N-[3-(DIMETHYLAMINO)PROPYL]STEARAMIDE MONOACETATE

(CAS #13282-70-7)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: July 31, 2023

Expiration Date: July 31, 2028

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GreenScreen® Executive Summary for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

N-[3-(Dimethylamino)propyl]stearamide monoacetate is the monoacetate of N-[3-(dimethylamino) propyl]stearamide, a C18 fatty acid amidopropyl dimethylamine. It functions as a strength reducer in the dyeing and finishing processes of interwoven fabrics, a friction modifier for engine oil, and a conditioning agent for hair products. N-[3-(Dimethylamino)propyl]stearamide monoacetate is a solid at standard temperature and pressure. It is lipophilic and a volatile organic compound (VOC).

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Health Hazard (developmental toxicity-D)
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
  - Very High Group II Human Health Hazard (eye irritation-IrE)
  - High Group II* Human Health Hazard (systemic toxicity – repeated exposure-STr*, skin sensitization-SnS*)

Data gaps (DG) exist for endocrine activity-E and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), N-[3-(dimethylamino)propyl]stearamide monoacetate meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if N-[3-(dimethylamino)propyl]stearamide monoacetate were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

The GreenScreen® Benchmark Score for N-[3-(dimethylamino)propyl]stearamide monoacetate is maintained over time. The original GreenScreen® assessment was performed in 2017 under version 1.3 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. In this report, the BM-2 score was maintained with a version 1.4 update. This assessment re-classified the scores and confidence levels for a few endpoints, without affecting the overall benchmark score.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, endocrine activity, and respiratory sensitization, and *in vitro* testing for genotoxicity and endocrine activity. 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 N-[3-(dimethylamino)propyl]stearamide monoacetate's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. N-[3-(dimethylamino)propyl]stearamide monoacetate's Type II (extrapolation output) uncertainties include lack of defined applicability domains of OECD QSAR Toolbox in examination of structural alerts, the low reliability of the two VEGA model predictions with acceptable global ADIs due to lack of, or additional, reactive moieties, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, and the limitations in the examination of structural alerts for

respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of N-[3-(dimethylamino)propyl]stearamide monoacetate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for N-[3-(Dimethylamino)propyl]stearamide Monoacetate

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS	SnR	IrS	IrE	AA	CA	P	B	Rx	F
						s	r*	s	r*	*	*								
L	**L**	*L*	*M*	DG	**M**	**M**	*H*	*L*	**L**	**H**	DG	**L**	**vH**	**vH**	*vH*	**vL**	*M*	*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 N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

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

GreenScreen® Assessment (v.1.3) Prepared By:
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Title: Toxicologist
Organization: ToxServices LLC
Date: July 17, 2017

Quality Control Performed By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: July 19, 2017

GreenScreen® Assessment (v.1.4) Prepared By:
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Title: Toxicologist
Organization: ToxServices LLC
Date: July 5, 2023; July 26, 2023

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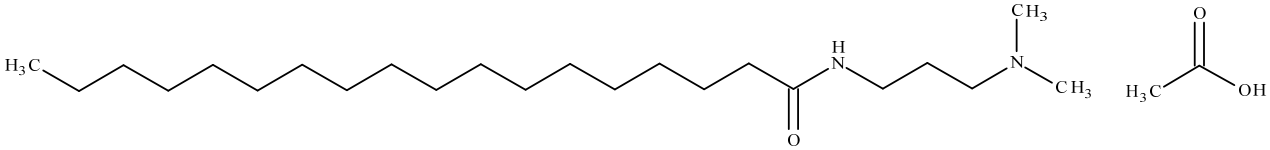
Organization: ToxServices LLC
Date: July 10, 2023; July 31, 2023

Expiration Date: July 31, 2028[2]

Chemical Name: N-[3-(Dimethylamino)propyl]stearamide monoacetate

CAS Number: 13282-70-7 (Deprecated CAS #'s: 133946-69-7, 3022-67-6) (PubChem 2023a)

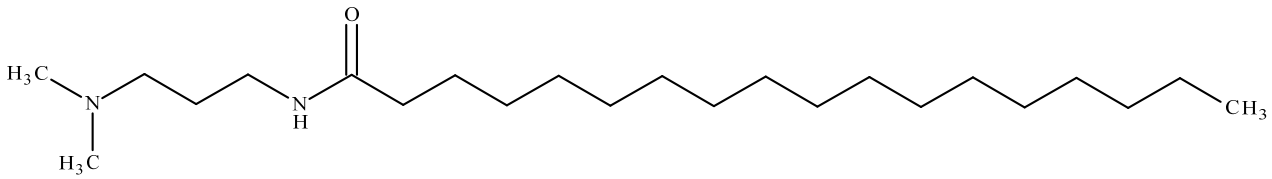
Chemical Structure(s):



Also called:
Octadecanamide, N-(3-(dimethylamino)propyl)-, monoacetate; N-(3-(Dimethylamino)propyl)stearamide monoacetate; acetic acid, N-[3-(dimethylamino)propyl]octadecanamide; EINECS 236-291-8; N-[3-(dimethylamino)propyl]stearamide monoacetate (PubChem 2023a, ECHA 2023a).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited data were identified for N-(3-(dimethylamino)propyl)-, monoacetate. This chemical consists of two moeities: N-[3-(dimethylamino)propyl]stearamide (CAS #7651-02-7) and acetic acid (CAS #64-19-7). As no additional systemic toxicity is expected from acetic acid since it is an essential component of cellular metabolism, ToxServices used data for N-[3-(dimethylamino)propyl]stearamide to address the data gaps for N-(3-(dimethylamino)propyl)-, monoacetate.

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



Surrogate: Stearamidopropyl dimethylamine (CAS #7651-02-7) (PubChem 2023b)

Identify Applications/Functional Uses (PubChem 2023a, CIR 2019)**:**
1. Strength reducer in the dyeing and finishing processes of interwoven fabrics
2. Friction modifier for engine oil
3. Conditioning agent for hair products.

Known Impurities[3]:
Common impurities of fatty acid amidopropyl dimethylamines include nitrosating agents and 3,3-dimethylaminopropylamine (DMAPA). Fatty acid aminopropyl dimethylamines should be formulated to avoid the formation of nitrosamines. The maximum level of DMAPA reported in cosmetics products for surrogate N-[3-(dimethylamino)propyl]stearamide was 30 ppm (CIR 2019). Furthermore, the Cosmetics Ingredient Review (CIR) Expert Panel concluded that the acceptable amount of DMAPA in fatty acid amidopropyl dimethylamines should be based on a quantitative risk assessment (QRA). The CIR's QRA identified a no expected sensitization induction level (NESIL) based on a weight of evidence approach for surrogate N-[3-(dimethylamino)propyl]stearamide of 1,000 µg/cm^2 (CIR 2019). According to the GreenScreen® Guidance, impurities present at < 100 ppm require a List Translator screening, while those present at > 100 ppm require separate full GreenScreen® evaluations. DMAPA (CAS #109-55-7) is an LT-UNK chemical. Impurities are not evaluated in this assessment. Instead, they are evaluated at the product level, should they be present at > 100 ppm.

GreenScreen® Summary Rating for N-[3-(Dimethylamino)propyl]stearamide Monoacetate[4,5 6,7]:
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Health Hazard (developmental toxicity-D)
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic toxicity-AA, chronic aquatic toxicity-CA)
  - Very High Group II Human Health Hazard (eye irritation-IrE)
  - High Group II* Human Health Hazard (systemic toxicity – repeated exposure-STr*, skin sensitization-SnS*)

Data gaps (DG) exist for endocrine activity-E and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance Section 11.2 (Step 8 – Conduct a Data Gap Analysis to assign a final

[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.

Benchmark score), N-[3-(dimethylamino)propyl]stearamide monoacetate meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if N-[3-(dimethylamino)propyl]stearamide monoacetate 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 N-[3-(Dimethylamino)propyl]stearamide Monoacetate

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). OECD QSAR Toolbox predicted two hydrolysis under basic conditions: stearic acid (CAS #57-11-4) and DMAPA (CAS #109-55-7), and no hydrolysis products were predicted under neutral or acidic conditions (OECD 2023, Appendix D). As N-[3-(dimethyl amino)propyl]stearamide monoacetate is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

No information was identified for the production of the target chemical; however, surrogate N-[3-(dimethylamino)propyl]stearamide is produced via the reaction of DMAPA and stearic acid (CIR 2019).

ToxServices assessed N-[3-(dimethylamino)propyl]stearamide monoacetate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate is not listed on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an

online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for N-[3-(dimethylamino)propyl]stearamide monoacetate can be found in Appendix C.

- N-[3-(Dimethylamino)propyl]stearamide monoacetate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- N-[3-(Dimethylamino)propyl]stearamide monoacetate is not listed on the U.S. DOT list.
- N-[3-(Dimethylamino)propyl]stearamide monoacetate is on the following list for multiple endpoints. It is not present on any GreenScreen®-specified lists for single endpoints.
    - EC – CEPA DSL – Inherently Toxic to the Environment (iTE)

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for N-[3-(dimethylamino)propyl]stearamide monoacetate; self-classifications by the authors of the REACH dossier and by the majority of notifiers are indicated in Table 1, below. The specific concentration limits, M-Factors were identified as M=1 for the target chemical in the Summary of Classification and Labeling (ECHA 2023b). 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 N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7) (ECHA 2023a,b)

H Statement	H Statement Details
H302	Harmful if swallowed.
H317	May cause an allergic skin reaction.
H318	Causes serious eye damage.
H400	Very toxic to aquatic life.
H410	Very toxic to aquatic life with long lasting effects.

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Appropriate eye protection, gloves, protective clothing. No respiratory protection is required; however, use of N95 or dust masks when protection from nuisance is desired.	Sigma-Aldrich 2020	None identified	Sigma-Aldrich 2020

Physicochemical Properties of N-[3-(Dimethylamino)propyl]stearamide Monoacetate:

N-[3-(Dimethylamino)propyl]stearamide monoacetate is a white, flaky solid at standard temperature and pressure. Its vapor pressure (5.7 x 10^{-6} mmHg) indicates that it will exist in the solid and vapor phases. Additionally, its boiling point in the range of 111 to 121°C indicates it is a VOC. N-[3-(Dimethyl

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

amino)propyl]stearamide monoacetate is moderately soluble in water (134 mg/L). It is much more soluble in octanol than water (log K_{ow} of 6.2).

Table 3: Physical and Chemical Properties of N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Property	Value	Reference
Molecular formula	C23-H48-N2-O.C2-H4-O2	PubChem 2023a
SMILES Notation	CCCCCCCCCCCCCCCCCC(=O)NCCCN(C)C.CC(=O)O	PubChem 2023a
Molecular weight	428.7 g/mol	PubChem 2023a
Physical state	Solid	ECHA 2023a
Appearance	White flakes	ECHA 2023a
Melting point	44 – 61°C (exp., OECD Guideline 102/EU Method A.1)	ECHA 2023a
Boiling point	> 111 – < 121°C Decomposition occurs at 190°C (exp., OECD Guideline 103/EU Method A.2)	ECHA 2023a
Vapor pressure	7.6 x 10^{-4} Pa (equivalent to 5.7 x 10^{-6} mmHg) at 25°C (exp., OECD Guideline 104/EU Method A.4)	ECHA 2023a
Water solubility	134 mg/L at 23°C (exp, OECD Guideline 105)	ECHA 2023a
Dissociation constant	Not applicable	
Density/specific gravity	Relative density: 1.02 at 20°C (exp., OECD Guideline 109/EU Method A.3)	ECHA 2023a
Partition coefficient	Log K_{ow} = 6.2 at 25°C (exp., OECD Guideline 117/EU Method A.8)	ECHA 2023a

Toxicokinetics

No data were identified for the toxicokinetics of the target chemical or the chemical category of fatty acid amidopropyl dimethylamines (CIR 2019, AICIS 2019, ECHA 2023a,c).

- *Absorption:* Fatty acid amidopropyl dimethylamines are expected to be absorbed via the oral route and excreted unchanged in feces (AICIS 2019).
    - *Oral:* The molecular weight of < 500 favors absorption, but the low water solubility does not favor passive diffusion. The high log K_{ow} of > 4 indicates lipophilicity and absorption may occur by micellular solubilization. However, hydrolysis of the compound may affect the degree of absorption (ECHA 2017a). The authors of the ECHA dossier for surrogate (hydrolysis product) N-[3-(dimethylamino)propyl]stearamide predicted an oral absorption rate of 100% based on its physiochemical properties with a log K_{ow} in the range of 2.00 – 2.57 (depending on pH) and a molecular weight of 368.64 g/mol (ECHA 2023c).
    - *Dermal:* The physical state of flakes does not favor absorption. The molecular weight of between 100 and 500 suggests a limited absorption potential. The water solubility of between 100 and 10,000 mg/L indicates a moderate to high absorption potential across the stratum corneum, but the log K_{ow} of > 6 slows down the transfer between stratum corneum and the epidermis, resulting in slow uptake into the stratum corneum (ECHA 2017). Overall, the dermal absorption of the compound is likely low.
    - *Inhalation:* The boiling point of less than 150°C suggests some level of volatility, while the vapor pressure of < 0.5 kPa does not suggest high volatility. The log K_{ow} > 4 indicates that absorption may occur by micellular solubilization. However, hydrolysis of the compound

may affect the degree of absorption (ECHA 2017a). The authors of the ECHA dossier for surrogate (hydrolysis product) N-[3-(dimethylamino)propyl]stearamide predicted an inhalation absorption rate of 100% as a worst-case scenario as there is a lack of toxicokinetic and systemic toxicity data for this route of exposure (ECHA 2023c).

- *Distribution:* The log K_{ow} of >0 favors distribution into cells and fatty tissues. However, the hydrolysis/metabolism of the compound may change tissue distribution (ECHA 2017).
- *Metabolism:* Based on the structure of the target chemical, it is likely to undergo hydrolysis into its two components, N-[3-(dimethylamino)propyl]stearamide and acetic acid (OECD 2023, Appendix C). N-[3-(dimethylamino)propyl]stearamide may undergo further hydrolysis by amidases into stearic acid and DMAPA. Stearic acid is expected to enter normal fatty acid metabolism and break down into carbon dioxide and C_2 fragments, re-esterified to triacylglycerols, metabolized for energy, or stored in adipose tissue. Low primary aliphatic amines such as DMAPA are metabolized into the corresponding carboxylic acid and urea (ECHA 2023c). Lastly, acetic acid is readily metabolized by most tissues and may produce ketone bodies as intermediates. It may be partially converted to formic acid (HSDB 2015).
- *Elimination:* The molecular weight of > 300 does not favor urine excretion, but favors bile excretion (feces) in the unchanged form (ECHA 2017a). The DMAPA metabolites are likely to be excreted via urine based on the physiochemical properties typical for urinary excretion, good water solubility and low molecular weight (< 300 g/mol; mostly anionic and cationic compounds) (ECHA 2023c).

In summary, no data were available for N-[3-(dimethylamino)propyl]stearamide acetate; therefore, based on physiochemical properties of the target chemical and surrogate and/or expert judgement it is predicted to be bioavailable primarily via the oral and inhalation routes, distributed to fatty tissues, metabolized into surrogate N-[3-(dimethylamino)propyl]stearamide and acetic acid which are further metabolized into smaller substances important for energy formation, and/or excreted via urine or unchanged in the feces.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for carcinogenicity based on negative and in domain predictions from both statistical-based models (Danish (Q)SAR database), and a rule-based models (Oncologic, OECD Toolbox structural alerts) for the target chemical. 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 based on modeling due to lack of reliable, measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - ToxServices evaluated N-[3-(dimethylamino)propyl]stearamide monoacetate using OECD Toolbox v.4.6 (OECD 2023); no structural alerts for genotoxic or nongenotoxic carcinogenicity were found (Appendix D).
- VEGA 2023

- ToxServices predicted the carcinogenicity potential of N-[3-(dimethylamino)propyl]stearamide monoacetate (VEGA could only evaluate connected structures. Therefore, ToxServices removed the monoacetate structure in the modeling input). using the following six VEGA v1.3.18 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/Antares v1.0.2, IRFMN/ISSCAN-CGX v1.0.2, IRFMN Oral Classification 1.0.1, and IRFMN Inhalation Classification 1.0.1 models. If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
- The global ADI was < 0.70 for four out of the six models: CAESAR v2.1.10, non-carcinogen (ADI = 0), ISS v.1.0.3, non-carcinogen (ADI = 0), IRFMN/Antares v1.0.0, possible non-carcinogen (ADI = 0.608), and IRFMN Oral Classification 1.0.1, carcinogen (ADI = 0.604); therefore, the results of these models are not suitable for a weight of the evidence evaluation. The global ADI was > 0.70 for two of the six models: IRFMN/ISSCAN-CGX v1.0.2, carcinogen (ADI = 0.805), and IRFMN Inhalation Classification 1.0.1, non-carcinogen (ADI = 0.716). However, a manual inspection of the read-across chemicals selected by both models reveals that these compounds either contain structural alerts for carcinogenicity that are not present in the target chemical (such as N-N=O), or do not contain the critical functional group (i.e. amide) in the target chemical. Additionally, the IRFMN-ISSCAN-CGX model has a concordance index of < 0.7 (0.676), and IRFMN Inhalation Classification 1.0.1 model has an accuracy index < 0.70 (0.494), therefore, the results of these models were not included in the weight of evidence (Appendix E).

- U.S. EPA 2019, 2021
  - ToxServices attempted to evaluate N-[3-(dimethylamino)propyl]stearamide monoacetate using OncoLogic (v9.0) (U.S. EPA 2021). However, OncoLogic 9.0 could not evaluate N-[3-(dimethylamino)propyl]stearamide monoacetate; therefore, ToxServices evaluated the carcinogenic potential of N-[3-(dimethylamino)propyl]stearamide monoacetate as its two constituents, stearic acid (aliphatic carboxylic acid) and N-[3-(dimethylamino)propyl]stearamide (aliphatic amine), following cleavage of the amide functional group using OncoLogic (v8.0) (U.S. EPA 2019).
  - According to OncoLogic, aliphatic carboxylic acids are of low carcinogenic concern. OncoLogic v8.0 divides aliphatic carboxylic acids into high molecular weight (MW) (C < 20), medium size (C = 6-20) and low MW (C < 6). A number of metabolically persistent aliphatic carboxylic acids (i.e., perflourinated fatty acid like perfluoroooctanoic acid; ω – 1 branched fatty acids like 2-ethylhexanoic acid) have been shown to be nongenotoxic carcinogens, particularly in those peaking around 7 – 9 carbons. Stearic acid is a C18 aliphatic carboxylic acid, it does not have these structural features; therefore, stearic acid has low cancer concern.
  - According to OncoLogic, aliphatic amines are generally considered not to have significant carcinogenicity unless the alkyl group is small or specific functional groups are present. These include unhindered terminal double bonds, terminal mono-halogens, and N-hydroxylated amines. Since N-[3-(dimethylamino)propyl]stearamide does not contain any of the three specific functional groups identified above and is not diethanolamine or triethanolamine, the carcinogenic potential of N-[3-(dimethylamino)propyl]stearamide is low.

  - Overall, the carcinogenic potential of N-[3-(dimethylamino)propyl]stearamide monoacetate is low (Appendix F).
- DTU 2023
  - ToxServices evaluated N-[3-(dimethylamino)propyl]stearamide monoacetate with the Danish (Q)SAR Database for carcinogenicity (DTU 2023, Appendix G). N-[3-(dimethyl amino)propyl]stearamide monoacetate is in the domains of all seven E Ultra and all seven Leadscope FDA RCA cancer models and predicted to be negative in all models (i.e., male rat, female rat, rat, male mouse, female mouse, mouse, and rodent). Regarding the liver specific cancer in rat or mouse model, Case Ultra, SciQSAR, and overall battery predictions are negative and the compound is within their applicability domains; N-[3-(dimethylamino)propyl]stearamide monoacetate is outside the applicability domain of the Leadscope model (Appendix G).
- Based on the weight of evidence, a score of Low was assigned. Based on the lack of experimental data identified for the target chemical and surrogates, modeling with statistical based, and expert rule-based models (i.e., OECD Toolbox, VEGA, Oncologic, and Danish QSAR) were used to evaluate the carcinogenicity of N-[3-(dimethylamino)propyl]stearamide monoacetate. Two of the six carcinogenicity predictions in VEGA were within the applicability domain; however, ToxServices discounted both predictions based on lack of similarity in critical functional groups compared to the target compound. OECD Toolbox did not identify structural alerts for non-genotoxic and genotoxic carcinogenicity. OncoLogic predicted it to be of low concern and Danish QSAR predicted the target chemical to be non-carcinogenic in all models within their applicability domains. Based on the overall negative predictions from rule-based (OncoLogic, and OECD Toolbox) and statistical-based (Danish QSAR) models, N-[3-(dimethylamino)propyl]stearamide monoacetate is not likely to be carcinogenic.

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for mutagenicity/genotoxicity based on the negative results for mutagenicity and clastogenicity obtained in *in vitro* studies performed with the target chemical. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). Confidence in the score is high based on high quality, measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation test conducted according to OECD Guideline 471. *Salmonella typhimurium* tester strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* tester strain WP_2 *uvr A* were exposed to N-[3-(dimethylamino)propyl]stearamide monoacetate (purity unspecified) in sterile water at concentrations up to 5,000 µg/plate with and without metabolic activation (liver homogenate (S9) prepared from male Sprague-Dawley rats induced with Aroclor 1254). Negative and positive controls (4-nitroquinoline-N-oxide, 9-aminoacridine, 2-nitrofluorene, sodium azide, benzo(a)pyrene, and 2-aminoanthracene) were reported as valid. No cytotoxicity was reported, but the compound was tested up to guideline limit concentrations, precipitating concentrations for TA98 tester strains of 667 µg/plate without metabolic activation and 1,000 µg/plate with metabolic activation, and precipitating concentrations for TA100 tester strain 3,333 667 µg/plate with and without

metabolic activation. No increase in the mutation frequency was reported in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).

- *In vitro*: Negative results were obtained in a GLP-compliant chromosome aberration test conducted according to OECD Guideline 473/EU Method B.10. Human peripheral blood lymphocytes (HPBL) were exposed to N-[3-(dimethylamino)propyl]stearamide monoacetate (purity unspecified) in water up to 5 µg/mL with metabolic activation for 20-hours, up to 10 µg/mL with metabolic activation for 4-hours and a 16-hour recovery, and up to 5 µg/mL and up to 2.5 µg/mL without metabolic activation (S9) for 4 and 20 hours, respectively. Test concentrations were determines based on a preliminary test with concentrations up to 2,000 µg/mL. Positive (i.e., mitomycin C and cyclophosphamide), and vehicle controls were reported as valid. No cytotoxicity or precipitation were observed, but the compound was tested up to the guideline limit concentration in the preliminary study. No increase in the frequency of chromosome aberrations was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for lack of specific reproductive toxicity observed with the target chemical in repeated dose toxicity studies and with the surrogate N-[3-(dimethylamino)propyl]stearamide in reproductive and developmental toxicity screening tests and repeated dose toxicity studies. Reduced number of implantation sites were found in the presence of maternal toxicity in rats exposed to surrogate N-[3-(dimethylamino)propyl]stearamide in a reproduction / developmental toxicity screening test, which attributed to parental systemic toxicity rather than direct reproductive toxicity. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and there is no evidence of reproductive toxicity (CPA 2018b). The confidence in the score is low as it is based on screening assays.

- 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 2023a
  - *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (5/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in propylene glycol at 0, 20, 100, 250, and 500 mg/kg/day via gavage daily for 14 days. For 100 mg/kg males, absolute accessory sex organ weights were significantly different than controls; however, this was considered incidental and, therefore, not treatment-related. Furthermore, there was no evidence of a dose-dependent response for this effect and no gross pathology or histopathology findings for the accessory sex organs. No other effects were found on reproductive organs (Klimisch 1, reliable without restriction).
    - Note: the above study was used as the range-finding study for the OECD Guideline 421 study summarized below.
  - *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 5, 25, 100, and 250 mg/kg/day via gavage daily for 28 days. There were no adverse treatment related effects on organ weights, histopathology and gross pathology of reproductive organs. (Klimisch 1, reliable without restriction).

- ECHA 2023c
    - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: A GLP-compliant repeated dose toxicity study conducted in a manner similar to OECD Guideline 407/EU Method B.7 was performed with Crl:WI(Han) rats (3/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide (purity not specified) in propylene glycol at 0, 50, 200, or 500 mg/kg/day via gavage for 14 days. The animals were evaluated for clinical signs of toxicity, body weight, body weight changes, food consumption, hematology, clinical chemistry, organ weights, gross pathology, and histopathology. All animals in the high dose group were sacrificed on days 6-8 for humane reasons. No mortality was observed in the low or mid dose groups. High dose animals exhibited reduced size of the seminal vesicles, prostate, and epididymides. No treatment-related effects on histopathological observations were observed in the low or mid dose groups. In the high dose group, histopathological changes included slight degeneration of spermatids and massive degree of absence of spermiation in the testes, massive degree of oligospermia and slight seminiferous cell debris in the epididymides, slight reduced prostate content, and moderate reduced contents of the seminal vesicles (Klimisch 1, reliable without restriction).
        - Note: the above study was used as the range-finding study for the OECD Guideline 421 study summarized below.
    - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: A GLP-compliant reproduction / developmental toxicity screening test conducted according to OECD Guideline 421/OPPTS 870.3550 was performed with Crl:WI(Han) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide (100% active ingredient (a.i.)) in propylene glycol at 0, 20, 70, or 200 mg/kg/day via gavage. Males were dosed for a total of 28 days, including two weeks prior to mating, during mating, and up to the day prior to sacrifice. Females were dosed for 41-54 days covering two weeks prior to mating, during mating, during gestation, and until postnatal day 4. The parental animals were evaluated for clinical signs of toxicity, sperm parameters, reproductive indices, gross pathology, and histopathology. Litter observations included the number and sex of pups, survival, body weight, and presence of gross external abnormalities. No treatment-related effects were observed on clinical signs of toxicity, sperm parameters, or parental gross pathological or histopathological findings. Parental males in the high dose group exhibited decreased body weights during the first 2 weeks of treatment. Although body weight gain increased subsequently, mean body weights were less than controls during the treatment period. Decreased body weight gains were measured for mid and high dose females prior to mating or during the mating phase, and for high dose females during pregnancy. In the high dose group, food intake was decreased in males during the pre-treatment period and in females during the first week of premating period and during pregnancy and lactation. A statistically significant decrease in the number of implantation sites was observed at 200 mg/kg/day, but this was attributed to low numbers for two females in this group; after excluding the values for these two females, the results were not significantly different between the high and mid dose groups. No treatment-related effects were observed on mating, fertility and conception indices, pre-coital time, the number of corpora lutea, gestation index and duration, parturition, or maternal care. Additionally, no adverse effects on early postnatal development were observed with treatment. However, significantly decreased mean number of living pups were observed in the mid and high dose groups: 4/9 high dose females had litter sizes of 3-9 pups (the lowest litter sizes belonged to the two females with decreased number of implantation sites) and 5/9 females had litter sizes of 7-9 pups compared to 12-15 for most of the control animals and 11.8 for the historical controls.

Due to the correlation between lower litter size and lower number of implantation sites, study authors study authors concluded that the lower number of of living pups at 70 and 200 mg/kg/day were the results of lower implantation. The study authors attributed the reduced number of implantation sites and subsequent decreased litter size on the reduced body weight gain and food consumption observed in the high dose females. The study authors identified a parental toxicity NOAEL of 70 mg/kg/day based on reduced body weight and food consumption, a female reproductive NOAEL and LOAEL of 70 and 200 mg/kg/day, respectively, based on the decreased number of implantation sites, and a male reproductive NOAEL of 200 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).

- *Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: Based on this weight of evidence, the authors of the ECHA dossier for N-[3-(dimethylamino)propyl] stearamide concluded reproductive effects of reduced implantation sites resulting in lower litter size were secondary to maternal toxicity (i.e., reduced body weight/weight gain and food consumption).

- MHLW 2014
  - **Note:** The text of the study summarized below was only available in Japanese. However, the tables summarizing the results provided in the report are written in English and ToxServices relied on the information included in the tables and Google translate to write the following summary.
  - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: A combined repeat dose toxicity study with reproductive/developmental toxicity screening test, conducted according to Japanese Chemical Substances Control Law, was performed with Crl:CD(SD) rats (12/sex/dose group) administered oral doses of N-[3-(dimethylamino) propyl]stearamide (purity not specified) in water at 0, 15, 50, or 150 mg/kg/day. Males were dosed for up to 42 days and females were dosed for 2 weeks prior to pregnancy, through mating and gestation, and up to day 4 of lactation for a total of 42 – 49 days. The parental animals were evaluated for estrous cyclicity, reproductive performance, length of gestation, implantation index, delivery index, number of corpora lutea, and number of implantation scars. No treatment-related effects were observed on these parameters. However, high dose males had increased relative epididymis weights, which was not found in animals that were allowed to recover for 15 days at the end of the study. No histopathological findings were reported for epididymis.
- AICIS 2019
  - *Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: The Australian Industrial Chemicals Introduction Scheme (AICIS) evaluated the reproductive toxicity of fatty acid amido propyl dimethylamines, including the surrogate. AICIS concluded the reproductive effects found in the range finding and main study were not considered direct effects but rather secondary effects following maternal toxicity caused by the corrosivity of the test substance.
- Based on the weight of evidence, a score of Low was assigned. No treatment related effects on reproductive organs (i.e., organ weight, histopathology, and gross pathology of reproductive organs) were found in two subacute GLP-compliant, OECD Guideline 407/EU Method B.3 oral repeated dose toxicity studies in rats, even in the presence of significant systemic toxicities. However, no data for the target chemical examining reproductive parameters during mating through gestation were identified for the target chemical; therefore, repeated dose toxicity study and reproductive and developmental screening test results were included for surrogate N-[3-(dimethylamino)propyl] stearamide, the metabolite/hydrolysis product of the target chemical. In an oral combined repeat dose toxicity study with reproductive/developmental toxicity screening test in rats, increased relative

epididymis weights in high dose males (150 mg/kg/day) were reported in which the effect resolved after removal of treatment and a 15-day recovery period. Additionally, microscopic changes on the seminal vesicles, prostate, and epididymis of male rats were found in a 14-day range finding study (500 mg/kg/day). While in the main study, a GLP-compliant reproduction / developmental toxicity screening test conducted according to OECD Guideline 421/OPPTS 870.3550 in rats, no microscopic or macroscopic changes to reproductive organs were found up to the highest dose tested, 200 mg/kg/day. However, a NOAEL of 70 mg/kg/day and LOAEL of 200 mg/kg/day was identified for parental toxicity and female reproductive toxicity based on reduced number of implantation sites. The authors of the ECHA dossier (ECHA 2023c) and AICIS (2019) concluded these effects were secondary effects caused by the corrosivity of surrogate N-[3-(dimethylamino)propyl]stearamide likely affecting the ability to consume food and, therefore, causing reduced body weight gain in dams. The study authors attributed the reduced number of implantation sites and subsequent decreased litter size on the reduced body weight gain and food consumption observed in the high dose females. Furthermore, no treatment related effects were reported in any of the remaining reproductive parameters, including mating, fertility, and conception indices, male reproductive organ weight, or spermatogenesis. Based on this weight of evidence, ToxServices did not classify the target chemical as a reproductive toxicant, which is supported by a lack of authoritative listings..

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Moderate for developmental toxicity based on the reduced pup body weights in the presence of maternal toxicity observed in the combined repeat dose toxicity study with reproductive/developmental toxicity screening test in rats exposed to surrogate N-[3-(dimethylamino)propyl]stearamide. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity is observed in animals (CPA 2018b). The confidence in the score is low as it is not clear if the reduced pup body weights is secondary to maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023c
  - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: In the previously described GLP-compliant reproduction / developmental toxicity screening test conducted according to OECD Guideline 421/OPPTS 870.3550 was performed with Crl:WI(Han) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino) propyl]stearamide (100% a.i.) in propylene glycol at 0, 20, 70, or 200 mg/kg/day via gavage. Females were dosed for 41-54 days covering two weeks prior to mating, during mating, during gestation, and until postnatal day 4. Litter observations included the number and sex of pups, survival, body weight, and presence of gross external abnormalities. No treatment-related effects were observed on these parameters. The study authors identified a maternal toxicity NOAEL of 70 mg/kg/day based on reduced body weight/weight change and food consumption, and a developmental toxicity NOAEL of 200 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction).
  - *Dermal: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: A GLP-compliant prenatal developmental toxicity test conducted in a manner similar to OECD Guideline 414 was performed with pregnant female New Zealand White rabbits (20/dose group) administered dermal doses of N-[3-(dimethylamino)propyl]stearamide (purity not specified) in 30% isopropanol/70% water at 0, 5, 100, or 200 mg/kg/day on gestational days

7-18. The animals were sacrificed on gestational day 23. Maternal examinations included clinical signs of toxicity, body weight, body weight gain, and ovarian and uterine content. Fetal examinations included examinations for external, visceral, head, and skeletal malformations. Mid and high dose dams exhibited alopecia, excess lacrimation, ungroomed coat, and green-matted fur around the mouth and rump. Decreased maternal body weight gains and food consumption were observed in the mid and high dose groups. The treatment did not adversely impact the pregnancy incidence, the numbers of corpora lutea, or resorption. The incidence of fetal malformations did not increase with treatment and no effects on fetal body weights per litter or percentage male fetuses were observed. The study authors identified a maternal toxicity NOAEL and LOAEL of 5 and 100 mg/kg/day, respectively, based on the decreased body weights and food consumption, and a developmental toxicity NOAEL of 200 mg/kg/day, the highest dose tested, based on the lack of adverse effects on development (Klimisch 2, reliable with restrictions).

- MHLW 2014
  - **Note:** The text of the study summarized below was only available in Japanese. However, the tables summarizing the results provided in the report are written in English and ToxServices relied on the information included in the tables and Google translate to write the following summary.
  - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: In the previously described combined repeat dose toxicity study with reproductive/developmental toxicity screening test, conducted according to Japanese Chemical Substances Control Law, was performed with Crl:CD(SD) rats (12/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide (purity not specified) in water at 0, 15, 50, or 150 mg/kg/day. Males were dosed for up to 42 days and females were dosed for 2 weeks prior to pregnancy, through mating and gestation, and up to day 4 of lactation for a total of 42 – 49 days. No treatment-related effects were measured on the body weights of female rats. High dose females exhibited decreased reticulocyte counts at the end of the treatment period. High dose females in the satellite group exhibited increased blood urea nitrogen (BUN) and alkaline phosphatase (ALP) at the end of the dosing period, and high dose females in the recovery group exhibited increased serum total cholesterol. At the end of the recovery period, high dose females exhibited decreased relative brain, thyroid, and adrenal weights. Histopathological changes observed in at least 3 high dose females but not in at least 3 control females were limited to very slight microgranuloma of the liver. For the satellite group, histopathological changes observed in high dose group females were observed in the forestomach (very slight squamous cell hyperplasia, moderate to marked edema of the lamina propria/submucosa, and very slight inflammatory cellular infiltration of the submucosa) and kidney (very slight basophilic tubule of the cortex and very slight interstitial lymphocytic cellular infiltration). The offspring were evaluated for number at birth, number live pups, sex ratio, delivery index, birth index, live birth index, number live on postnatal day 4, viability index, body weight, and number of external abnormalities. Decreased body weights on postnatal day 4 were measured for male and female pups born to high dose dams. No other treatment-related effects were observed. ToxServices identified a maternal toxicity NOAEL and LOAEL of 50 and 150 mg/kg/day, respectively, based on the treatment-related effects on hematology, clinical biochemistry, organ weights, and histopathology in the liver, for stomach, and kidney observed in the high dose group females, and a developmental toxicity NOAEL and LOAEL of 50 and 150 mg/kg/day, respectively, based on the decreased offspring body weights on postnatal day 4.

- Based on the weight of evidence, a score of Moderate was assigned. No adverse treatment-related effects on development were identified up to 200 mg/kg/day, the highest dose tested, in a GLP-compliant OECD Guideline 421 oral reproduction / developmental toxicity screening test in rats, and a GLP-compliant dermal prenatal developmental toxicity study conducted in a manner similar to OECD Guideline 414 in rabbits exposed to surrogate N-[3-(dimethylamino)propyl]stearamide. However, treatment-related effects (i.e., reduced offspring weights on postnatal day 4) were reported in the presence of maternal toxicity at 150 mg/kg/day in an oral combined repeated dose toxicity study with reproduction/developmental toxicity screen test in rats exposed to surrogate N-[3-(dimethylamino)propyl]stearamide. Based on the limited evidence of developmental toxicity in this study, ToxServices conservatively assigned a score of Moderate.

Endocrine Activity (E) Score (H, M, or L): DG
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Data Gap for endocrine activity based on a lack of sufficient data identified for this endpoint. No endocrine effects (specific effects examined were unspecified) were found in a 28-day oral study with the target compound, and modeling did not identify any endocrine activity concerns. Adrenal and thyroid weights were changed without histopathological changes in an oral combined repeated dose toxicity study with reproductive and developmental toxicity screening for the surrogate. Due to insufficient *in vivo* data for all relevant endocrine pathways (i.e., estrogen agonism and antagonism, androgen agonism and antagonism, thyroid, and steroidogenesis), a Data Gap was assigned.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 5, 25, 100, and 250 mg/kg/day via gavage daily for 28 days. There were no adverse treatment related effects on endocrine exam (specific parameters evaluated unknown), and organ weights, histopathology and gross pathology of endocrine organs (Klimisch 1, reliable without restriction).
- MHLW 2014
  - *Oral: Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: In a previously described combined repeat dose toxicity study with reproductive/developmental toxicity screening test, Crl:CD(SD) rats (12/sex/dose group) were administered oral doses of N-[3-(dimethylamino)propyl]stearamide (purity not specified) in water at 0, 15, 50, or 150 mg/kg/day. Males were dosed for up to 43 days, and females were dosed for up to 22 days prior to pregnancy, 26 days of pregnancy, and up to day 5 of lactation, for a total of 53 days. Recovery groups of 5 males and females were dosed with 0 or 150 mg/kg/day as above and then maintained for 15 days without dosing, and satellite groups of 10 females were dosed with 0 or 150 mg/kg/day for up to 43 days. High dose males had increased relative adrenal weight at the end of the dosing period and decreased relative adrenal weight at the end of the recovery period. High dose females had decreased relative thyroid and adrenal weights at the end of the recovery period. However, no histopathological changes were found in these organs.

        - Due to the lack of histological changes to the adrenal gland and thyroid and the lack of examination of hormone levels in this study, the significance of changed endocrine organ weights is unclear.
- U.S. EPA 2023b
    - N-[3-(Dimethylamino)propyl]stearamide monoacetate was not evaluated as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century; however, the ToxCast CERAPP Potency Level model predicted N-[3-(dimethylamino)propyl]stearamide monoacetate was inactive for estrogen receptor agonist, antagonist, and binding (Appendix H).
- DTU 2023
    - Modeling in the Danish QSAR database provides the following results that are within the applicability domains of the models (Appendix I):
        - N-[3-(Dimethylamino)propyl]stearamide monoacetate is predicted to be negative for estrogen receptor α binding (full training set, human *in vitro*) and androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by the CaseUltra, Leadscope, and SciQSAR models;
        - N-[3-(Dimethylamino)propyl]stearamide monoacetate is predicted to be negative for estrogen receptor α binding (balanced training set, human *in vitro*) by the model battery consisting of negative and in domain predictions by the CaseUltra and SciQSAR models;
        - N-[3-(Dimethylamino)propyl]stearamide monoacetate is predicted to be negative for estrogen receptor α activation (human *in* vitro) by the model battery consisting of negative and in domain predictions by the Leadscope and SciQSAR models;
        - N-[3-(Dimethylamino)propyl]stearamide monoacetate is predicted to be negative for estrogen receptor activation (CERAPP data *in vitro*) and for androgen receptor activation (CoMPARA data *in vitro*) and thyroperoxidase (TPO) inhibition (QSAR1 and QSAR2, rat *in vitro*) by the Leadscope models.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): M

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of was assigned a score of Moderate for acute toxicity based on an oral LD_{50} value of 1,403 mg/kg in rats exposed to the target chemical. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are greater than 300 to 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on measured data from guideline studies on the target compound.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
    - *Oral*: LD_{50} (female Crj:CD(SD) rat) = 1,403 mg/kg (GLP-compliant, OECD Guideline 425) (Klimisch 1, reliable without restriction)
    - *Inhalation*: 4-hour aerosol LC_{50} (male and female Crj:CD(SD) rat) > 0.66 mg/L, the maximum attainable aerosol concentration (GLP-compliant, OECD Guideline 403) (Klimisch 1, reliable without restriction)

- ECHA 2023a, U.S. EPA 2014
    - *Dermal*: LD_{50} (male and female Crj:CD(SD) rat) ≥ 5,000 mg/kg (GLP-compliant, OECD Guideline 402/EU Method B.3) (Klimisch 1, reliable without restriction)

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Moderate for systemic toxicity (single dose) ToxServices classifying it to GHS Category 3 for respiratory irritation. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation (CPA 2018b). Confidence in the score is high based on high quality measured data on the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
    - *Oral*: In the previously described GLP-compliant oral acute toxicity study conducted according to OECD Guideline 425, female Crj:CD(SD) rats (3/dose) were exposed to a single dose of 175, 550, 1,750, 2,000, 5,000 mg/kg N-[3-(dimethylamino)propyl]stearamide monoacetate (purity unspecified) in 0.1% Tween in deionized water via gavage and observed for 14 days. No treatment related effects were reported on body weights/weight changes, organ weights, and histopathology. At the top doses, 2,000 and 5,000 mg/kg/day, all animals died within a day after dosing with clinical signs of abnormal gait, cold to touch, dehydration, diarrhea, eyelid ptosis, hunched posture, decreased activity, moribund status, decreased muscle tone, pallor, high posture, prostrate, salivation, soiled skin or fur, and wet fur preceding death. No mortalities were reported for remaining doses. At 1,750 mg/kg/day, clinical signs of diarrhea, soiled skin or fur, and wet fur were reported in all animals between days 2 and 3. At 500 mg/kg/day, only diarrhea and soiled skin or fur were reported in 2/3 animals between days 1 and 3. At the lowest dose, 175 mg/kg/day, no clinical signs were reported. Furthermore, gross pathology findings of 4 animals, including three 2,000 mg/kg/day and one 5,000 mg/kg/day animals, found brown/green staining of the perineum in all animals and yellow/clear fluid in the small intestines and cecum whole body thinness (Klimisch 1, reliable without restriction).
        - ToxServices noted that at non-lethal doses, clinical signs including diarrhea, soiled skin, and wet fur were reversible and not sufficient for GHS classification. There were no gross pathology findings at non-lethal doses.
    - *Inhalation:* In the previously described GLP-compliant acute inhalation study conducted according to OECD Guideline 403, male and female Crj:CD(SD) rats (5/sex) were exposed nose-only to the maximum attainable concentration of 4 mg/L of a water-diluted atmosphere of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) for 4 hours. This is equivalent to 0.66 mg/L solid aerosol of the test compound. All animals survived the exposure period; however, 2/5 and 1/5 mortalities were reported for males and females, respectively, during the 14-day observation/recovery period. Clinical signs of labored breathing occurred in 3/5 males and 3/5 females between days 1 and 4, lung noise in 1/5 males between days 2 and 4 and in 1/5 females on day 4, reduced respiration in 1/5 males on day 2, red discharge in all animals on days 1 to 4, gasping in 3/5 males and 3/5 females on days 1-4, and discolored yellow, fur in 1/5 males on day 2 and in 2/5 females on days 2 to 4. All male rats lost 6.6 – 13% of their body weight on test day 2, with two males dying later, one on the same day (day 2) and the other on day 3. One of the three surviving males lost

7.7% and 1.7% of his body weight on test days 3 and 4, respectively. For female rats, 3/5 lost 12-13% of their body weight on test day 2 with one of these females dying on the same day. Of the four surviving females, 2/4 lost < 7% of their body weight on test day 3, and one of the 4 lost 4.1% of her body weight on test day 4. No treatment related effects were reported for remaining animals on body weight/ body weight gain or gross pathology. Macroscopic abnormalities were reported for 3 male and 4 female rats, including 2 dead males and 1 dead female. Five animals (2 males and 3 females) had multifocal to diffuse dark discoloration of the lungs (mostly in the cranial portion of the lungs). Both deceased males had red staining on the face, with expanded lungs and cloudy discoloration of the left eye reported in one of the deceased males. Macroscopic findings of deceased females included thick, tan discoloration of the trachea (Klimisch 1, reliable without restriction).

    - ToxServices notes that the treatment related effects (breathing difficulties and macroscopic abnormalities of the lungs) observed in this study are related to respiratory irritation, likely from the corrosive nature of the test substance.

- ECHA 2023a, U.S. EPA 2014
    - *Dermal*: In the previously described GLP-compliant acute dermal toxicity test conducted according to OECD Guideline 402/EU Method B.3, male and female rats (5/sex) were administered topical applications of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in deionized water at 5,000 mg/kg under semi-occlusive dressing for 24 hours. An observation period of 14 days followed the exposure period. No mortalities occurred and no treatment related effects were reported on body weight or gross pathology. One female exhibited ulceration of the skin on days 2 and 3, but this effect resolved by day 4. Clinical signs of toxicity observed in all animals between days 3 and 8 included desquamation, hyperkeratosis, and epidermal scaling. Scabbing on the back of one female was present on days 12-14. Dermal edema was observed in 5/5 males and 4/5 females on day 2 but all signs of edema cleared by day 3. Erythema was observed in all animals on days 2 and 3, and one female exhibited erythema on days 4-9 (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, a score of Moderate was assigned. In a GLP-compliant, OECD Guideline 425 study, a lack of systemic toxicity (excluding neurotoxicity) was reported in surviving animals following single oral doses up to 1,750 mg/kg in rats exposed to the target chemical, which indicates that the LOAELs would exceed the guidance value of 300 mg/kg for Category 1. Furthermore, reported clinical signs are related to neurotoxicity and/or local irritation (see neurotoxicity and irritation endpoints) that are likely related to the corrosivity of the target chemical; therefore, N-[3-(dimethylamino)propyl]stearamide monoacetate is not a concern for systemic toxicity with single oral exposure at non-corrosive concentrations. For the dermal route, a lack of systemic toxicity effects were reported in the only acute dermal toxicity study, a GLP-compliant OECD Guideline 402/EU Method B.3 study, identified for the target chemical. For the inhalation route, there were no systemic toxicity effects reported in surviving animals following single inhalation exposures up to the maximum attainable concentration of 4 mg/L, equivalent to 0.66 mg/L solid aerosol concentration in rats in a GLP-compliant OECD Guideline 403 study. Reduced body weight and lung pathology were found in surviving animals, but were likely related to the corrosiveness of the compound. Respiratory effects (i.e., labored breathing and discolored lungs) were observed in this study up to day 4 in surviving animals and appear to have resolved by the end of the observation period. Therefore, ToxServices classified N-[3-(dimethylamino)propyl]stearamide monoacetate as GHS Category 3. While these effects were observed at a concentration of 0.66 mg/L, that is below the guidance value for GHS Category 1 (i.e.,

1 mg/L for aerosol), they were transient and the severity does not warrant worse GHS classifications than Category 3.

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of High for systemic toxicity (repeated dose) based on ToxServices classifying the target chemical as a Category 1 repeated dose systemic toxicant under GHS criteria. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when they are classified as GHS Category 1 repeated dose systemic toxicants (CPA 2018b). The confidence in the score is reduced as the effects reported are likely related to local irritation from the corrosivity of 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 2023a
  - *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (5/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 20, 100, 250, and 500 mg/kg/day via gavage daily for 14 days. No mortality was observed in the low or mid dose groups; however, four rats in the high dose group were sacrificed on day 13 for humane reasons, with weight loss and reduced in food consumption reported prior to sacrifice. Clinical signs of reflux rhinitis was reported for high dose animals and one 250 mg/kg/day male, including reflux/regurgitation of the test substance into the nasal passages followed by gray material assumed to the test substance, erosions/ulcers and acute to severe inflammation of the nasal cavity. Adverse treatment related effects on body weight, body weight gain, food consumption, and food efficiency were reported in high dose animals. Body weights for high dose males were 14% lower than controls on day 14. Body weights for high dose females were 11% lower than controls on day 8, and comparable to controls by the end of the study. Similarly, body weight gain for high dose females was 95% lower than control during week 1 (days 1-8), it was comparable to controls during week 2 (days 8-14). Overall body weight gains (days 1-14) for high dose males and females were 43% and 33%, respectively, lower than controls during the study was not significantly different than controls. Mean daily food consumption for high dose males (32%) and females (29%) were significantly lower than controls, and the mean daily food efficiency for high dose males (18%) and females (4%) was not significantly lower than controls. Furthermore, significant reduced food efficient was reported for high dose females during days 1-8. Overall food consumption for high dose males and females was 18% and 4%, respectively, lower than the control group. Significant changes in mean clinical chemistry parameters and urinalysis were reported; however, these were considered non-adverse because the effects lacked a concentration-related pattern and/or were not associated with changes in related parameters. No adverse treatment related effects were reported on hematology, functional observation battery, organ weights (females), and gross pathology. High dose males exhibited significant treatment-related organ weight changes; however, due to the small number of surviving animals, there is uncertainty regarding if these effects were due to body weight loss (17.3%). In high dose animals, non-neoplastic lesions were found in the stomach (hyperplasia, inflammation, degeneration, erosion/ulcer), likely the result of irritation from the test substance. In 250 mg/kg males and 500 mg/kg males and females, non-neoplastic

lesions were found in the nose (minimal to severe reflex rhinitis). Additionally, in 250 and 500 mg/kg males and females, lesions found in the thymus (necrosis, atrophy), pancreas (decrease of zymogen granules, and salivary glands (atrophy) were considered secondary to test substance induced stress. The study authors identified a male and female systemic toxicity NOAEL of 100 and 250 mg/kg/day, respectively, based on the reductions in body weight and nutritional parameters in males and females at 500 mg/kg/day, adverse histopathology findings of the nose in males at 250 mg/kg/day and of the nose and stomach in males and females at 500 mg/kg/day (Klimisch 1, reliable without restriction).

- Note: the above study was used as the range-finding study for the 28-day OECD Guideline 407 study summarized below.

- *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 5, 25, 100, and 250 mg/kg/day via gavage daily for 28 days. There were no adverse treatment related effects on water consumption, ophthalmology, clinical chemistry, endocrine exam, urinalysis, and histopathology (neoplastic). One 250 mg/kg male was sacrificed on day 12 for humane reasons, histopathology and gross pathology examinations found lesions induced by treatment related gastrointestinal distension with gas. In the 100 and 200 mg/kg/day dose groups, treatment related clinical signs included labored and rapid breathing, gasping, lung noise, distended abdomen, diarrhea, and brown/red skin discoloration. Body weights were reduced by 10% and 17% at 100 and 250 mg/kg/day, respectively, in males. Overall body weight gain were also significantly reduced (80 and 60%, respectively) compared to controls. For the top dose males these effects correlated with reduced nutritional parameters, while no effects were reported for food consumption and food efficiency. Adverse treatment-related effects on hematology for top dose animals, included an increase in absolute neutrophil count which was considered an indication of an inflammatory response likely due to reflux rhinitis, a slight increase in red cell mass in males which was considered an indication of secondary hemoconcentration. For the males and females of dose groups at and above 25 mg/kg, rhinitis was reported due to reflux of the test substance into the nasal cavity. In top dose males and females, non-neoplastic lesions in the larynx were reported. Additionally, at 250 mg/kg, adverse test article-related microscopic changes were found in the stomach (mucosal epithelial vesicle formation, mucosal hyperplasia, and inflammation in the forestomach), duodenum (crypt hyperplasia), jejunum (crypt hyperplasia, males only), and mesenteric lymph nodes (histiocytosis). Non-neoplastic lesions of the stomach, small intestine, and thymus were also reported for top dose animals. Effects found in the lymphoid organs of top dose animals and 100 mg/kg males, along with adrenal and lymphoid weight changes reported for top dose animals were considered stress-related and secondary to severe nasal lesions from reflux rhinitis. The study authors identified a systemic toxicity NOAEL of 5 mg/kg/day, based on pathology findings of rhinitis due to exposure of the test substance in the nasal cavity at the LOAEL of 25 mg/kg/day (Klimisch 1, reliable without restriction).

  - As the duration of exposure in the above study was less than 90 days, ToxServices modified the GHS guidance values of 10 and 100 mg/kg/day (UN 2021) by a factor of 3 (28 days are roughly one third of 90 days) to 30 and 300 mg/kg/day. As the LOAEL of 25 mg/kg/day is less than the adjusted guidance value of 30 mg/kg/day, ToxServices classified N-[3-(dimethylamino)propyl]stearamide monoacetate as a Category 1 repeated dose systemic toxicant under GHS criteria.

- AICIS 2019
    - *Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*: The AICIS evaluated the systemic toxicity of fatty acid amido propyl dimethylamines, including the surrogate. AICIS concluded the toxicity effects reported for this chemical class were caused by their corrosivity.
- Based on the weight of evidence, a score of High was assigned. A high degree of systemic toxicity was found in two subacute GLP-compliant, OECD Guideline 407/EU Method B.3 oral repeated dose toxicity studies in rats. For the 14-day study, a systemic toxicity NOAEL of 100 mg/kg/day, was identified for males based on histopathology findings of the nose. For the 28-day study, a systemic toxicity NOAEL and LOAEL of 5 and 25 mg/kg/day, respectively, was established based on rhinitis due to exposure of the test substance in the nasal cavity. This LOAEL is below the adjusted GHS guidance value of 30 mg/kg/day for Category 1 (UN 2021). While the effects reported are likely related to the corrosivity of the target chemical (ECHA 2023a, AICIS 2019), the severity of the effects and the LOAEL value warrant GHS classification. Therefore, ToxServices classified N-[3-(dimethylamino)propyl]stearamide monoacetate as a Category 1 specific target organ toxicant following repeated oral exposure under GHS criteria (UN 2021).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for neurotoxicity (single dose) based on lack of clinical signs and gross pathology findings indicative of specific neurotoxicity at non-lethal doses in acute oral, dermal and inhalation studies. Reported clinical signs were mostly likely secondary to the corrosivity of the test compound. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is low as the acute toxicity studies did not perform neurobehavioral exams.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
    - *Oral*: In the previously described GLP-compliant oral acute toxicity study conducted according to OECD Guideline 425, female Crj:CD(SD) rats (3/dose) were exposed to a single dose of 175, 550, 1,750, 2,000, 5,000 mg/kg N-[3-(dimethylamino)propyl]stearamide monoacetate (purity unspecified) in 0.1% Tween in deionized water via gavage and observed for 14 days. The study authors established an oral LD_{50} of 1,430 mg/kg. No treatment related effects were reported on body weights/weight changes, organ weights, and histopathology. At the top doses, 2,000 and 5,000 mg/kg/day, all animals died within a day after dosing with clinical signs of abnormal gait, cold to touch, dehydration, diarrhea, eyelid ptosis, hunched posture, decreased activity, moribund status, decreased muscle tone, pallor, high posture, prostrate, salivation, soiled skin or fur, and wet fur preceding death. No mortalities were reported for remaining doses. At 1,750 mg/kg/day, clinical signs of diarrhea, soiled skin or fur, and wet fur were reported in all animals between days 2 and 3. At 500 mg/kg/day, only diarrhea and soiled skin or fur were reported in 2/3 animals between days 1 and 3. At the lowest dose, 175 mg/kg/day, no clinical signs were reported (Klimisch 1, reliable without restriction).
        - ToxServices noted that although clinical signs of abnormal gait, hunched posture, decreased activity, and prostration may suggest neurotoxicity, these effects may be secondary to systemic toxicity related to local irritation from the corrosivity of the target chemical**.**

- *Inhalation:* In the previously described GLP-compliant acute inhalation study conducted according to OECD Guideline 403, male and female Crj:CD(SD) rats (5/sex) were exposed nose-only to the maximum attainable concentration of a water-diluted atmosphere of 4 mg/L N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) for 4 hours. This is equivalent to 0.66 mg/L solid aerosol of the test compound. All animals survived the exposure period; however, 2/5 and 1/5 mortalities were reported for males and females, respectively, during the 14-day observation/recovery period. Clinical signs of labored breathing occurred in 3/5 males and 3/5 females between days 1 and 4, lung noise in 1/5 males between days 2 and 4 and in 1/5 females on day 4, reduced respiration in 1/5 males on day 2, red discharge in all animals on days 1 to 4, gasping in 3/5 males and 3/5 females on days 1-4, and discolored yellow, fur in 1/5 males on day 2 and in 2/5 females on days 2 to 4. All male rats lost 6.6 – 13% of their body weight on test day 2, with two males dying later, one on the same day (day 2) and the other on day 3. One of the three surviving males lost 7.7% and 1.7% of his body weight on test days 3 and 4, respectively. For female rats, 3/5 lost 12-13% of their body weight on test day 2 with one of these females dying on the same day. Of the four surviving females, 2/4 lost < 7% of their body weight on test day 3, and one of the 4 lost 4.1% of her body weight on test day 4. No treatment related effects were reported for remaining animals on body weight/ body weight gain or gross pathology. No macroscopic abnormalities related to brain or spinal cord physiology were reported (Klimisch 1, reliable without restriction).
    - ToxServices notes that the treatment related effects (breathing difficulties) observed in this study may be related to neurotoxicity; however, these effects are also common with respiratory irritation caused by corrosive substances. As other signs (i.e., red nasal discharge, discolored fur, macroscopic abnormalities of the lungs) are reported that are inconsistent with neurotoxicity, ToxServices did not consider these signs reflective of specific neurotoxicity.
- *Dermal*: In the previously described GLP-compliant acute dermal toxicity test conducted according to OECD Guideline 402/EU Method B.3, male and female rats (5/sex) were administered topical applications of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in deionized water at 5,000 mg/kg under semi-occlusive dressing for 24 hours. An observation period of 14 days followed the exposure period. The study authors established a dermal LD_{50} of ≥ 5,000 mg/kg. No mortalities occurred and no treatment related neurotoxicity effects were reported on clinical signs, body weight, or gross pathology (Klimisch 1, reliable without restriction).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for neurotoxicity (repeated dose) based on ToxServices not classifying it as a repeated dose neurotoxicant under GHS. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data are available, and they are not GHS-classified (i.e., 28-day oral LOAEL values greater than 300 mg/kg/day) (CPA 2018b). The confidence in the score is high based on reliable data 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 2023a
    - *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats

(5/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 20, 100, 250, and 500 mg/kg/day via gavage daily for 14 days. No mortality was observed in the low or mid dose groups; however, four rats in the high dose group were sacrificed on day 13 for humane reasons, with weight loss and reduced in food consumption reported prior to sacrifice. A lack of neurotoxic effects were reported for all parameters of the study, including clinical signs, functional observation battery, and organ weights, histology and gross pathology of the brain and spinal cord (Klimisch 1, reliable without restriction).

- ToxServices identified a neurotoxicity NOAEL of 500 mg/kg/day, the highest dose tested.
- Note: the above study was used as the range-finding study for the 28-day OECD Guideline 407 study summarized below.

- *Oral:* A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407/EU Method B.7 was performed with male and female Crl:CD(SD) rats (10/sex/dose group) administered oral doses of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in 0.1% Tween 80 in deionized water at 0, 5, 25, 100, and 250 mg/kg/day via gavage daily for 28 days. Neurobehavioral examinations included a functional observation battery – sensory activity, grip length, and motor activity. In the 100 and 200 mg/kg/day dose groups, treatment related clinical signs included labored and rapid breathing, gasping, lung noise, distended abdomen, diarrhea, and brown/red skin discoloration. In 250 mg/kg males and females and 100 mg/kg/day males a reduction in the duration of movement and ambulatory movements were reported during the function observation battery; however, reduced motor activity was considered secondary to systemic toxicity. Furthermore, no treatment-related effects were reported for organ weights, histopathology, and gross pathology of the brain and spinal cord (Klimisch 1, reliable without restriction).
  - ToxServices identified a neurotoxicity NOAEL of 250 mg/kg/day, based on the lack of direct effects in the functional observation battery.
  - As the duration of exposure in the above study was less than 90 days, ToxServices modified the GHS guidance values of 10 and 100 mg/kg/day (UN 2021) by a factor of 3 (28 days are roughly one third of 90 days) to 30 and 300 mg/kg/day. The NOAEL of 250 mg/kg/day is within the adjusted guidance values of 30 and 300 mg/kg/day (highest dose tested) for a GHS Category 2 repeated-dose neurotoxicant. However, GHS classification is based on LOAEL rather than NOAEL, and significant systemic toxicity already occurred with a LOAEL of 25 mg/kg (see repeated dose systemic toxicity section above). Therefore, testing at the GHS cutoff of 300 mg/kg/day is not feasible, and ToxServices did not classify N-[3-(dimethylamino)propyl]stearamide monoacetate as neurotoxicant under GHS criteria (UN 2021).

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of High for skin sensitization based on ToxServices classifying it as a GHS Category 1A skin sensitizer due to an EC3 value of < 2% in a GLP-compliant OECD Guideline 429 mouse local lymph node assay (LLNA). GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when they are classified as GHS Category 1a skin sensitizers (CPA 2018b). The confidence in the score is high as it is based on high quality, measured data on the target compound.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a, U.S. EPA 2014
  - A GLP-compliant mouse LLNA conducted according to OECD Guideline 429 was performed with female CBA/JHsd mice (5-6/dose group) administered topical applications of N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) in propylene glycol at 0%, 5%, 25%, 50%, or 70% to the dorsal surface of each ear on three consecutive days. On the sixth day of the study, the animals were sacrificed and the draining auricular lymph nodes were isolated for the proliferation assay. Stimulation indices (SI) were greater than 3.0 for all test concentrations. The EC3 value was calculated by the study authors to be 0.6%, indicating the test substance was a strong sensitizer. The positive control performed as expected (Klimisch 1, reliable without restriction).
    - Based on the results of the above study, ToxServices classified N-[3-(dimethylamino)propyl]stearamide monoacetate as a Category 1A skin sensitizer under GHS criteria (UN 2021). GHS Criteria define Category 1A skin sensitizers as chemicals that produce EC3 values no greater than 2% in an LLNA.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): DG
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Data Gap for respiratory sensitization based on the lack of sufficient 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.
- OECD 2023
  - N-[3-(Dimethylamino)propyl]stearamide monoacetate does not contain any structural alerts for respiratory sensitization (Appendix D).
- DTU 2023
  - N-[3-(dimethylamino)propyl]stearamide monoacetate is predicted to be negative for respiratory sensitization in humans by the SciQSAR model. The predictions from the remaining models were outside their applicability domains (Appendix J).
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of N-[3-(dimethylamino)propyl] stearamide monoacetate according to ECHA's guideline (ECHA 2017), which states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017b). 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 2017b). N-[3-(Dimethylamino) propyl]stearamide monoacetate does not contain any structural alerts for respiratory sensitization, but is a skin sensitizer based on positive experimental data. According to the ECHA guidance, the positive skin sensitization results in animals and lack of structural alerts and evidence of respiratory sensitization indicate that there are insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient).

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation detected in a GLP-compliant, OECD Guideline 404 study in rabbits testing slightly moistened target chemical. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score was high as it was based on reliable, high quality measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - A GLP-compliant skin irritation test conducted according to OECD Guideline 404 was performed with three New Zealand White rabbits (sex unspecified) administered topical applications of 500 mg N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) moistened in water to skin under semi-occlusive conditions for 4 hours. An observation period of up to 72 hours followed the exposure period. At 24, 48, and 72 hours, the individual erythema and edema scores for animals 1, 2, and 3 were 0. No skin irritation was reported at any treated site during the study. The study authors concluded that N-[3-(dimethylamino)propyl]stearamide monoacetate was not irritating to the skin in this study (Klimisch 1, reliable without restriction).

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

N-[3-(dimethylamino)propyl]stearamide monoacetate was assigned a score of Very High for eye irritation/corrosivity based on the severe ocular effects observed in a GLP-compliant, OECD Guideline 405 rabbit study for the target compound, leading to Category 1 classification under GHS criteria. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when they are classified as GHS Category 1 eye irritants (CPA 2018b). The confidence in the score is high as it is based on high quality, measured data on the target compound.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a, U.S. EPA 2014
  - A GLP-compliant ocular irritation test conducted according to OECD Guideline 405 was performed with one New Zealand White rabbit administered an ocular instillation of 0.1 mL N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) and observed up to 24 hours. The eye irritation was evaluated via the Draize method. Within 1 hour after instillation, conjunctival redness, chemosis, and discharge were observed, and the individual conjunctivae, chemosis, iritis, and cornea opacity scores were 1, 3, 3, and 4. After 24 hours, corneal opacity, redness, iritis, chemosis, and discharge were observed, and the individual conjunctivae, chemosis, iritis, and cornea opacity scores were 2, 4, 2, and 4. Irritation was reported as not reversible. The animal was euthanized due to the severity of the scores at 24 hours. No further details were provided. The study authors concluded that N-[3-(dimethylamino)propyl]stearamide monoacetate was corrosive to the eye in this study (Klimisch 1, reliable without restriction).
    - Based on the irreversible effects to the eye in the above study, ToxServices classified N-[3-(dimethylamino)propyl]stearamide as a Category 1 eye irritant under GHS criteria (UN 2021). GHS criteria define Category 1 eye irritants as chemicals that produce corrosive or irreversible effects to the eye.

Ecotoxicity (Ecotox)

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Very High for acute aquatic toxicity based on the measured EC_{50} value of 0.19 mg/L (i.e., ≤ 1 mg/L) in a GLP-compliant, OECD Guideline 201 study for acute aquatic toxicity to algae. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are no greater than 1 mg/L (CPA 2018b). The confidence in the score is high as it is based on high quality, measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any authoritative lists for this endpoint.
- ECHA 2023a
  - 96-hour LC_{50} (*Globiocypris rarus*, rare gudgeon) = 2.14 mg/L (GLP-compliant, equivalent to OECD Guideline 203) (Klimisch 2, reliable with restrictions).
  - 48-hour EC_{50} (*Daphnia magna*) = 0.29 mg/L based on mobility (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction).
  - 72-hour EC_{50} (*Chlorella vulgaris*, freshwater algae) = 0.19 mg/L based on growth rate (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Very High for chronic aquatic toxicity based on the measured NOEC value of 0.1 mg/L in a GLP-compliant, OECD Guideline 212 study for chronic aquatic toxicity to fish for the surrogate. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are no greater than 0.1 mg/L (CPA 2018b). The confidence in the score is reduced as the true NOEC may be higher than 0.1 mg/L, if tested, in the critical study in fish, and data for the other two trophic levels support a High score instead.

- 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 2023a
  - 72-hour NOEC (*C. vulgaris*, freshwater algae) = 0.19 mg/L (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction)
- ECHA 2023c
  - <u>*Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*</u>: 9-day behavior NOEC and LOEC (*Danio rerio*, zebrafish) = 0.1 and 0.316 mg/L, respectively (nominal) (GLP-compliant, OECD Guideline 212) (Klimisch 1, reliable without restriction). *Note: additional NOEC and LOEC values for other effects were reported for this study in the ECHA dossier; however, the behavior NOEC and LOEC values were the most conservative.*
  - <u>*Surrogate: N-[3-(Dimethylamino)propyl]stearamide (CAS #7651-02-7)*</u>: 21-day mortality NOEC (*D. magna*) = 0.2 mg/L (nominal) (GLP-compliant, OECD Guideline 211) (Klimisch 1, reliable without restriction).

Environmental Fate (Fate)

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Very Low for persistence based on the target chemical meeting the 10-day window in a ready biodegradation test with soil/ sediment expected as the dominant environmental compartment due to its use pattern, ionic nature and low vapor pressure. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when water, soil or sediment is the dominant environmental compartment and the 10-day window is met (CPA 2018b). The confidence in the score is high as it is based on high quality, measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301F (Manometric respirometry test) was performed with non-adapted, domestic, activated sludge exposed to N-[3-(dimethylamino)propyl]stearamide monoacetate (purity not specified) at 29.9 mg/L for 28 days. The degree of degradation (O_2 consumption) was 97% after 28 days, and 75.7% at the end of the 10-day window. The 10-day window was met and the study authors concluded that N-[3-(dimethylamino)propyl]stearamide monoacetate was readily biodegradable in this study (Klimisch 1, reliable without restriction).
  - A GLP-compliant adsorption-desorption study using equilibrium method conducted according to OECD Guideline 106 was performed with 5 different soil types consisting of loam, silty clay loam, and three silt loams at pH 4.6 with low % organic carbon, pH 7.84 with high % org. carbon, and pH 7.96 with low % org. carbon. The test substance was disassociated in water and the cation form, the fatty acid chain, was measured by HPLC-MS/MS. The test substance was almost completely adsorbed on the soils, and it was not detectable in the water phase of the five soils (< 0.01 mg//L) (Klimisch 1, reliable without restriction).

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

N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Moderate for bioaccumulation based on the measured BCF of 677.5. GreenScreen® criteria classify chemicals as a Moderate hazard for bioaccumulation when BCF/BAF values are greater than 500 to 1,000 (CPA 2018b). The confidence in the score is low as the critical study was reported from an SDS with limited details.

- 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 2023a
  - A GLP-compliant partition coefficient (n-octanol/water) test using the HPLC method according to OECD Guideline 117, reported a measured log K_{ow} of 6.2 at 25°C for N-[3-(dimethylamino)propyl]stearamide monoacetate (Klimisch 1, reliable without restriction).
- Chemours 2020
  - A material safety data sheet for tradename Zelan R3 reports that according to Directive 92/69/EEC, N-[3-(dimethylamino)propyl]stearamide monoacetate has a measured BCF of 677.5. No additional details were reported.
- U.S. EPA 2010

- U.S. EPA in its evaluation of fatty nitrogen derived amides concluded that Subcategory III: fatty acid reaction products including structurally similar chemicals to the target chemical and surrogate, such as amides, coco, N-[3-(dimethyl amino)propyl (CAS #68140-01-2), containing C8 to C18 fatty acid chains, are expected to have moderate bioaccumulation potential (B2).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was low as it was not based on an authoritative list or measured data on the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023b
  - The authors of the ECHA dossier reported that N-[3-(dimethylamino)propyl]stearamide monoacetate was non-explosive and non-oxidizing due to a lack of chemical groups associated with explosive and oxidizing properties, and non-oxidizing on the basis of its chemical structure. Additionally, no evidence of pyrophoric properties was identified by the authors of the ECHA dossier.
  - In a GLP-compliant relative self-ignition temperature for solids test conducted according to EU Method A.16, N-[3-(dimethylamino)propyl]stearamide monoacetate had an auto-ignition temperature in the range of ≥ 400°C (Klimisch 1, reliable without restriction).
- Chemours 2020
  - A material safety data sheet for N-[3-(dimethylamino)propyl]stearamide monoacetate (as tradename: Zelan R3, ≥ 0.1 to <1% purity) reports that N-[3-(dimethylamino)propyl]stearamide monoacetate has an instability rating of 0 from the National Fire Protection Association (NFPA) ("Normally stable, even under fire exposure conditions, and is not reactive with water").
- Based on the weight of evidence, ToxServices did not identify N-[3-(dimethylamino)propyl] stearamide monoacetate as reactive. N-[3-(dimethylamino)propyl]stearamide monoacetate is not self-heating up to 400°C under standard pressure. It is not expected to be explosive or self-reactive based on chemical structure and an NFPA instability rating of 0. N-[3-(dimethylamino)propyl] stearamide monoacetate has no reactive functional groups that would make it oxidizing or explosive, and it is not a peroxide. As it is not explosive, it does not require desensitization. Overall, N-[3-(dimethylamino)propyl]stearamide monoacetate is not classified for any of the reactivity sub endpoints under GHS (UN 2021). No data were found regarding corrosivity to metal.

Flammability (F) Score (vH, H, M, or L): L
N-[3-(Dimethylamino)propyl]stearamide monoacetate was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score is high as it is based on high quality, measured data for the target chemical.

- Authoritative and Screening Lists

  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2023b
  - In a GLP-compliant flammability (solids) test conducted according to EU Method A.10, N-[3-(dimethylamino)propyl]stearamide monoacetate melted on application and burned for approximately 20 seconds with a yellow flame prior to extinguishing, and the flame did not propagate along the test pile. The study authors concluded the test substance was not highly flammable (Klimisch 1, reliable without restriction).
  - As previously described, in a GLP-compliant relative self-ignition temperature for solids test conducted according to EU Method A.16, N-[3-(dimethylamino)propyl]stearamide monoacetate had an auto-ignition temperature in the range of ≥ 400°C (Klimisch 1, reliable without restriction).
- Chemours 2020
  - A material safety data sheet for N-[3-(dimethylamino)propyl]stearamide monoacetate (as tradename: Zelan R3, ≥ 0.1 to <1% purity) has reported a flammability rating of 1 from NFPA ("Materials that require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur (e.g., mineral oil, ammonia). Includes some finely divided suspended solids that do not require heating before ignition can occur. Flash point at or above 93.3°C (200 °F)").
- Based on the above data, ToxServices did not classify N-[3-(dimethylamino)propyl]stearamide monoacetate as a flammable solid under GHS criteria (UN 2021).

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

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

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

As shown in Table 4, Type I (input data) uncertainties in N-[3-(dimethylamino)propyl]stearamide monoacetate's NAMs dataset include no or insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. N-[3-(dimethylamino)propyl]stearamide monoacetate's Type II (extrapolation output) uncertainties include lack of defined applicability domains of OECD QSAR Toolbox in examination of structural alerts, the low reliability of the two VEGA model predictions with acceptable global ADIs due to lack of, or additional, reactive moieties, limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, uncertain *in vivo* relevance of *in silico* receptor binding activity predictions, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of N-[3-(dimethylamino)propyl]stearamide monoacetate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

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

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Endocrine activity:** Insufficient *in vivo* data for hormone signaling pathways are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: OECD Toolbox structural alerts screening does not define applicability domains. Of the two models in VEGA that produced reliable (i.e., Global AD index > 0.7) predictions, the read-across chemicals selected had extra structural alerts for carcinogenicity, or lack the critical structural features of the target compound**.**

[9] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

	Genotoxicity: The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[10]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[11] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[12]. **Endocrine activity:** ToxCast models don't define applicability domains. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/OECD Toolbox/OncoLogic/Danish QSAR
Mutagenicity	Y	*In vitro* data: bacterial reverse mutation assay/mammalian cell gene mutation assay/chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: Danish QSAR/ ToxCast models
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	

[10] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[11] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[12] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/ Danish QSAR
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	Non-animal testing: OECD 301F Biodegradation tests
Bioaccumulation	N	

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

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 / N-[3-(Dimethylamino)propyl]stearamide monoacetate / **13282-70-7**	*L*	**L**	*L*	*M*	DG	**M**	**M**	*H*	*L*	**L**	**H**	DG	**L**	**vH**	**vH**	*vH*	**vL**	*M*	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
N-[3-(Dimethylamino)propyl]stearamide monoacetate	2

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

Table 6

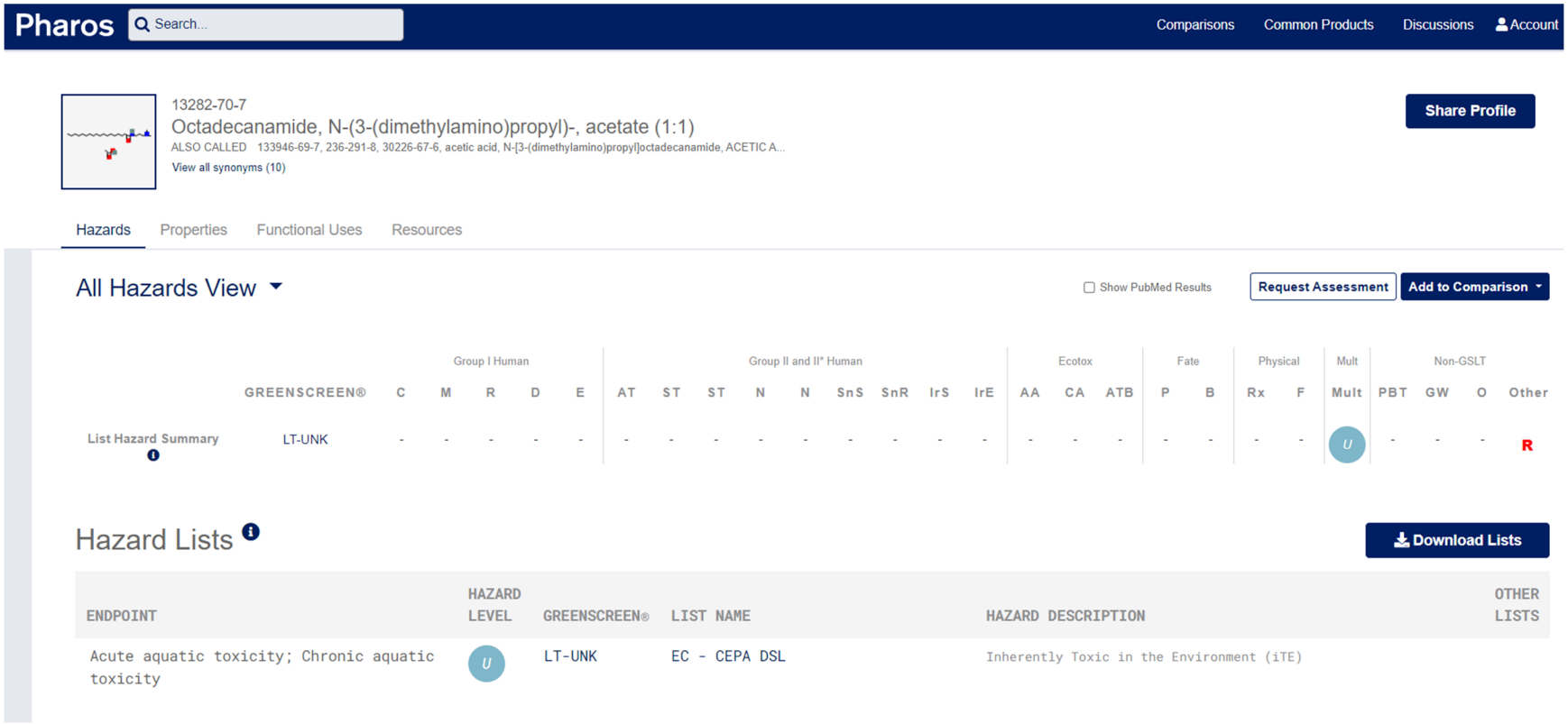
Chemical Name	Final GreenScreen® Benchmark Score
N-[3-(Dimethylamino)propyl]stearamide monoacetate	2

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

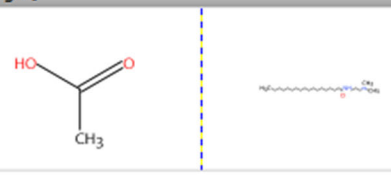
Table 5: Data Gap Assessment Table

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												

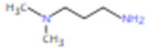
APPENDIX C: Pharos Output for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)



APPENDIX D: OECD Toolbox Profiling Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:2362918
CAS Number	13282-70-7
CAS-SMILES relation	High
Chemical name(s)	N-[3-(dimethylamino)propyl]octadecanamide acetate
Identity	Sources:7
Molecular formula	C25H52N2O3
Predefined substance type	Multi constituent
SMILES	CC(O)=O.CCCCCCCCCCCCCCCCCC(=O)NCCCN(C)C
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Predefined	
Database Affiliation	Does not belong to any database
Inventory Affiliation	AIIC
OECD HPV Chemical Categories	Aliphatic acids
Substance type	Mixture
US-EPA New Chemical Categories	Aliphatic Amines
Endpoint Specific	
Carcinogenicity (genotox and nongenotox) alerts by ISS	No alert found
in vitro mutagenicity (Ames test) alerts by ISS	No alert found
in vivo mutagenicity (Micronucleus) alerts by ISS	No alert found
Oncologic Primary Classification	Not classified
Respiratory sensitisation	No alert found
Metabolism/Transformation	
Hydrolysis simulator (acidic)	0 metabolite(s)
Hydrolysis simulator (basic)	2 metabolite(s)
Hydrolysis simulator (neutral)	0 metabolite(s)

Hydrolysis simulator (basic)

metabolite #1	metabolite #2
No CAS number	No CAS number
	

APPENDIX E: VEGA Carcinogenicity Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.13
P(NON-Carcinogen): 0.87
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 75881-20-8
Dataset id:558 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.811
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #2

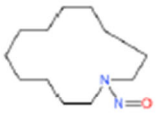
CAS: 55090-44-3
Dataset id:554 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.785
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #3

CAS: 1643-20-5
Dataset id:273 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.773
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Compound #4

CAS: 68107-26-6
Dataset id:603 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.77
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 40580-89-0
Dataset id:586 (Training Set)
SMILES: O=NN1CCCCCCCCCCCC1
Similarity: 0.759
Experimental value : Carcinogen
Predicted value : Carcinogen

Compound #6

CAS: 75881-22-0
Dataset id:559 (Training Set)
SMILES: O=NN(C)CCCCCCCCCC
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.797 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✔	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✔	Model class assignment reliability Pos/Non-Pos difference = 0.739 Explanation: model class assignment is well defined..
✔	Neural map neurons concordance Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

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

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural Alerts: -
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 75881-20-8
Dataset id:579 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.811
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups

Compound #2

CAS: 55090-44-3
Dataset id:547 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.785
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups

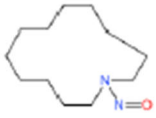
Compound #3

CAS: 1643-20-5
Dataset id:879 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.773
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #4

CAS: 68107-26-6
Dataset id:527 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.77
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups



Compound #5

CAS: 40580-89-0
Dataset id:553 (Training Set)
SMILES: O=NN1CCCCCCCCCCCC1
Similarity: 0.759
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups

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

Compound #6

CAS: 75881-22-0
Dataset id:762 (Training Set)
SMILES: O=NN(C)CCCCCCCCCC
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.797 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✔	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✖	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.Anyway some issues could be not optimal:
- Only moderately similar compounds with known experimental value in the training set have been found
- some similar molecules found in the training set have experimental values that disagree with the predicted value
The following relevant fragments have been found: Carcinogenity alert no. 7

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 7
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 75881-20-8
Dataset id:489 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.811
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27

Compound #2

CAS: 55090-44-3
Dataset id:458 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.785
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27

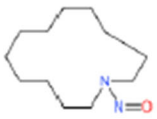
Compound #3

CAS: 1643-20-5
Dataset id:777 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.773
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

Compound #4

CAS: 68107-26-6
Dataset id:439 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.77
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27



Compound #5

CAS: 40580-89-0
Dataset id:464 (Training Set)
SMILES: O=NN1CCCCCCCCCCC1
Similarity: 0.759
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27

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

Compound #6

CAS: 75881-22-0
Dataset id:595 (Training Set)
SMILES: O=NN(C)CCCCCCCCCC
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.805
Explanation: The predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.789
Explanation: Only moderately similar compounds with known experimental value in the training set have been found..

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

Concordance for similar molecules
Concordance index = 0.676
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..

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

Symbols explanation:

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

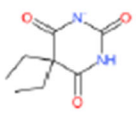
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: Carcinogenity alert no. 7

Structural alert for carcinogenity defined by the SMARTS:NCCCN

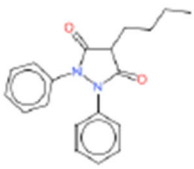
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 144-02-5
Dataset id:798 (Training Set)
SMILES: O=C1[N-]C(=O)C(C(=O)N1)(CC)CC
Similarity: 0.618

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

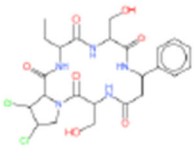


CAS: 50-33-9
Dataset id:530 (Training Set)
SMILES: O=C3N(c1ccccc1)N(c2ccccc2)C(=O)C3CCCC
Similarity: 0.612

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

Alerts (not found also in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 32; Carcinogenity alert no. 42



CAS: 12663-46-6
Dataset id:274 (Training Set)
SMILES:
O=C2NC(C(=O)N3CC(C(C3(C(=O)NC(C(=O)NC(C(=O)NC(c1ccccc1)C2)CO)CC))Cl)Cl)CO
Similarity: 0.607

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 7

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 11; Carcinogenity alert no. 25; Carcinogenity alert no. 40

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is Possible NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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

Compound #1

CAS: 75881-20-8
Dataset id:558 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.811
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

Compound #2

CAS: 55090-44-3
Dataset id:554 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.785
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

Compound #3

CAS: 1643-20-5
Dataset id:273 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCCC
Similarity: 0.773
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

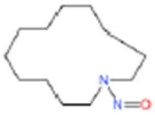
Alerts (not found also in the target): Carcinogenity alert no. 64

Compound #4

CAS: 68107-26-6
Dataset id:603 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.77
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

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



Compound #5

CAS: 40580-89-0
Dataset id:586 (Training Set)
SMILES: O=NN1CCCCCCCCCCC1
Similarity: 0.759
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 5; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 53; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

Compound #6

CAS: 75881-22-0
Dataset id:559 (Training Set)
SMILES: O=NN(C)CCCCCCCCCC
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 4; Carcinogenity alert no. 8; Carcinogenity alert no. 9; Carcinogenity alert no. 10; Carcinogenity alert no. 15; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.608 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.789 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.676 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0.324 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

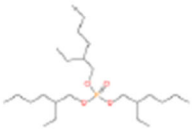
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 2439-10-3
Dataset id:490 (Training Set)
SMILES: N(=C(N)N)CCCCCCCCCCCC
Similarity: 0.735
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

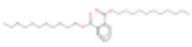
Compound #2

CAS: 103-23-1
Dataset id:94 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.723
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



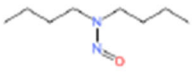
Compound #3

CAS: 78-42-2
Dataset id:313 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.688
Experimental value : Carcinogen
Predicted value : Carcinogen



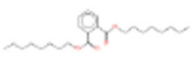
Compound #4

CAS: 3648-20-2
Dataset id:488 (Training Set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.686
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 924-16-3
Dataset id:224 (Test Set)
SMILES: O=NN(CCCC)CCCC
Similarity: 0.672
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 117-84-0
Dataset id:614 (Training Set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.672
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.604 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.729 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.506 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.494 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- Only moderately similar compounds with known experimental value in the training set have been found
- Accuracy of prediction for similar molecules found in the training set is not adequate

Compound: Molecule 0
Compound SMILES: O=C(NCCCN(C)C)CCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

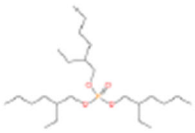
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

Compound #1

CAS: 2439-10-3
Dataset id:462 (Training Set)
SMILES: N(=C(N)N)CCCCCCCCCCCC
Similarity: 0.735
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

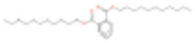
Compound #2

CAS: 103-23-1
Dataset id:391 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.723
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



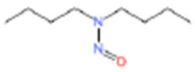
Compound #3

CAS: 78-42-2
Dataset id:741 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.688
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



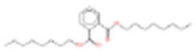
Compound #4

CAS: 3648-20-2
Dataset id:460 (Test Set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.686
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 924-16-3
Dataset id:192 (Training Set)
SMILES: O=NN(CCCC)CCCC
Similarity: 0.672
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 117-84-0
Dataset id:597 (Training Set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.672
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.716 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.729 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.494 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✔	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

APPENDIX F: OncoLogic Carcinogenicity Results N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : 13282Fattyacid

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Carboxylic Acids*

Aliphatic carboxylic acids (R-COOH) may be loosely divided into (a) high M.W.fatty acids (C > 20), (b) medium size carboxylic acids (C = 6 to 20), and (c) low M.W. carboxylic acids (C < 6). In general, aliphatic carboxylic acids (especially group (a)) have low potential to be significant carcinogens. However, a number of metabolically persistent aliphatic carboxylic acids (e.g., perflourinated fatty acid like perfluoroooctanoic acid; ω – 1 branched fatty acids like 2-ethylhexanoic acid) have been shown to be nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Among low M.W. carboxyxlic acids, those with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens whereas some unsubstituted saturated fatty acids (e.g., pentanoic acid) may be of marginal concern via dermal route due to their irritancy.

---

*This is only a brief summary of the structure activity relationships (SAR) knowledge of this class. A more detailed decision logic will be developed in future version of OncoLogic. If the compound of your interest has been tested in any short-term predictive tests, the results of the tests should be entered into OncoLogic's Functional Arm to give an evaluation of carcinogenic potential based on short-term predictive tests.

OncoLogic Justification Report

CODE NUMBER: 13282Amine

SUBSTANCE ID:

Final level of concern for this compound is LOW(*).

(*) Caution: Functional arm should be used if short term prediction test data are available

APPENDIX G: Danish QSAR Carcinogenicity Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

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

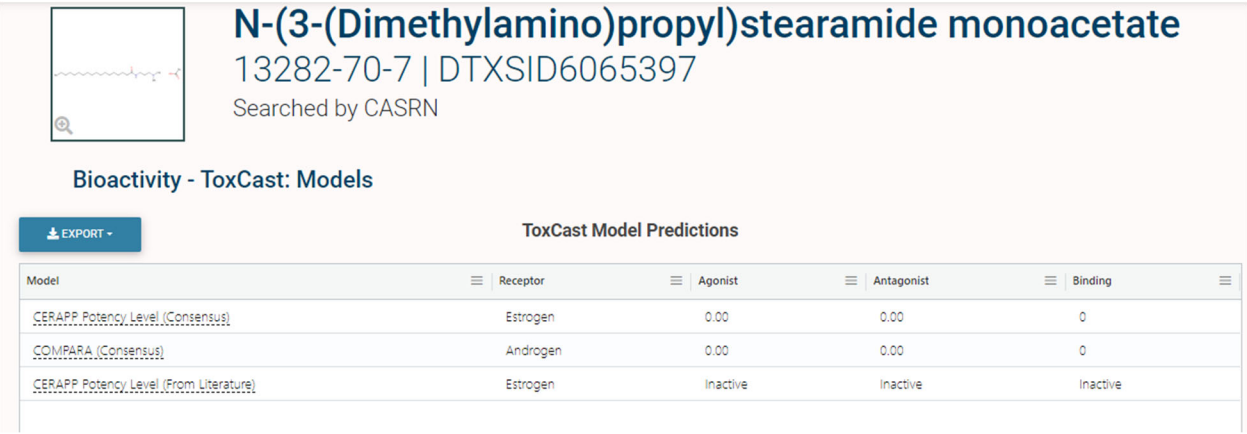
OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

APPENDIX H: ToxCast Model Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)



N-(3-(Dimethylamino)propyl)stearamide monoacetate

13282-70-7 | DTXSID6065397

Searched by CASRN

Bioactivity - ToxCast: Models

EXPORT

ToxCast Model Predictions

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

APPENDIX I: Danish QSAR Endocrine Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_IN	NEG_OUT	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	INC_OUT	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Sodium/iodide symporter (NIS), higher sensitivity		N/A	N/A	INC_OUT	N/A
Sodium/iodide symporter (NIS), higher specificity		N/A	N/A	NEG_OUT	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			58967.71	1883.798	42895.77
- µM			159955.8	5109.99	116359.1
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			1.543882	12.56621	1050.302
- µM			4.187935	34.0871	2849.05
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation – Random final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	NEG_IN	NEG_IN	INC_OUT	NEG_IN
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
CYP3A4 Induction (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_OUT	N/A

DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, non cyclic structure
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, non cyclic structure
- metabolites from Rat liver S9 metabolism simulator only	Non binder, non cyclic structure
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

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

APPENDIX J: Danish QSAR Sensitization Results for N-[3-(Dimethylamino)propyl]stearamide Monoacetate (CAS #13282-70-7)

Irritation and Sensitization

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Severe Skin Irritation in Rabbit		INC_OUT	INC_OUT	POS_IN	NEG_IN
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data only)				POS_IN	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based (open data and REACH-registrations)	N/A			POS_IN	
Skin sensitisation GHS/CLP at least Cat. 1, LLNA-based, only negative predictions (open data only)				N/A	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data only)				INC_OUT	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based (open data and REACH-registrations)	N/A			NEG_IN	
Skin sensitisation GHS/CLP Cat. 1A, LLNA-based, only positive predictions (open data and REACH-registrations)	N/A			N/A	
Allergic Contact Dermatitis in Guinea Pig and Human*	N/A	NEG_IN	NEG_IN	INC_OUT	NEG_IN
Respiratory Sensitisation in Humans		NEG_OUT	INC_OUT	NEG_OUT	NEG_IN

DTU-developed models

**Based on commercial training set*

Protein binding by OASIS, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	Aldehydes
- metabolites from auto-oxidation simulator only	
Protein binding by OECD, alerts in:	
- parent only	No alert found
- metabolites from skin metabolism simulator only	Mono-carbonyls
- metabolites from auto-oxidation simulator only	
Protein binding potency Cys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert

- metabolites from skin metabolism simulator only	DPRA above 21% (DPRA 13%) >> Non-Conjugated monoaldehydes (reactive); DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive)
- metabolites from auto-oxidation simulator only	
Protein binding potency Lys (DRPA 13%), alerts in:	
- parent only	DPRA less than 9% (DPRA 13%) >> No protein binding alert
- metabolites from skin metabolism simulator only	DPRA less than 9% (DPRA 13%) >> Non-alpha,beta-conjugated monoaldehydes (non reactive); DPRA less than 9% (DPRA 13%) >> Non-Conjugated carboxylic acids and esters (non reactive); Grey zone 9-21% (DPRA 13%) >> Non-alpha,beta-conjugated monoaldehydes (Grey zone)
- metabolites from auto-oxidation simulator only	
Keratinocyte gene expression, alerts in:	
- parent only	Not possible to classify according to these rules
- metabolites from skin metabolism simulator only	High gene expression >> Non-conjugated aldehydes and dialdehydes; Moderate gene expression >> Fragrance aldehydes
- metabolites from auto-oxidation simulator only	
Protein binding potency GSH, alerts in:	
- parent only	Not possible to classify according to these rules (GSH)

OECD QSAR Toolbox v.4.1 profilers

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

APPENDIX K: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for N-[3-(dimethylamino)propyl]stearamide Monoacetate. The GreenScreen® Benchmark Score for N-[3-(dimethylamino)propyl]stearamide monoacetate was maintained over time. The original GreenScreen® assessment was performed in 2017 under version 1.3 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. Most recently, the BM-2 score was maintained with a version 1.4 update in 2023. This update re-classified the scores and confidence levels for several endpoints, without affecting the overall benchmark score.

Table 5: Change in GreenScreen® Benchmark™ for N-[3-(Dimethylamino)propyl]stearamide Monoacetate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
July 17, 2017	BM-2	v. 1.3	Original GreenScreen® assessment.
July 10, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template. The BM-2 score was maintained and scores and/or confidence levels were re-classified for several endpoints, without affecting the overall benchmark score.
July 31, 2023	BM-2	V 1.4	No change in BM score. ToxServices included additional data and/or justification, and the confidence level for chronic aquatic toxicity was reduced based on Washington Ecology's comments.

Licensed GreenScreen® Profilers

N-[3-(Dimethylamino)propyl]stearamide Monoacetate GreenScreen® Evaluation Prepared and Updated by:

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N-[3-(Dimethylamino)propyl]stearamide Monoacetate GreenScreen® Evaluation QC'd by:

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