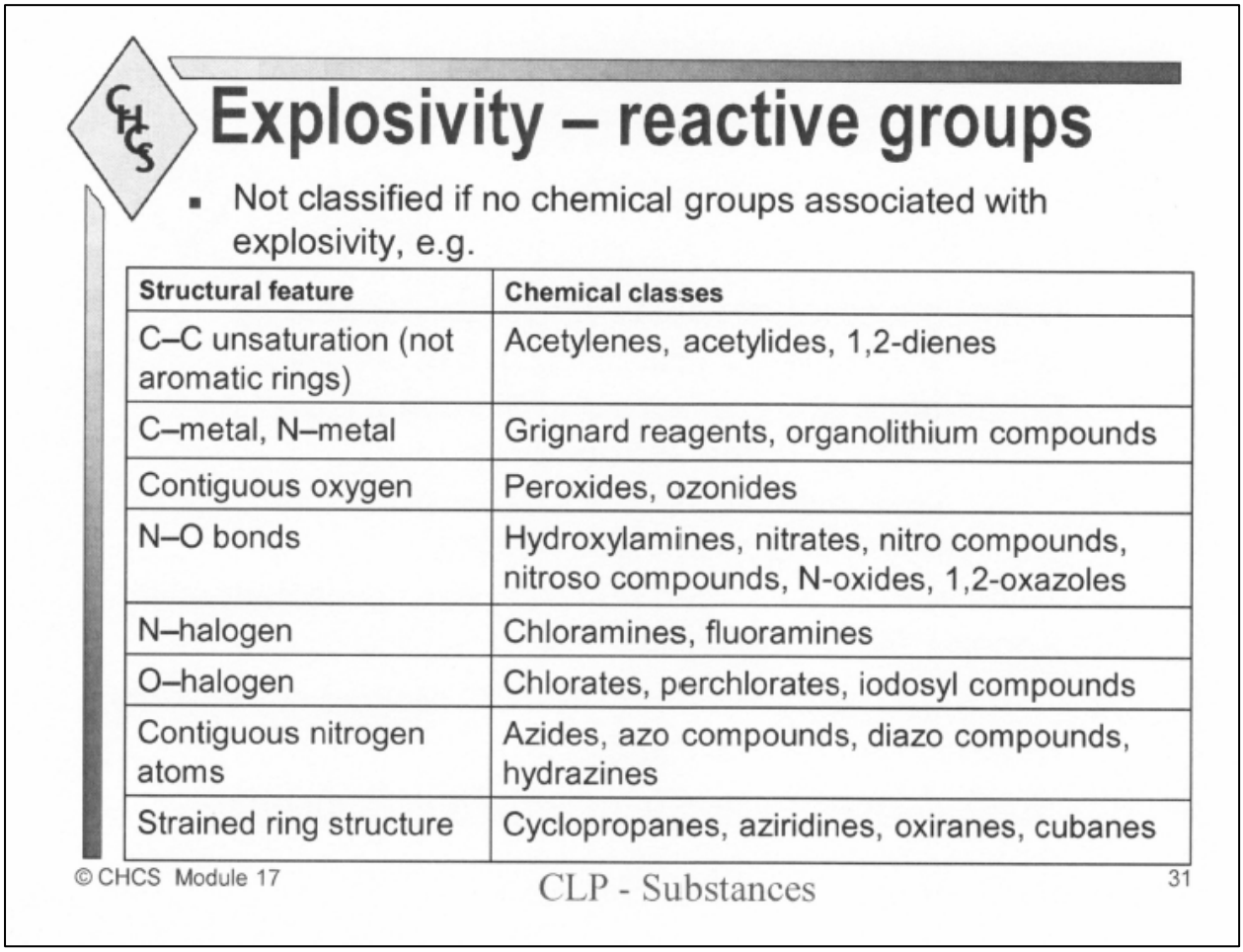
Ask a question about this chemical in the forums >

APPENDIX D: OECD Toolbox Profile for Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide (CAS #68155-09-9)



APPENDIX E: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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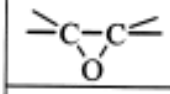
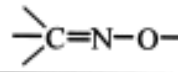
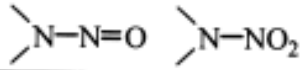
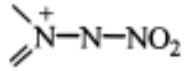
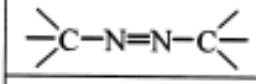
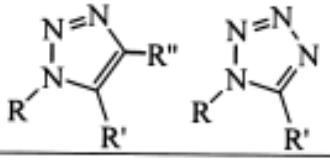
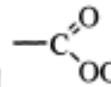
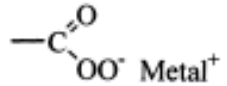
Explosivity – Full List

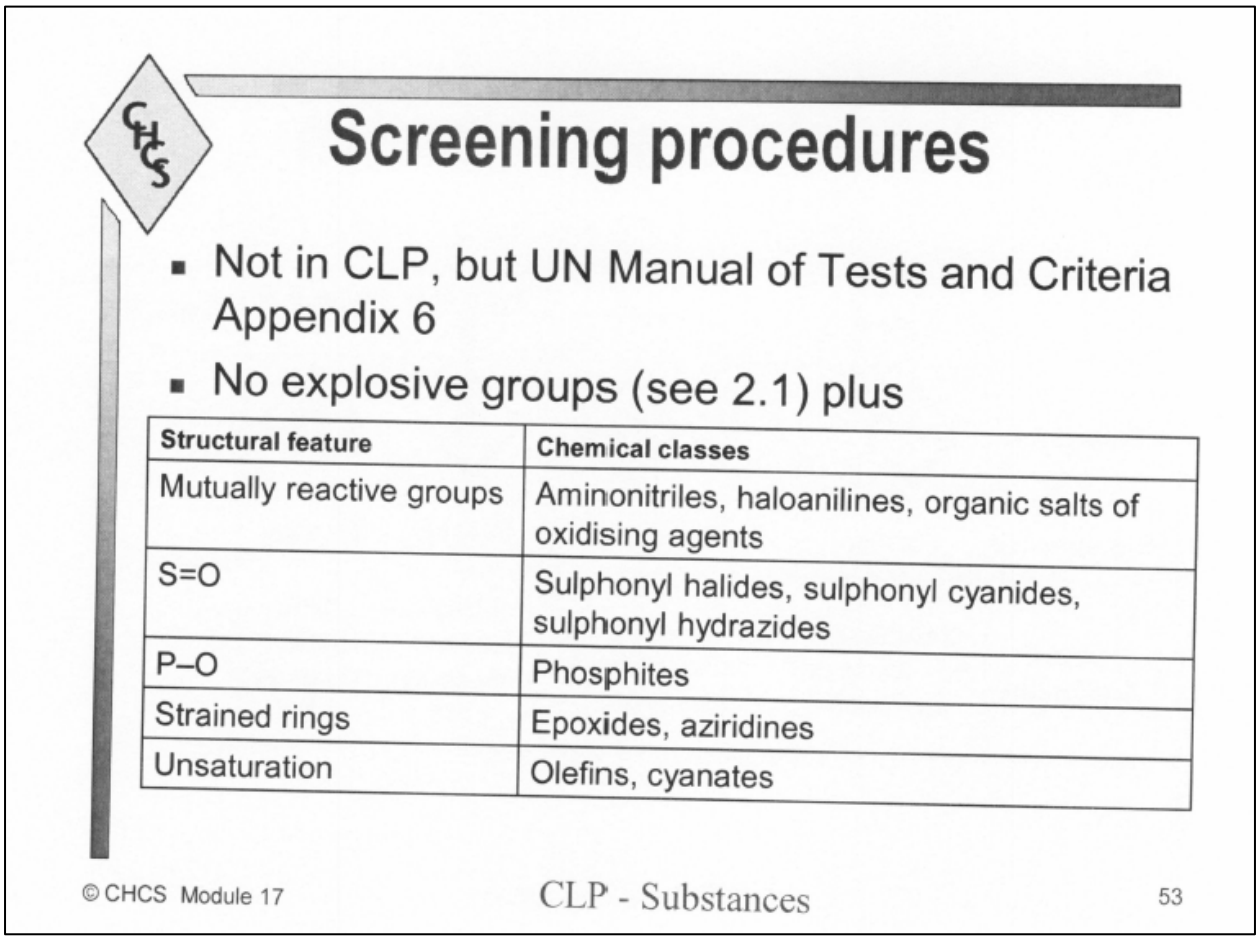
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



Screening procedures

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

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

Licensed GreenScreen® Profilers

Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Mouna Zachary, PhD
Toxicologist
ToxServices LLC

Amides, Coco, N-[3-(Dimethylamino)propyl], N-Oxides / Cocamidopropylamine Oxide GreenScreen® Evaluation QC'd by:

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