QUATERNARY AMMONIUM COMPOUNDS, (HYDROGENATED TALLOW ALKYL)BIS(HYDROXYETHYL)METHYL, ETHOXYLATED, CHLORIDES (15 EO) (CAS #68187-69-9)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

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TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1526 New Hampshire Ave., N.W., Suite 350
Washington, D.C. 20036

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GreenScreen® Executive Summary for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is an amber liquid under standard temperature and pressure. It is an ethoxylated quaternary ammonium compound that is soluble in water.

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) 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 2c
    - High persistence-P + Very High Ecotoxicity (acute aquatic toxicity-AA)
    - High P + High Ecotoxicity (chronic aquatic toxicity-CA)
    - High P + Very High Group II Human Health Hazard (skin irritation-IrS, eye irritation-IrE)
    - High P + Moderate Group II Human Health Hazard (acute toxicity-AT)
    - High P + Moderate Group II* Human Health Hazard (repeated dose systemic toxicity-STr*)
- Benchmark 2f
    - Very High Ecotoxicity (AA)
    - Very High Group II Human Health Hazard (IrS, IrE)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity and respiratory sensitization, non-animal tests for persistence, and *in vitro/in chemico* assays for genotoxicity, skin sensitization, and skin irritation. 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 quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'s NAMs dataset include no or insufficient experimental data for carcinogenicity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'s Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of VEGA, Oncologic, and Danish (Q)SAR database to evaluate its carcinogenic potential, the lack of metabolism incorporated into the *in chemico* and *in vitro* skin sensitization models, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the inability of the *in vitro* skin irritation assays to identify mild skin irritants (GHS Category 3). Some of quaternary ammonium compounds,

(hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'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 Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)

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

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

GreenScreen® Chemical Assessment for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 22, 2023

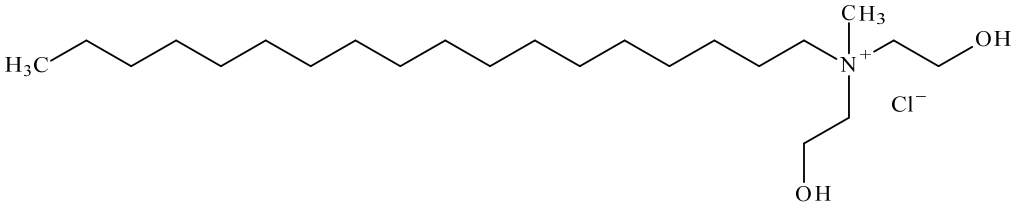
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 28, 2023

Expiration Date: August 28, 2028[2]

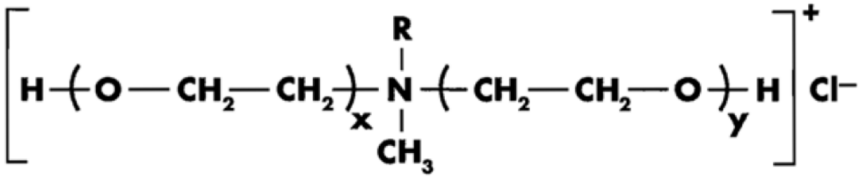
Chemical Name: Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)

CAS Number: 68187-69-9

Chemical Structure(s):

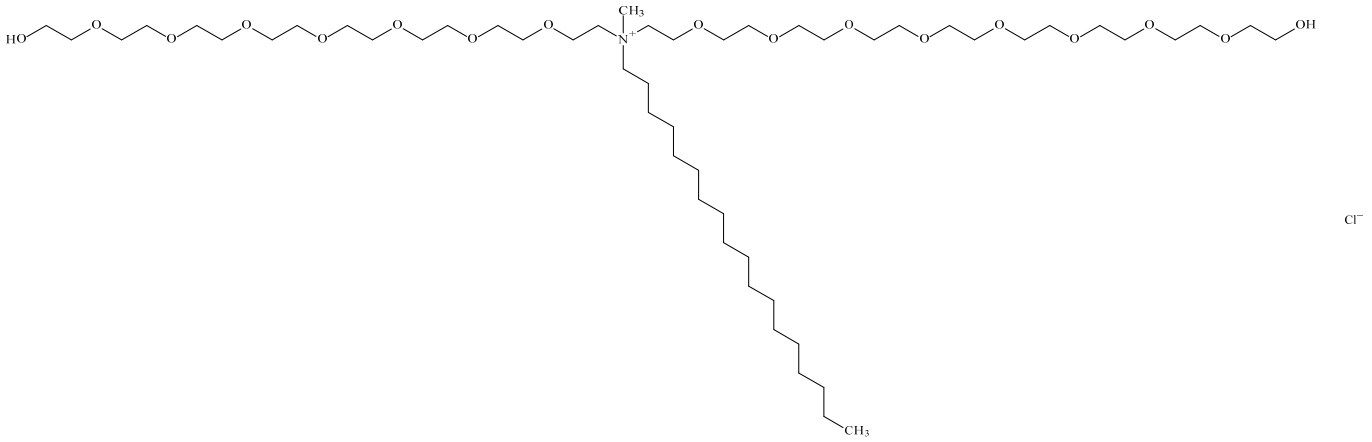


(C18 representative structure in U.S. EPA 2017)



Where R = hydrogenated tallow alkyls, and x + y = 15 (x and y cannot equal zero) (U.S. EPA 2009a). Tallow fatty acids consists of 37-43% oleic (C18:1), 24-32% palmitic (C16), and 20-25% stearic (C18) acids (CIR 1990).

[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).

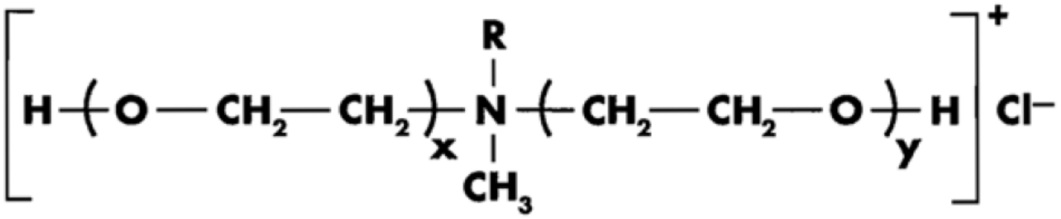


(Biovia 2019)

Also called:
EC 614-363-3; Ethoxylated (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl ammonium chlorides; Ethoxylated hydrogenated tallow alkylamine, quarternized (PubChem 2023); PEG-15 hydrogenated tallowmonium chloride; Methanaminium, N,N-bis(hydropoly(oxy-1,2-ethanediyl)-N-(hydrogenated tallow alkyl)-, chlorides (15 mol EO average molar ratio) (EC 2023)

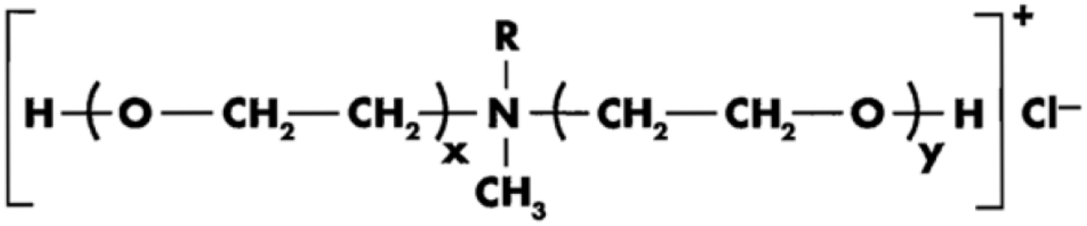
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited data were identified for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis (hydroxyethyl)methyl, ethoxylated, chlorides (15 EO). In an evaluation of methyl poly(oxyethylene) C8-C18 alkylammonium chlorides (MPOACs), which included quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides, the United States Environmental Protection Agency (U.S. EPA) considered quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9), also known as coco alkylbis (hydroxyethyl)methylammonium chlorides, to be a representative test compound for the group (U.S. EPA 2009a,b). Therefore, ToxServices used quaternary ammonium compounds, coco alkylbis (hydroxyethyl)methyl, chlorides as a surrogate for the present assessment.

Additionally, ToxServices considered quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4) to be a suitable surrogate since, when they share the same degree of ethoxylation, it and the target chemical quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides differ only in the length of the alkyl chains.



Where R = coconut alkyls, and x and y are both 1 (U.S. EPA 2009a). Coconut fatty acids consists of 6-10% capric (C10), 44-52% lauric (C12), 13-19% myristic (C14), 8-11% palmitic (C16) acids (CIR 2017).

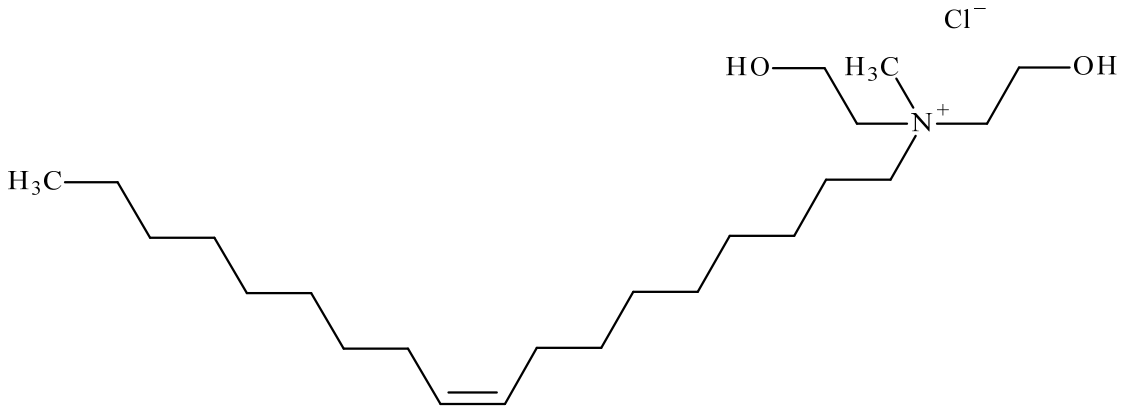
Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)



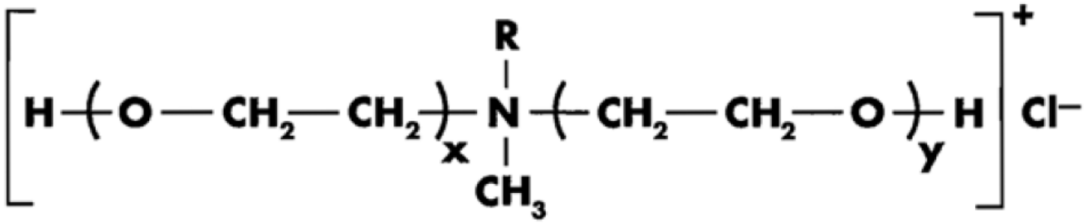
Where R = coconut alkyls, and x + y = 15 (x and y cannot equal zero) (U.S. EPA 2009a). Coconut fatty acids consists of 6-10% capric (C10), 44-52% lauric (C12), 13-19% myristic (C14), 8-11% palmitic (C16) acids (CIR 2017).

Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)

Finally, as U.S. EPA (2009a,b) considered quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9) as a representative compound for the MPOACs class of chemicals, ToxServices considered bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2) and quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2) as suitable surrogates since they represent the base constituents of the un-hydrogenated target chemical with no ethoxylation units.



Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)



Where R = 12-18, and x and y are both 1 (U.S. EPA 2009a).

Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)

Identify Applications/Functional Uses:
1. Antistatic and hair conditioning agent in personal care products and cosmetics (EC 2023)

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

GreenScreen® Summary Rating for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)[3,4 5,6]: Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This preliminary score is based on the following hazard score combinations:

- Benchmark 2c
  - High persistence-P + Very High Ecotoxicity (acute aquatic toxicity-AA)
  - High P + High Ecotoxicity (chronic aquatic toxicity-CA)
  - High P + Very High Group II Human Health Hazard (skin irritation-IrS, eye irritation-IrE)
  - High P + Moderate Group II Human Health Hazard (acute toxicity-AT)
  - High P + Moderate Group II* Human Health Hazard (repeated dose systemic toxicity-STr*)
- Benchmark 2f
  - Very High Ecotoxicity (AA)
  - Very High Group II Human Health Hazard (IrS, IrE)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) 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 Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)

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

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

[3] 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.
[4] See Appendix A for a glossary of hazard endpoint acronyms.
[5] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).
[6] 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.

Environmental Transformation Products

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not expected to be readily biodegradable (see Persistence section). Therefore, ToxServices used OECD QSAR Toolbox (OECD 2023a) to predict the hydrolysis products under acidic, neutral, and basic conditions. Based on the structure identified with Biovia (2019), no hydrolysis products are expected for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis (hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) under acidic, neutral, and basic conditions (Appendix C). Therefore, ToxServices did not modify the Benchmark Score for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) based on transformation products.

Introduction

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) functions as an antistatic and hair conditioning agent in personal care products and cosmetics (EC 2023).

ToxServices assessed quaternary ammonium compounds, (hydrogenated tallow alkyl)bis (hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) 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 (SCIL)

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).

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not listed on the U.S. EPA's 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),[7] 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 quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) can be found in Appendix D.

- Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not listed on the U.S. DOT list.

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

- Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is on the following list for multiple endpoints:
    - EC - CEPA DSL - Inherently Toxic in the Environment (iTE).
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

A majority of EU notifiers self-classified quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) with the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements H302 and H411 (ECHA, CAS #68187-69-9, 2023; PubChem 2023), as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO).

Table 1: GHS H Statements for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9) (ECHA, CAS #68187-69-9, 2023; PubChem 2023)

H Statement	H Statement Details
H302	Harmful if swallowed
H411	Toxic to aquatic life with long lasting effects

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Goggles, gloves, protective clothing, respirator	TRC 2018	None identified	N/A

Physicochemical Properties of Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is an amber liquid under standard temperature and pressure. It is soluble in water.

Table 3: Physical and Chemical Properties of Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

Property	Value	Reference
Molecular formula	Variable - UVCB	N/A
SMILES Notation	Variable - UVCB CCCCCCCCCCCCCCCCCCC[N+](CCO)(CCO)(C).[Cl-] (representative structure) [Cl-].CCCCCCCCCCCCCCCCCCC[N+](C)(CCOCCOCCOCCOCCOCCOCCO)C	U.S. EPA 2017 Biovia 2019

Table 3: Physical and Chemical Properties of Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)		
Property	**Value**	**Reference**
	COCCOCCOCCOCCOCCOCCOCCOC CO (C18 constituent)	
Molecular weight	Variable - UVCB	N/A
Physical state	Liquid	TRC 2018
Appearance	Amber	TRC 2018
Melting point	Not identified	N/A
Boiling point	Not identified	N/A
Vapor pressure	Not identified	N/A
Water solubility	Soluble	TRC 2018
Dissociation constant	Not identified	N/A
Density/specific gravity	9.01 lb./gal (1.08 g/mL)	TRC 2018
Partition coefficient	N/A surface active agent	TRC 2018
Supplier, Tradename(s)	Not specified	N/A
Ethoxylated or propoxylated?	Ethoxylated	N/A
# EO Units	15	N/A
# PO Units	N/A	N/A
EO/PO Ratio	N/A	N/A

Toxicokinetics

No toxicokinetics data were identified for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) or a suitable surrogate.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for carcinogenicity based on negative predictions from a rule-based model (Toxtree) and a statistical-based model (Danish (Q)SAR models). GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative, and they are not classified under GHS (CPA 2018b). Confidence in the score is low due to the lack of experimental data and the sole reliance on modeled 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.
- U.S. EPA 2009a
  - "No carcinogenicity studies are available for the MPOACs. A qualitative structure activity relationship database, DEREK Version 11, identified no structural alerts suggestive of carcinogenicity."
- Toxtree 2018
  - Based on the representative structure in the EPI Suite™ (U.S. EPA 2017) database, quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl,

ethoxylated, chlorides (15 EO) does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (Appendix E).

- VEGA 2023
    - ToxServices predicted the carcinogenicity potential of quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) using the representative structure in the EPI Suite™ (U.S. EPA 2017) database and following six VEGA v1.2.3 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/ISSCAN-CGX v1.0.2, IRFMN/Antares v1.0.2 models, IRFMN oral classification v1.0.1, and IRFMN inhalation classification v1.0.1 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 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). Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is outside the AD for the CAESAR, ISS, IRFMN-ANTARES, IRFMN oral classification, and IRFMN inhalation classification models. Therefore, the results of these models are not incorporated into ToxServices' weight of the evidence evaluation (Appendix F).
    - Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is within the AD of the IRFMN-ISSCAN-CQX model (global AD index = 0.799) and the model predicts that it is a carcinogen. The similarity and accuracy indices of 0.786 and 1.00, respectively, support the use of this model while the concordance index of 0.659 does not support the use of this model since some of the similar chemicals have experimental results that conflict with the predicted value. Therefore, ToxServices did not include the results of the IRFMN-ISSCAN-CGX model in the weight of evidence evaluation (Appendix F).
- U.S. EPA 2021
    - ToxServices attempted modeling with OncoLogic™, but quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not supported by the current version of the software (Appendix G).
- DTU 2023
    - ToxServices attempted modeling using the Danish (Q)SAR database but quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not listed in the database via CASRN or the SMILES corresponding to the representative structure in the EPI Suite™ (U.S. EPA 2017) database (Appendix H).
    - However, the default SMILES structure from EPI Suite™ with the chloride ion removed, and be modeled using the liver specific cancer (rat/mouse *in vivo*) model in the Danish (Q)SAR models website. The results are in domain and negative (Appendix H).

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for mutagenicity/genotoxicity based on negative mutagenicity and clastogenicity results obtained for the surrogates. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for strong surrogates.

- 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 2009a,b
    - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides was negative for mutagenicity in an Ames test. No additional details were provided.
- ECHA, CAS #18448-65-2, 2023
    - *In vitro*: *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: Negative mutagenicity results were obtained for the surrogate bis(hydroxyethyl)methyloleylammonium chloride in a GLP-compliant, OECD Guideline 471 bacterial reverse mutation assay. *Salmonella typhimurium* tester strains TA1535, TA1537, TA98, and TA100 and *Escherichia coli* strain WP_2 *uvr* A were exposed to bis(hydroxyethyl)methyloleylammonium chloride (96% purity) in dimethyl sulfoxide (DMSO) at ≤ 5,000 µg/plate with and without exogenous metabolic activation (rat liver S9). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and positive (4-nitroquinoline-N-oxide, 9-aminoacridine, 2-nitrofluorene, sodium azide, benzo(a)pyrene, 1-aminoanthracene) controls were reported as valid (Klimisch Score 1, reliable without restriction).
    - *In vitro*: *Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)*: Negative clastogenicity results were obtained for the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides in a GLP-compliant, OECD Guideline 487 micronucleus assay. Human lymphocytes were exposed to quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (purity not specified) in cell culture medium at ≤ 500 µg/L without and ≤ 250 µg/L with exogenous metabolic activation (rat liver S9). Treatment did not increase the frequency of micronuclei in the presence or absence of metabolic activation. The results for the vehicle and positive (ethylmethanesulphonate, colcemid, and cyclophosphamide) controls were not reported (Klimisch Score 1, reliable without restriction).
    - *In vitro*: *Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)*: Negative mutagenicity results were obtained for the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides in a GLP-compliant, OECD Guideline 476/EU Method B.17/EPA OPPTS 870.5300 test. Mouse lymphoma L5178Y cells were exposed to quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (purity not specified) in cell culture medium at ≤ 15 µg/L without and ≤ 25 µg/L with exogenous metabolic activation (S9 mix from livers of phenobarbital and ß-naphthoflavone-induced Wistar rats). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The untreated negative and positive (benzo(a)pyrene, ethylmethanesulphonate, and methylmethanesulfonate) controls were reported as valid (Klimisch Score 1, reliable without restriction).

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for reproductive toxicity based on the lack of reproductive toxicity produced by the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides in a repeated dose toxicity study with reproductive and developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA

2018b). The confidence in the score is low as it is based on results of a screening test that evaluated fewer endpoints than a full multi-generation reproductive toxicity test.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Exponent 2008; U.S. EPA 2009a,b; ECHA, 18448-65-2, 2023
  - *Oral: Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* In a repeated dose toxicity study with reproductive and developmental toxicity screening test conducted according to OECD Guideline 422/OPPTS 870.3650, male and female HanRcc: WIST(SPF) rats (10/sex/dose) received 0, 25, 50, or 100 mg/kg/day quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (75% purity/23% anhydrous isopropanol; U.S. EPA specifies doses were adjusted to correct for purity and control animals received 23% isopropanol) via gavage beginning 14 days prior to mating and for a minimum of 28 days for males and through lactation day 4 for females. The high dose was discontinued after four doses because all animals died or were sacrificed in extremis. Clinical signs included piloerection, diarrhea, reduced activity, and general bad condition. There were no treatment-related effects on reproductive performance (fertility, gestation interval, or number of litters) in the evaluated groups (0, 25, and 50 mg/kg/day); however, U.S. EPA (2009a) notes that the number of females evaluated at 50 mg/kg/day was lower than required under the guideline. U.S. EPA identified a NOAEL of 25 mg/kg/day for reproductive toxicity because this was the highest dose with a sufficient number of animals, and did not identify a LOAEL (Klimisch Score 1, reliable without restriction).

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for developmental toxicity based on the lack of developmental toxicity induced by the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides in a prenatal developmental toxicity test and the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides in a repeated dose toxicity study with reproductive and developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for strong surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #18448-65-2, 2023
  - *Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)*: A GLP-compliant, OECD Guideline 414/EPA OPPTS 870.3700 prenatal developmental toxicity test was performed with pregnant female Sprague-Dawley rats (24/group) administered gavage doses of the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (75% purity) in water at 0, 5, 15, or 25 mg/kg/day on gestation days 3-19. Maternal evaluations included clinical signs of toxicity, body weights, food and water consumption, ovaries, and uterine content. Fetal examinations included fetal weights and evaluation of skeletal malformations. Two high dose females exhibited noisy respiration, possible related to the irritative properties of the test substance. Treatment did not adversely affect maternal body weights, food

consumption, or water intake. One mid dose female had 100% post implantation loss, with no live fetuses detected on gestation day 20. Since no high dose females exhibited increased post implantation loss, the authors considered this finding to be incidental. Treatment did not adversely affect fetal weights. Fetuses in the high dose group exhibited a decreased incidence of incomplete ossification of the hyoid, parietal, and jugal regions, although this is not considered an adverse effect. Based on the lack of adverse, treatment-related effects up to the highest dose tested, the authors identified maternal toxicity and developmental toxicity NOAELs of 25 mg/kg/day (Klimisch Score 1, reliable without restriction).

- Exponent 2008; U.S. EPA 2009a,b; ECHA, 18448-65-2, 2023
    - *Oral: Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* In a repeated dose toxicity study with reproductive and developmental toxicity screening test conducted according to OECD Guideline 422/OPPTS 870.3650, male and female HanRcc: WIST(SPF) rats (10/sex/dose) received 0, 25, 50, or 100 mg/kg/day quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (75% purity/23% anhydrous isopropanol; U.S. EPA specifies doses were adjusted to correct for purity and control animals received 23% isopropanol) via gavage beginning 14 days prior to mating and for a minimum of 28 days for males and through lactation day 4 for females. The high dose was discontinued after four doses because all animals died or were sacrificed in extremis. There were no treatment-related effects on developmental outcomes (postnatal survival, pup body weights) in the evaluated groups (0, 25, and 50 mg/kg/day); however, U.S. EPA (2009a) notes that the number of females evaluated at 50 mg/kg/day was lower than required under the guideline. U.S. EPA identified a NOAEL of 25 mg/kg/day for developmental toxicity because this was the highest dose with a sufficient number of animals, and did not identify a LOAEL (Klimisch Score 1, reliable without restriction).

Endocrine Activity (E) Score (H, M, or L): DG
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Data Gap for endocrine activity based on the lack of data identified for this endpoint.

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

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*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Moderate for acute toxicity based on the majority of EU notifiers self-classifying it as a GHS Category 4 acute oral toxicant (H302). This classification is supported by the oral LD_{50} of 435 mg/kg for the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when they produce oral LD_{50} values > 300 – 2,000 mg/kg or are classified as GH Category 4 acute oral toxicants (CPA 2018b). The confidence in the score is low since the available data for the target chemical conflict with the self-classification by the EU notifiers.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #68187-69-9, 2023; PubChem 2023
  - A majority of EU notifiers have self-classified quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides as a GHS Category 4 acute oral toxicant (H302 - Harmful if swallowed).
- TRC 2018
  - *Oral*: LD_{50} (rat) > 2,150 mg/kg
  - *Dermal*: LD_{50} (rabbit) > 5,000 mg/kg
- Procter & Gamble 1992a
  - *Oral*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: LD_{50} (male and female Sprague-Dawley rats) = 580 mg/kg (75% solution in isopropyl alcohol) (equivalent to 435 mg/kg active substance[8]).
- Procter & Gamble 1992b
  - *Dermal*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: LD_{50} (male and female New Zealand white rabbits) = < 2 mL/kg (75% solution in 25% isopropyl alcohol) (equivalent to < 1,614 mg/kg active substance[9]).
- Evonik 2017
  - *Oral*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: LD_{50} (rat, sex and strain not specified) > 2,000 mg/kg

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for systemic toxicity (single dose) based on the lack of gross pathological findings in rats administered single oral doses of the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Procter & Gamble 1992a
  - *Oral*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: In the acute oral toxicity test that identified an oral LD_{50} of 580 mg/kg (435 mg/kg active substance) in male and female Sprague-Dawley rats dosed with a 75% solution of the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides in isopropyl alcohol, animals were dosed with 350, 490, 686, or 960 mg/kg test substance. Animals in all dose groups exhibited ataxia and animal dosed with ≥ 490 mg/kg exhibited diarrhea, piloerection, hypoactivity, loss of righting reflex, and high carriage. The majority of animals dosed with 680 and 960

[8] 580 mg/kg * 0.75 = 435 mg/kg active substance.
[9] Based on a density of 1.076 g/mL (Akzo Nobel 2007): 2 mL/kg * 1.076 g/mL = 2.16 g/kg * 1,000 mg/g * 0.75 = 1,614 mg/kg active substance.

mg/kg died prior to the scheduled sacrifice. Surviving animals appeared normal by observation day 5. Treatment did not adversely affect body weight gains or alter gross pathological findings at necropsy.

- Procter & Gamble 1992b
    - *Dermal*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: In the acute dermal toxicity study that identified a dermal LD_{50} < 2 mL/kg (equivalent to < 1,614 mg/kg) in male and female New Zealand white rabbits dosed with a 75% solution of the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides in isopropyl alcohol, the dose was applied to intact or abraded skin. Treatment produced severe dermal reactions characterized as severe erythema, slight edema, slight to moderate atonia, and eschar at the application sites that persisted until death. Clinical signs of toxicity identified prior to death included general listlessness and anorexia. Deaths were assumed to be due to "severe cutaneous disease and its pathophysiologic sequelae." No data were provided for body weights or gross pathological findings.

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Moderate for systemic toxicity (repeated dose) based on a LOAEL of 100 mg/kg/day produced by the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides in a subchronic repeated oral dose toxicity test. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when they produce LOAELs > 10 – 100 mg/kg/day in subchronic repeated oral dose toxicity tests (CPA 2018b). The confidence in the score is high as it is based on measured data for a strong surrogate.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- Exponent 2008; U.S. EPA 2009a,b; ECHA, CAS #18448-65-2, 2023
    - *Oral: Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* In a repeated dose toxicity study with reproductive and developmental toxicity screening test conducted according to OECD Guideline 422/OPPTS 870.3650, male and female HanRcc: WIST(SPF) rats (10/sex/dose) received 0, 25, 50, or 100 mg/kg/day quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (75% purity/23% anhydrous isopropanol; U.S. EPA specifies doses were adjusted to correct for purity and control animals received 23% isopropanol) via gavage beginning 14 days prior to mating and for a minimum of 28 days for males and through lactation day 4 for females. The high dose was discontinued after four doses because all animals died or were sacrificed in extremis. Clinical signs included piloerection, diarrhea, reduced activity, and general bad condition. Food consumption at 50 mg/kg/day was decreased by 10.7% for males and 10.2% for females during the pre-mating period, but the changes were not statistically significant. Body weight gain was sporadically statistically significantly reduced at 50 mg/kg/day between pre-mating days 6 and 10. There were statistically significant reductions in absolute and relative spleen weights in males at 25 mg/kg/day. Histopathology revealed inflammatory lesions due to the gavage dosing of the test substance. There were no effects on hematology. Liver enzymes (unspecified) were increased in males at 25 and 50 mg/kg/day and females at 50 mg/kg/day, but there were no effects on organ weights and the U.S. EPA (2009a,b) did not consider the changes in liver

enzymes to be toxicologically relevant due to the lack of histopathological findings. The U.S. EPA identified a NOAEL of 25 mg/kg/day and a LOAEL of 50 mg/kg/day for this study, based on mortality and forestomach inflammation. U.S. EPA (2009b) also noted that the mortality is likely a result of the forestomach irritation due to the corrosivity of the test substance rather than a systemic effect, and that the effects in rats are likely to be significantly more severe than in humans (Klimisch Score 1, reliable without restriction).

- AkzoNobel 2016
  - *Oral: Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* An OECD Guideline 408 subchronic repeated oral dose toxicity test was performed with Wistar Han™:RccHan™: WIST Strain rats (10/sex/group) provided diets containing quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (purity not specified) at 0, 150, 400, or 1,500 ppm (contributing doses of 0, 10, 30, and 100 mg/kg/day, respectively) for 90 days. High dose males and females exhibited decreased food conversion efficiency throughout the exposure period. Treatment statistically significantly increased the total leukocyte and neutrophil counts in high dose males and females relative to the concurrent and historical controls. Relative to the concurrent control group, females in all treatment groups exhibited a statistically significant decrease in mean corpuscular hemoglobin concentration, males in all treatment groups exhibited statistically significant decreases in serum phosphorus and albumin levels, males in the mid and high dose groups exhibited statistically significantly decreased serum chloride levels, and high dose males exhibited statistically significantly decreased albumin/globulin ratio and increased urea levels; however, the treated animal values were within the background control ranges. Treatment at the high dose statistically significantly increased alanine aminotransferase and aspartate aminotransferase activities in males and females. Females in all dose groups exhibited increased bile acid levels relative to concurrent controls, but the levels were within the historical control range. At necropsy, high dose males and females exhibited raised non-glandular regions of the stomach. Treatment increased the incidence of hypertrophy of the adrenal zona glomerulus and hyperplasia with inflammation of the caecum mucosa in high dose males and females. In the kidney, high dose treatment increased the incidence of brown pigment deposition, basophilic tubules, and tubular dilation especially of the medullary tubules. Treatment increased the incidence of periportal basophilia ("homogenous, darker staining cells") in 5/10 high dose males. The mesenteric lymph nodes of 6/10 (60%) high dose males exhibited erythrocytosis (high red blood cell concentration) compared to 7/70 (1%) controls. Treatment induced histopathological changes, characterized as erosion, hyperplasia, and ulceration, to the non-glandular stomach of all males and 9/10 females in the high dose group. No additional details were provided. ToxServices identified a systemic toxicity NOAEL/LOAEL of 30/100 mg/kg/day based on the histopathological changes identified in the high dose group.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for neurotoxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant following single exposure for narcotic effects under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as acute toxicity tests do not include specific neurotoxicity assessments.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Procter & Gamble 1992a
  - *Oral*: *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: In the acute oral toxicity test that identified an oral LD_{50} of 580 mg/kg (435 mg/kg active substance) in male and female Sprague-Dawley rats dosed with a 75% solution of the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides in isopropyl alcohol, animals were dosed with 350, 490, 686, or 960 mg/kg test substance. Animals in all dose groups exhibited ataxia and animal dosed with ≥ 490 mg/kg exhibited diarrhea, piloerection, hypoactivity, loss of righting reflex, and high carriage. The majority of animals dosed with 680 and 960 mg/kg died prior to the scheduled sacrifice. Surviving animals appeared normal by observation day 5.
- Although animals dosed with the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides exhibited ataxia, hypoactivity, and loss of righting reflex, which are potential signs of narcotic effects identified in Section 3.8.2.2. of the GHS criteria (UN 2021), ToxServices considered the etiology of these effects to result from the irritating nature of the test substance and other quaternary compounds (see the skin and eye irritation sections and discussions of the OECD Guideline 422 study performed with the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides in the repeated exposure systemic toxicity section), ToxServices did not classify quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) as a specific target organ toxicant following single exposure for narcotic effects under GHS criteria (UN 2021).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): *L*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurobehavioral effects produced by the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides in an OECD Guideline 422 repeated dose toxicity study with reproductive and developmental toxicity screening test. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as the NOAEL, which was the highest dose tested, was below the duration-adjusted oral GHS guidance level of 300 mg/kg/day for GHS Category 2 (i.e., 100 mg/kg/day x 90 days/ 30 days).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Exponent 2008; U.S. EPA 2009a,b; ECHA, CAS #18448-65-2, 2023
  - *Oral: Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9):* In a repeated dose toxicity study with reproductive and developmental toxicity screening test conducted according to OECD Guideline 422/OPPTS 870.3650, male and female HanRcc: WIST(SPF) rats (10/sex/dose) received 0, 25, 50, or 100 mg/kg/day quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (75% purity/23% anhydrous isopropanol; U.S. EPA specifies doses were adjusted to correct for purity and control animals received 23% isopropanol) via gavage beginning 14 days prior to mating and for a minimum of 28 days for males and through lactation day 4 for females. The high dose was discontinued after four doses because all animals died or were sacrificed

in moribund condition. Observations noted in the functional observational battery (FOB) included ruffle fur in both sexes at 50 mg/kg/day in the open arena observation. The number of rearings was decreased in two males at 25 mg/kg/day and one male at 50 mg/kg/day, and activity was reduced in one male at 50 mg/kg/day. No additional details were provided. Based on its review of this study, the U.S. EPA (2009a,b) concluded that there was no evidence of neurotoxicity based on a lack of treatment-related effects on FOB and motor activity. Therefore, ToxServices identified a NOAEL of 50 mg/kg/day for neurotoxicity (Klimisch Score 1, reliable without restriction).

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for skin sensitization based on results of *in vitro* and *in chemico* tests performed with the surrogate bis(hydroxyethyl)methyloleylammonium chloride and the "2 out of 3" defined approach (OECD 2023b). GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #18448-65-2, 2023
  - *In vitro*: *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*:A GLP-compliant, OECD Guideline 442D keratinocyte activation study was performed with bis(hydroxyethyl)methyloleylammonium chloride (purity not specified) at concentrations ≤ 2,0000 µM in the KeratinoSens prediction model. Treatment did not statistically significantly increase luciferase induction in a repeatable manner across three independent experiments. Since the negative and positive (cinnamic aldehyde) controls were reported as valid, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was not sensitizing under the tested conditions (Klimisch Score 1, reliable without restriction).
  - *In chemico*: *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: A GLP-compliant, OECD Guideline 442C direct peptide reactivity assay (DPRA) was performed with bis(hydroxyethyl)methyloleylammonium chloride (purity not specified) incubated with cysteine and lysine. Treatment produced a mean peptide depletion of 4.385%. Since the peptide depletion was less than 6.38%, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was not active reactive towards the peptides under the tested conditions (Klimisch Score 1, reliable without restriction).
  - *In vitro: Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: A GLP-compliant, OECD Guideline 442E dendritic cell activation assay (human cell line activation test, h-CLAT) was performed with bis(hydroxyethyl)methyloleylammonium chloride (purity not specified). No additional experimental details were provided. Treatment produced a CD54 EC_{200} of 254 µg/mL and a CD86 EC_{150} of 286 µg/mL. Since the treatment produced CD54 activation ≥ 200% and CD86 activation ≥ 150%, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was sensitizing under the tested conditions (Klimisch Score 1, reliable without restriction).
- In summary, the surrogate bis(hydroxyethyl)methyloleylammonium chloride was negative in a keratinocyte activation study and a DPRA but was positive in an h-CLAT. Per OECD Guideline 497 ("Guideline on Defined Approaches for Skin Sensitisation") (OECD 2023b), the "2 out of 3" defined approach is used to classify chemicals as skin sensitizers using a combination of results

obtained form *in vitro*/*in chemico* assays corresponding to the first three key events of the skin sensitization adverse outcome pathway (AOP). Since the OECD Guideline 442C, 442D, and 442E assays correspond to the first three key events and bis(hydroxyethyl)methyloleylammonium chloride was positive in only one of these assays, ToxServices concludes that bis(hydroxyethyl)methyloleylammonium chloride is not classified as a skin sensitizer per the "2 out of 3" defined approach.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for respiratory sensitization based on ECHA's guidance on respiratory sensitization evaluation. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023a
  - Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) does not contain any structural alerts for respiratory sensitization (Appendix C).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not expected to be sensitizing to the skin based on surrogate data (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO), and as quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) does not contain any structural alerts for respiratory sensitization (OECD 2022), quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *vH*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Very High for skin irritation/corrosivity based on the irreversible/corrosive effects to rabbit skin produced by the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides. GreenScreen® criteria classify chemicals as a Very High hazard for skin irritation/corrosivity when they produce irreversible/corrosive effects to the skin or are classified as GHS Category 1 skin irritants (H314) (CPA 2018b). The confidence in the score is low due to the differential results produced by the surrogates quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides and bis(hydroxyethyl)methyloleylammonium chloride.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #18448-65-2, 2023
    - *Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)*: A GLP-compliant, OECD Guideline 404/EU Method B.4/EPA OPPTS 870.2500 dermal irritation test was performed with a New Zealand White rabbit administered a topical application of 0.5 mL quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (77.3% in isopropyl alcohol) to shaved skin under semi-occlusive dressing for up to 4 hours. At 24, 48, and 72 hours, the 4-hour exposure produced a mean erythema score of 4 and a mean edema score of 2. The dermal irritation was not fully reversible within the 14-day observation period. Therefore, the authors concluded the test substance was corrosive to the skin under the tested conditions (Klimisch Score 1, reliable without restriction).
    - *In vitro*: *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: A GLP-compliant, OECD Guideline 431 *in vitro* skin corrosion test was performed with the reconstructed human epidermal model Epiderm™ exposed to 25 mg bis(hydroxyethyl)methyloleylammonium chloride (purity not specified) for 3 or 60 minutes. Tissue viabilities were 81.4% and 89% after the 3- and 60-minute exposures, respectively. Since the tissue viabilities were > 50% after 3 minutes and > 15% after 60 minutes, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was not corrosive to the skin under the tested conditions (Klimisch Score 1, reliable without restriction).
    - *In vitro*: *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: A GLP-compliant, OECD Guideline 439 *in vitro* skin irritation test was performed with an unspecified human skin model exposed to an unspecified amount of bis(hydroxyethyl)methyloleylammonium chloride (purity not specified) for 60 minutes. The cells were then incubated without test substance exposure for 42 hours. At the end of the incubation period, the tissue viability was 3.917%. Since the test substance produced a viability < 50%, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was irritating under the tested conditions (Klimisch Score 1, reliable without restriction).
- While the surrogate bis(hydroxyethyl)methyloleylammonium chloride was irritating but not corrosive in *in vitro* tests, the surrogate quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides produced irreversible effects to the skin of rabbits. Therefore, ToxServices conservatively classified quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) as a Category 1 skin irritant (H314 - Causes severe skin burns and eye damage) under GHS criteria (UN 2021).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *vH*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Very High for eye irritation/corrosivity based on the GHS Category 1 skin irritant classification (H314 - Causes severe skin burns and eye damage) (see skin irritation endpoint). 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 low based on the uncertainty in the skin irritation/corrosiveness 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.

- TRC 2018
    - "Causes serious eye irritation."

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): vH
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Very High for acute aquatic toxicity based on acute aquatic toxicity values as low as 0.4165 mg/L across the three trophic levels. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are ≤ 1 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for strong surrogates.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment (iTE).
- TRC 2018
    - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) = 12 mg/L
- U.S. EPA 2023b
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 1.2 mg/L (unspecified EO)
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour LC_{50} (*Lepomis macrochirus*, bluegill) = 1.6 mg/L (unspecified EO)
- Akzo Nobel 2007
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour LC_{50} (trout) = 24 mg/L (15 EO)
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour EC_{50} (algae) = 3.9 mg/L (15 EO)
- Evonik 2017
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour LC_{50} (*Pimephales promelas,* fathead minnow) = 10-20 mg/L (15 EO)
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour EC_{50} (algae) = 1-5 mg/L (15 EO)
- West Pentone 2017
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour LC_{50} (*P. promelas*, fathead minnow) = 26.7 mg/L (15 EO)
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 48-hour EC_{50} (*Daphnia magna*, water flea) = 42 mg/L (15 EO)
    - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: 96-hour EC_{50} (*Selenastrum capricornutum*, green algae) = 3.1 mg/L (15 EO)
- ECHA, CAS #18448-65-2, 2023
    - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: Nominal 96-hour LC_{50} (*Danio rerio*, zebrafish) = 1.84 mg active

ingredient/L (GLP-compliant, OECD Guideline 203) (Klimisch Score 2, reliable with restrictions).
- *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: Nominal 21-day mortality EC_{50} (*D. magna*) = 465 µg active ingredient/L (0.465 mg active ingredient/L) (GLP-compliant, OECD Guideline 211) (Klimisch Score 1, reliable without restriction).
- *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: Nominal 72-hour growth rate EC_{50} (*Raphidocelis subcapitata*, algae) = 413.5 µg active ingredient/L (0.4165 mg active ingredient/L) (GLP-compliant, OECD Guideline 201) (Klimisch Score 1, reliable without restriction).

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): H
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of High for chronic aquatic toxicity based on chronic aquatic toxicity values as low as 0.121 mg/L for a surrogate. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are > 0.1 to 1.0 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate. Although chronic aquatic toxicity data were not identified for fish, acute aquatic toxicity data indicate aquatic vertebrates are not the most sensitive trophic level for the toxicity of the target chemical or the surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* EC - CEPA DSL - Inherently Toxic in the Environment (iTE).
- ECHA, CAS #68187-69-9, 2023; PubChem 2023
  - A majority of EU notifiers have self-classified quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) as a GHS Category 2 chronic aquatic toxicant (H411 - Toxic to aquatic life with long lasting effects).
- ECHA, CAS #18448-65-2, 2023
  - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: Nominal 21-day reproduction NOEC (*D. magna*) = 268 µg active ingredient/L (0.268 mg active ingredient/L) (GLP-compliant, OECD Guideline 211) (Klimisch Score 1, reliable without restriction).
  - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: Nominal 72-hour growth rate EC_{10} (*R. subcapitata*, algae) = 121 µg active ingredient/L (0.121 mg active ingredient/L) (GLP-compliant, OECD Guideline 201) (Klimisch Score 1, reliable without restriction).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of High for persistence based on data for the surrogate quaternary ammonium compounds (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides demonstrating slow biodegradability. GreenScreen® criteria classify chemicals as a High hazard for persistence when the chemical is not recalcitrant but takes an extended period of time to degrade in the environment (CPA 2018b). The confidence in the score is low as limited details are available for the key study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Akzo Nobel 2007
  - *Surrogate: Quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (CAS #61791-10-4)*: Quaternary ammonium compounds (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides (as ETHOQUAD® C/25, unspecified EO number) degraded 11% in 28 days and 26% in 112 days in a closed bottle test (CBT). No further details were reported.
    - The trade name ETHOQUAD® C/25 contains 15 EO units.[10]
- ECHA, CAS #18448-65-2, 2023
  - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: A GLP-compliant, OECD Guideline 301 D (closed bottle) ready biodegradability test was performed with river water exposed to the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (77% active compound, 20% isopropyl alcohol, 3% water) at 2 mg/L for 28 days. The test substance degraded 70% within 28 days based on O_2 consumption, but the 10-day window was not met. The reference compound, sodium acetate, performed as expected. The authors concluded quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides was readily biodegradable under the tested conditions (Klimisch Score 1, reliable without restriction).
  - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: A GLP-compliant, OECD Guideline 301 D (closed bottle) ready biodegradability test was performed with river water exposed to the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (67% active compound, 32% diethylene glycol, 1% water) at 2 mg/L for 28 days. The test substance degraded 64% within 28 days based on O_2 consumption, but the 10-day window was not met. The reference compound, sodium acetate, performed as expected. The authors concluded quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides was readily biodegradable under the tested conditions (Klimisch Score 1, reliable without restriction).
  - *Surrogate: Quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (CAS #70750-47-9)*: A non-GLP-compliant, OECD Guideline 301 D (closed bottle) ready biodegradability test was performed with non-adapted, activated sludge exposed to the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides (76% purity, 21% isopropyl alcohol, 3% water) at 1-2 mg/L for 28-60 days. After 28 days, the test substance degraded 63%. No information on the 10-day window was provided. The authors concluded quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides was readily biodegradable under the tested conditions (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: A non-GLP-compliant, OECD Guideline 301 D (closed bottle) ready biodegradability test was performed with non-adapted, activated sludge exposed to bis(hydroxyethyl)methyloleylammonium chloride (99.45% purity) at 44 mg test material/L (20 mg TOC/L) for 36 days. The test substance degraded 14.3% after 28 days and -15.3% after 36 days. The authors indicate the negative degradation value suggests an inhibitory

[10] https://www.nouryon.com/globalassets/inriver/resources/pds-ethoquad-c25-na-en.pdf, https://www.knowde.com/stores/nouryon/products/ethoquad-c-25

effect of the inoculum by the test substance. Based on the expected performance of the reference substance sodium benzoate, the authors concluded bis(hydroxyethyl)methyloleylammonium chloride was not biodegradable under the tested conditions (Klimisch Score 2, reliable with restrictions).

- Although the surrogate quaternary ammonium compounds, coco alkylbis(hydroxyethyl)methyl, chlorides demonstrated significant biodegradation in OECD Guideline 301 D tests, the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides did not demonstrate significant biodegradation in a closed bottle test. The 26% degradation after 112 days suggests that the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides may be ultimately biodegradable and not recalcitrant. Since the surrogate quaternary ammonium compounds, (coco alkyl) bis(hydroxyethyl) methyl, ethoxylated, chlorides is more structurally similar to the target chemical and it demonstrated a low capacity to biodegrade over the tested exposure duration, ToxServices assigned a High score for persistence to quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO). EPI Suite™ modeling is not feasible for this compound as surfactants are outside the model's applicability domain.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Very Low for bioaccumulation based on the calculated log K_{ow} of -0.12 for a surrogate. The GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4. The confidence in the score is low due to the uncertain relationships between bioaccumulation potential and the log K_{ow} for surface active chemicals.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #71808-53-2, 2023
  - *Surrogate: Quaternary ammonium compounds, C12-18-alkylbis(hydroxyethyl)methyl, chlorides (CAS #71808-53-2)*: Due to the surfactant properties, the partition coefficient could not be determined using standard methods. Instead, according to ISO/IEC 17025, the REACH dossier authors calculated the log K_{ow} as -0.12 based on the measured water solubility of 343 g/L in octanol and 450 g/L in water.
- Surfactants and chemicals with surfactant properties are outside the applicability domain of EPI Suite™ (U.S. EPA 2017).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score is low due to the lack of authoritative classifications or measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.

- No measured data were identified for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO). Therefore, screening procedures for explosivity were used here to estimate the reactivity property of quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO). These procedures are listed in the GHS (UN 2021).
    - Based on the structure of its components or moieties, quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix I).
    - Based on the structure of its components or moieties, quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) has multiple oxygen atoms, which are all bonded only to carbon and hydrogen, classification is not warranted.
- ECHA, CAS #18448-65-2, 2023
    - *Surrogate: Bis(hydroxyethyl)methyloleylammonium chloride (CAS #18448-65-2)*: The surrogate bis(hydroxyethyl)methyloleylammonium chloride lacks structural alerts for oxidizing properties.
- Based on the lack of structural alerts for the target chemical and the surrogate, ToxServices did not classify quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) as a reactive chemical under GHS criteria (UN 2021).

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

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable liquid under GHS criteria (UN 2021). GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not classified as flammable under GHS criteria (CPA 2018b). The confidence in the score was high as it is based on a measured flash point 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.
- TRC 2018
    - Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (number of EO units not specified) has a flash point > 100°C.
- GHS criteria (UN 2021) define chemicals as flammable liquids when they have flash points ≤ 93°C. Based on the flash point > 100°C, ToxServices did not classify quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO) as a flammable liquid under GHS criteria.

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity and respiratory sensitization, non-animal tests for persistence, and *in vitro/in chemico* assays for genotoxicity, skin sensitization, and skin irritation. 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 quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'s NAMs dataset include no or insufficient experimental data for carcinogenicity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'s Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of VEGA, Oncologic, and Danish (Q)SAR database to evaluate its carcinogenic potential, the lack of metabolism incorporated into the *in chemico* and *in vitro* skin sensitization models, the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization, and the inability of the *in vitro* skin irritation assays to identify mild skin irritants (GHS Category 3). Some of quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO)'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. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). VEGA tool does not evaluate ionic substances (VEGA 2021). Danish (Q)SAR database contain predictions for a limited number of chemicals that does not include the target chemical (DTU 2023).

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

	Genotoxicity: The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12]. 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).[13] 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[14]. **Skin sensitization:** The *in silico* and *in vitro* assays evaluating key events in the skin sensitization adverse outcome pathway (AOP) don't typically include metabolism or abiotic transformation to address chemicals that are pro-haptens or pre-haptens, respectively. Further, each test has their applicable domain such as limitations in test substance solubility or log $K_{ow.}$[15] **Skin irritation**: The OECD Guideline 431 test is only used to identify corrosive substances (GHS Category 1)[16]; and OECD Guideline 439 test is only used to identify irritating substances (GHS Category 2) and non-irritating substances (no category), and does not allow the classification as a mild skin irritant (GHS Category 3)[17]. **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/Toxtree/ OncoLogic™/Danish QSAR

[12] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
[13] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[14] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[15] https://www.oecd-ilibrary.org/environment/test-no-442c-in-chemico-skin-sensitisation_9789264229709-en; https://www.oecd-ilibrary.org/environment/test-no-442d-in-vitro-skin-sensitisation_9789264229822-en; https://www.oecd-ilibrary.org/environment/test-no-442e-in-vitro-skin-sensitisation_9789264264359-en
[16] https://www.oecd-ilibrary.org/docserver/9789264264618-en.pdf?expires=1614097188&id=id&accname=guest&checksum=5C0F2BF5F910961BDDD2D30A71941A7D
[17] https://www.oecd-ilibrary.org/docserver/9789264242845-en.pdf?expires=1614097324&id=id&accname=guest&checksum=D664A7EDCDE297919BE9A478941EBEC6

Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* mammalian cell gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	Y	*In chemico/in vitro* data: OECD Guideline 442C DPRA, OECD Guideline 442D keratinocyte activation assay, and OECD Guideline 442E h-CLAT
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	Y	*In vitro* data: OECD Guideline 431 and 439 *in vitro* assays
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	Y	Non-animal testing: OECD Guideline 301 D 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 Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**Quaternary Ammonium Compounds,**	**68187-69-9**	*L*	**L**	*L*	**L**	DG	*M*	**L**	**M**	*L*	*L*	**L**	*L*	*vH*	*vH*	**vH**	**H**	*H*	*vL*	*L*	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Quaternary Ammonium Compounds,	2

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

Table 6

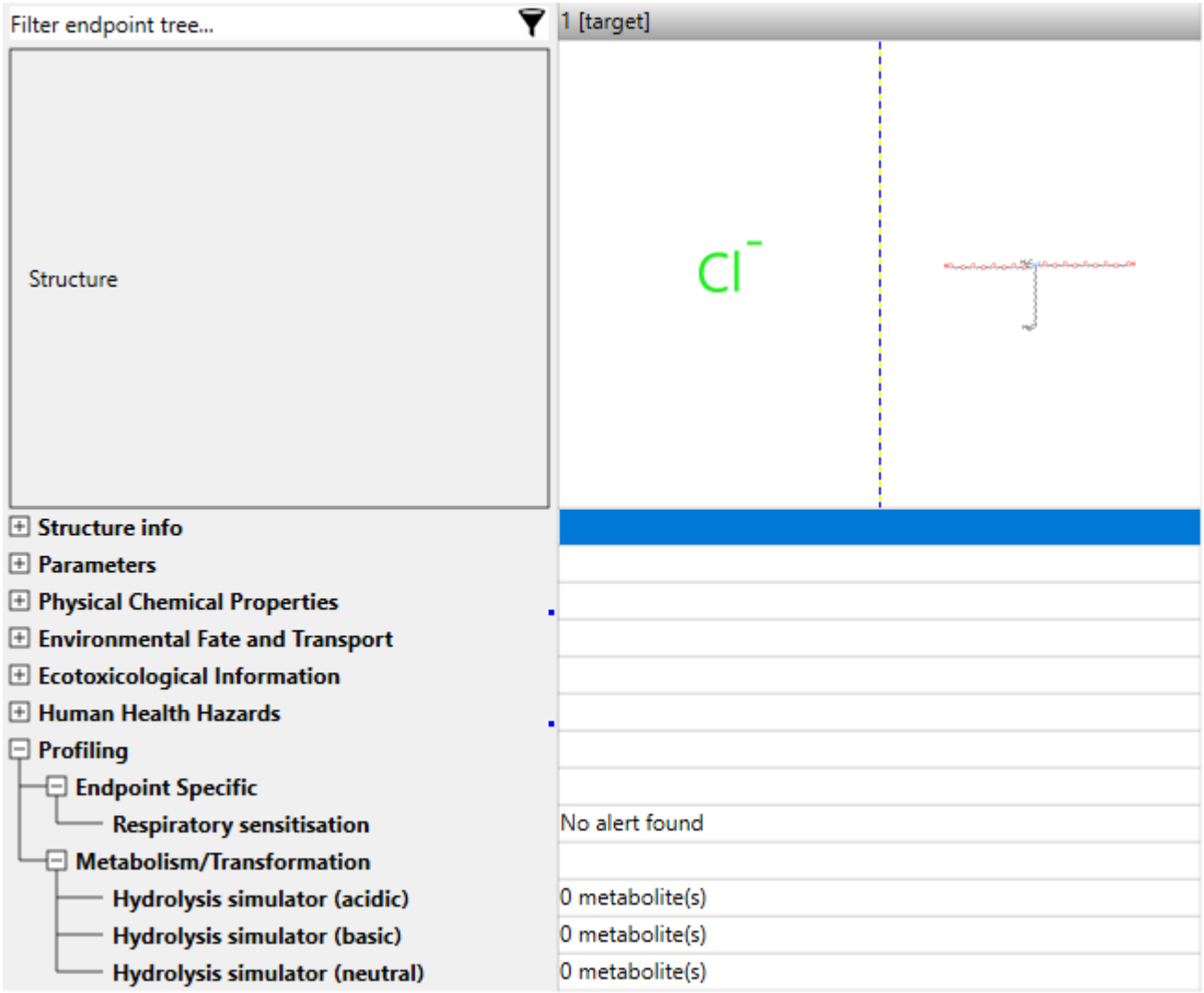
Chemical Name	Final GreenScreen® Benchmark Score
Quaternary Ammonium Compounds,	2

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

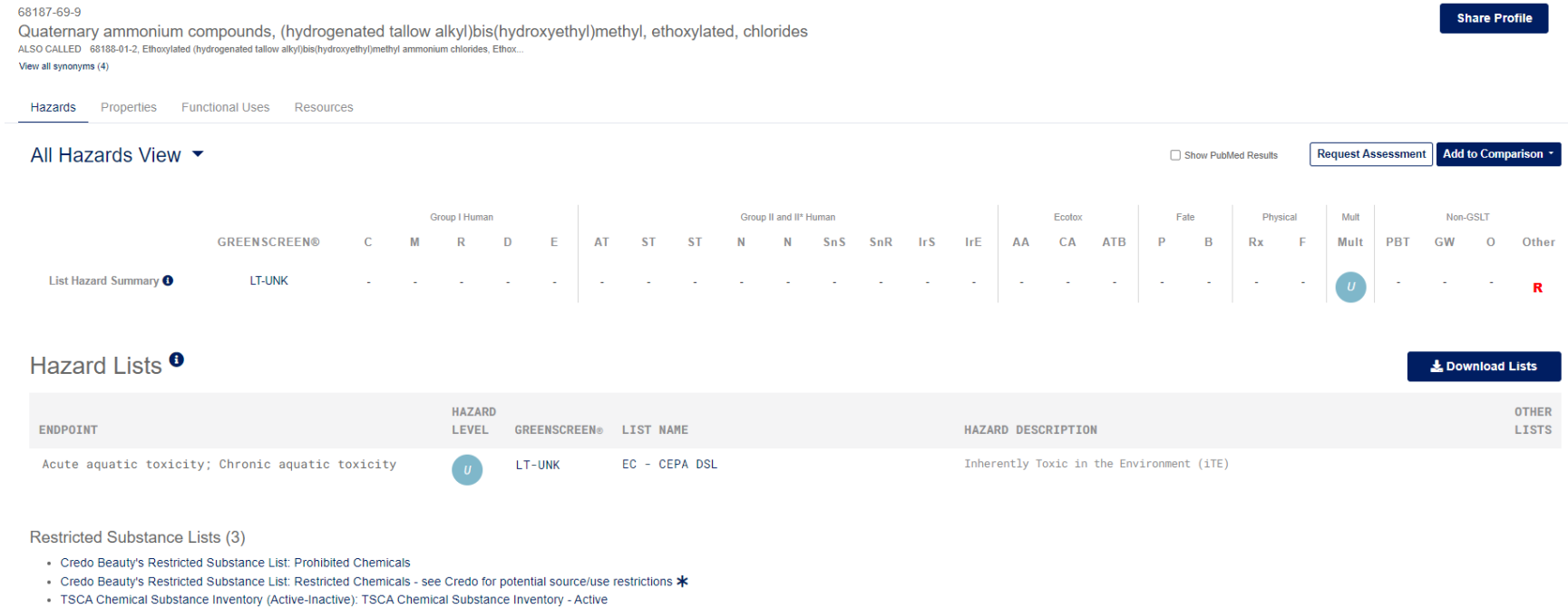
Table 5: Data Gap Assessment Table

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: OECD QSAR Toolbox Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)



APPENDIX D: Pharos Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)



68187-69-9

Quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides

ALSO CALLED 68188-01-2, Ethoxylated (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl ammonium chlorides, Ethox...

View all synonyms (4)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

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

Hazard Lists

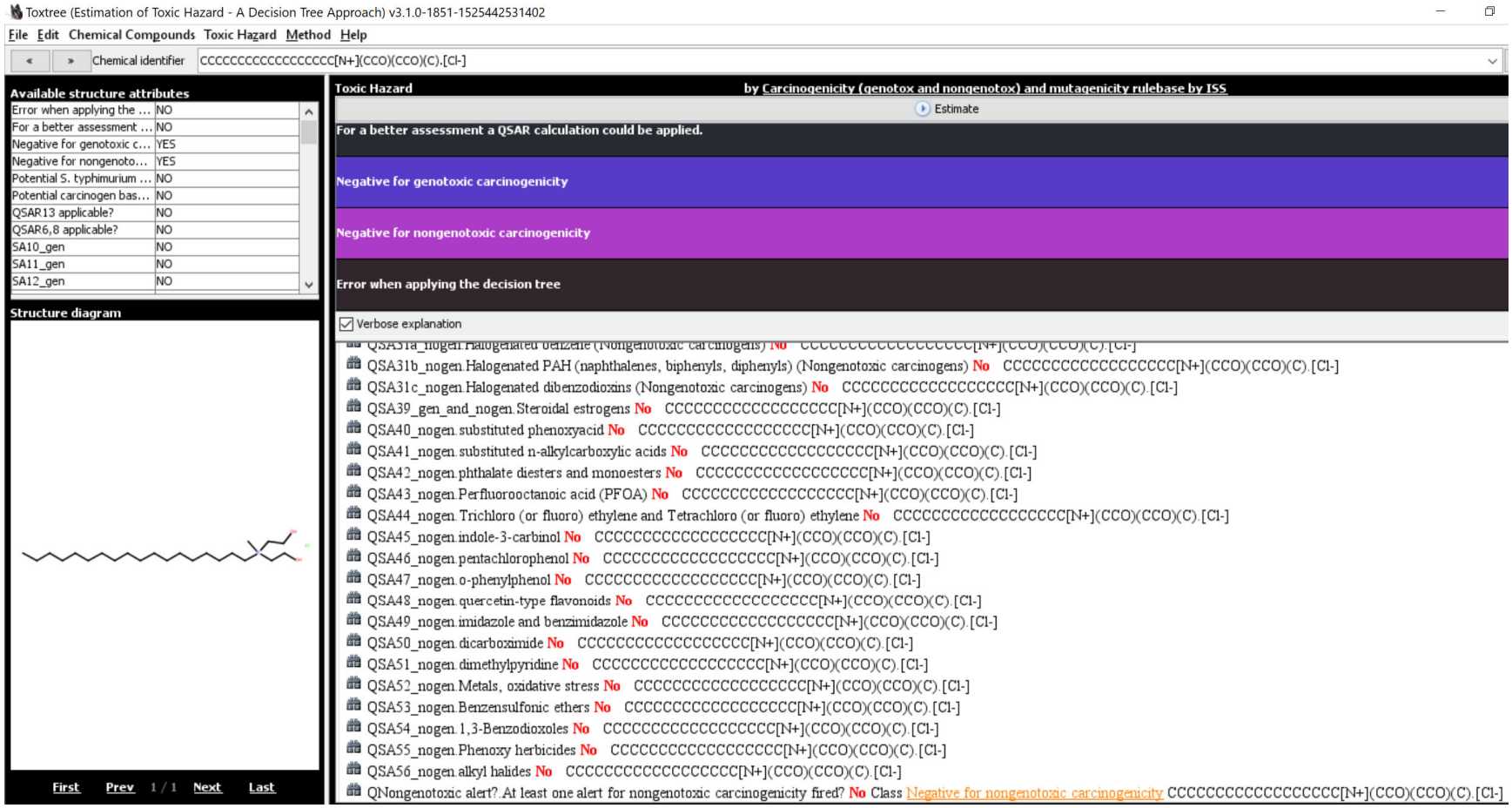
Download Lists

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	

Restricted Substance Lists (3)

- Credo Beauty's Restricted Substance List: Prohibited Chemicals
- Credo Beauty's Restricted Substance List: Restricted Chemicals - see Credo for potential source/use restrictions ✱
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

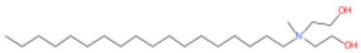
APPENDIX E: Toxtree Carcinogenicity Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)



APPENDIX F: VEGA Carcinogenicity Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)

1. Prediction Summary

Prediction for compound Molecule 0 -

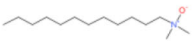


Prediction: Reliability:

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
- Accuracy of prediction for similar molecules found in the training set is not adequate
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

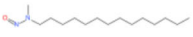
Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.13
P(NON-Carcinogen): 0.87
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



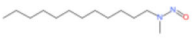
Compound #1

CAS: 1643-20-5
Dataset id:273 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.801
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



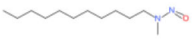
Compound #2

CAS: 75881-20-8
Dataset id:558 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCC
Similarity: 0.793
Experimental value : Carcinogen
Predicted value : Carcinogen



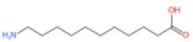
Compound #3

CAS: 55090-44-3
Dataset id:554 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.766
Experimental value : Carcinogen
Predicted value : Carcinogen



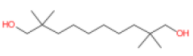
Compound #4

CAS: 68107-26-6
Dataset id:603 (Training Set)
SMILES: O=NN(C)CCCCCCCCCC
Similarity: 0.751
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 2432-99-7
Dataset id:50 (Test Set)
SMILES: O=C(O)CCCCCCCCCN
Similarity: 0.75
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 35449-36-6
Dataset id:345 (Training Set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.738
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.379 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 = 0.497 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
⚠	Concordance for similar molecules Concordance index = 0.503 Explanation: some 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 = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)..
✔	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.

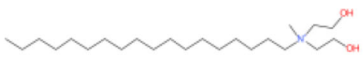
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: CN(C)(C)C
The fragment has never been found in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -

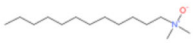


Prediction: Reliability:

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
- some similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
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



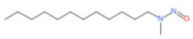
Compound #1

CAS: 1643-20-5
Dataset id:879 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.801
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

Compound #2

CAS: 75881-20-8
Dataset id:579 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.793
Experimental value : Carcinogen
Predicted value : Carcinogen

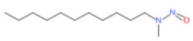
Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups



Compound #3

CAS: 55090-44-3
Dataset id:547 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.766
Experimental value : Carcinogen
Predicted value : Carcinogen

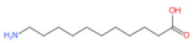
Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups



Compound #4

CAS: 68107-26-6
Dataset id:527 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.751
Experimental value : Carcinogen
Predicted value : Carcinogen

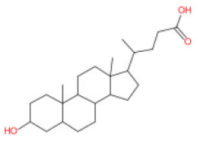
Alerts (not found also in the target): SA21 Alkyl and aryl N-nitroso groups



Compound #5

CAS: 2432-99-7
Dataset id:36 (Training Set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.75
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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



Compound #6

CAS: 434-13-9
Dataset id:117 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.735
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.639 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 = 0.503 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 = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

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.

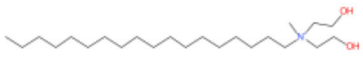
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: CN(C)(C)C
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -

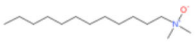


Prediction: Reliability:

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
- 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. 4; Carcinogenity alert no. 34

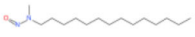
Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 2
Structural Alerts: Carcinogenity alert no. 4; Carcinogenity alert no. 34
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



Compound #1

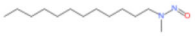
CAS: 1643-20-5
Dataset id:777 (Training Set)
SMILES: [O-][N+](C)(C)CCCCCCCCCCCC
Similarity: 0.801
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

CAS: 75881-20-8
Dataset id:489 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCCCC
Similarity: 0.793
Experimental value : Carcinogen
Predicted value : Carcinogen

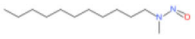
Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27



Compound #3

CAS: 55090-44-3
Dataset id:458 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCCC
Similarity: 0.766
Experimental value : Carcinogen
Predicted value : Carcinogen

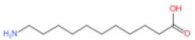
Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27



Compound #4

CAS: 68107-26-6
Dataset id:439 (Training Set)
SMILES: O=NN(C)CCCCCCCCCCC
Similarity: 0.751
Experimental value : Carcinogen
Predicted value : Carcinogen

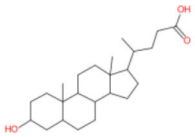
Alerts (not found also in the target): Carcinogenity alert no. 1; Carcinogenity alert no. 14; Carcinogenity alert no. 27



Compound #5

CAS: 2432-99-7
Dataset id:29 (Training Set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.75
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

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



Compound #6

CAS: 434-13-9
Dataset id:93 (Training Set)
SMILES: O=C(O)CCC(C)C2CCC3C4CCC1CC(O)CCC1(C)C4(CCC23(C))
Similarity: 0.735
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.799 Explanation: The predicted compound could be out of the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.786 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 = 0.659 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..

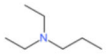
Symbols explanation:

✔ 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

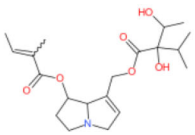
(Molecule 0) Reasoning on fragments/structural alerts - 1 of 2:.

Fragment found: Carcinogenity alert no. 4



Structural alert for carcinogenity defined by the SMARTS:CCCN(CC)CC

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

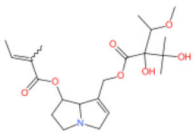


CAS: 22571-95-5
Dataset id:403 (Training Set)
SMILES: O=C(OC2CCN1CC=C(COC(=O)C(O)(C(O)C)C(C)C)C12)C(=CC)C
Similarity: 0.648

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 4

Alerts (not found also in the target): Carcinogenity alert no. 20; Carcinogenity alert no. 29

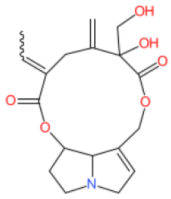


CAS: 303-34-4
Dataset id:160 (Training Set)
SMILES: O=C(OC2CCN1CC=C(COC(=O)C(O)(C(OC)C)C(O)(C)C)C12)C(=CC)C
Similarity: 0.64

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 4

Alerts (not found also in the target): Carcinogenity alert no. 20; Carcinogenity alert no. 29



CAS: 23246-96-0
Dataset id:716 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C(=C)CC1(=CC))CO)C23
Similarity: 0.628

Experimental value : Carcinogen
Predicted value : Carcinogen

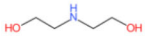
Alerts (found also in the target): Carcinogenity alert no. 4

Alerts (not found also in the target): Carcinogenity alert no. 20; Carcinogenity alert no. 29

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

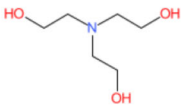
(Molecule 0) Reasoning on fragments/structural alerts - 2 of 2:.

Fragment found: Carcinogenity alert no. 34



Structural alert for carcinogenity defined by the SMARTS:N(CCO)CCO

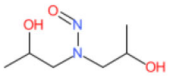
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 102-71-6
Dataset id:533 (Training Set)
SMILES: OCCN(CCO)CCO
Similarity: 0.662

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 34

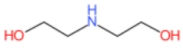


CAS: 53609-64-6
Dataset id:440 (Training Set)
SMILES: O=NN(CC(O)C)CC(O)C
Similarity: 0.644

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 34

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



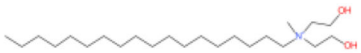
CAS: 111-42-2
Dataset id:500 (Training Set)
SMILES: OCCNCCO
Similarity: 0.638

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 34

1. Prediction Summary

Prediction for compound Molecule 0 -

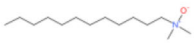
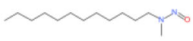
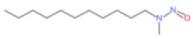


Prediction: Reliability:

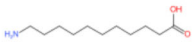
Prediction is Possible NON-Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- Only moderately similar compounds with known experimental value in the training set have been found
- 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
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
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

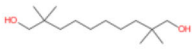
	Compound #1 CAS: 1643-20-5 Dataset id:273 (Training Set) SMILES: [O-][N+](C)(C)CCCCCCCCCCCC Similarity: 0.801 Experimental value : NON-Carcinogen Predicted value : Carcinogen Alerts (not found also in the target): Carcinogenity alert no. 64
	Compound #2 CAS: 75881-20-8 Dataset id:558 (Training Set) SMILES: O=NN(C)CCCCCCCCCCCCCC Similarity: 0.793 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: 55090-44-3 Dataset id:554 (Training Set) SMILES: O=NN(C)CCCCCCCCCCCC Similarity: 0.766 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 #4 CAS: 68107-26-6 Dataset id:603 (Training Set) SMILES: O=NN(C)CCCCCCCCCC Similarity: 0.751 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: 2432-99-7
Dataset id:50 (Test Set)
SMILES: O=C(O)CCCCCCCCCCN
Similarity: 0.75
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #6

CAS: 35449-36-6
Dataset id:345 (Training Set)
SMILES: OCC(C)(C)CCCCCCC(C)(C)CO
Similarity: 0.738
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.366 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.786 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.659 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0.341 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✖	Atom Centered Fragments similarity check ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)..

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.

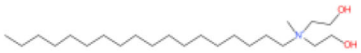
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: CN(C)(C)C
The fragment has never been found in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -

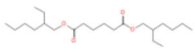


Prediction: Reliability:

Prediction is 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
- 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
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)

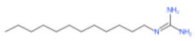
Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



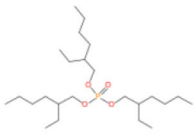
Compound #1

CAS: 103-23-1
Dataset id:94 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.724
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



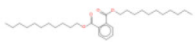
Compound #2

CAS: 2439-10-3
Dataset id:490 (Training Set)
SMILES: N(=C(N)N)CCCCCCCCCCCC
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



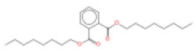
Compound #3

CAS: 78-42-2
Dataset id:313 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.718
Experimental value : Carcinogen
Predicted value : Carcinogen



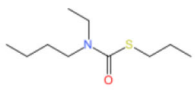
Compound #4

CAS: 3648-20-2
Dataset id:488 (Training Set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.689
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 117-84-0
Dataset id:614 (Training Set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.675
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 1114-71-2
Dataset id:622 (Training Set)
SMILES: O=C(N(CC)CCCC)SCCC
Similarity: 0.666
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.511 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.723 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.499 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✖	Concordance for similar molecules Concordance index = 0.501 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 = 0.85 Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent_fragments found)..

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.

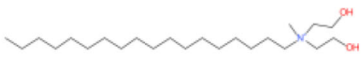
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

Fragment defined by the SMILES: CN(C)(C)C
The fragment has less than 3 occurrences in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0 -

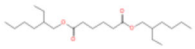


Prediction: Reliability:

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
- Accuracy of prediction for similar molecules found in the training set is not adequate
- a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)

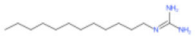
Compound: Molecule 0
Compound SMILES: OCC[N+](C)(CCO)CCCCCCCCCCCCCCCCCC
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



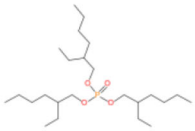
Compound #1

CAS: 103-23-1
Dataset id:391 (Training Set)
SMILES: O=C(OCC(CC)CCCC)CCCCC(=O)OCC(CC)CCCC
Similarity: 0.724
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



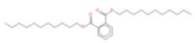
Compound #2

CAS: 2439-10-3
Dataset id:462 (Training Set)
SMILES: N(=C(N)N)CCCCCCCCCCCC
Similarity: 0.722
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



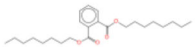
Compound #3

CAS: 78-42-2
Dataset id:741 (Training Set)
SMILES: O=P(OCC(CC)CCCC)(OCC(CC)CCCC)OCC(CC)CCCC
Similarity: 0.718
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



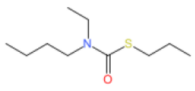
Compound #4

CAS: 3648-20-2
Dataset id:460 (Test Set)
SMILES: O=C(OCCCCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCCCCC)
Similarity: 0.689
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 117-84-0
Dataset id:597 (Training Set)
SMILES: O=C(OCCCCCCCC)c1ccccc1(C(=O)OCCCCCCCC)
Similarity: 0.675
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 1114-71-2
Dataset id:605 (Test Set)
SMILES: O=C(N(CC)CCCC)SCCC
Similarity: 0.666
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	Global AD Index AD index = 0.429 Explanation: The predicted compound is outside the Applicability Domain of the model.
⚠	Similar molecules with known experimental value Similarity index = 0.723 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
✖	Accuracy of prediction for similar molecules Accuracy index = 0.501 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 = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found)..

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.

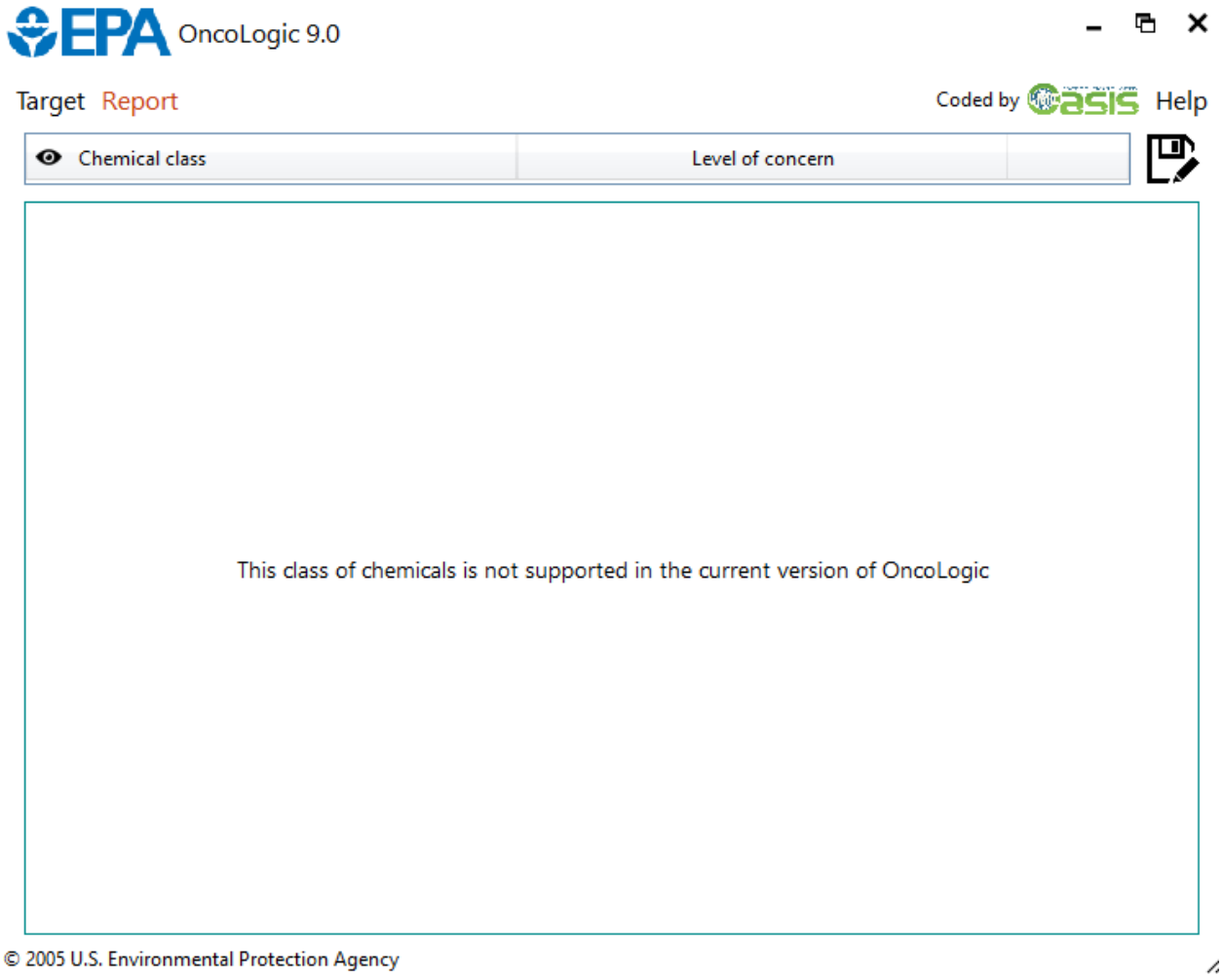
✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

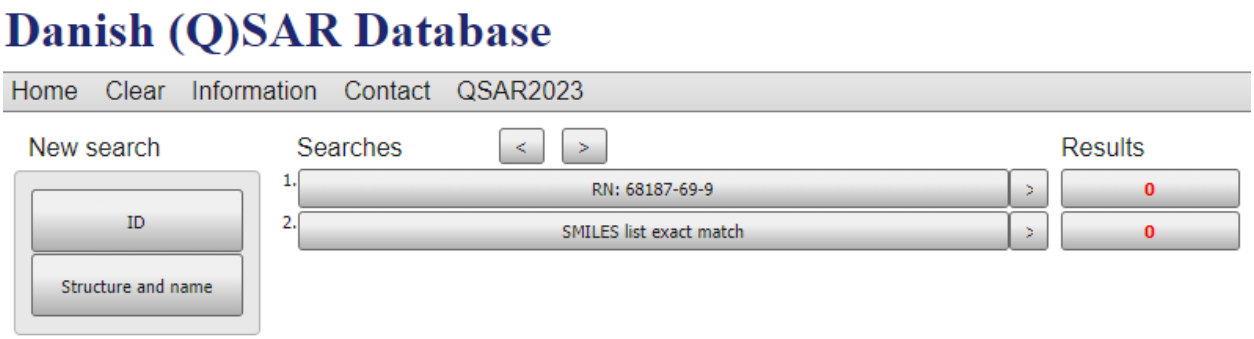
(Molecule 0) Reasoning on rare and missing Atom Centered Fragments .
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:

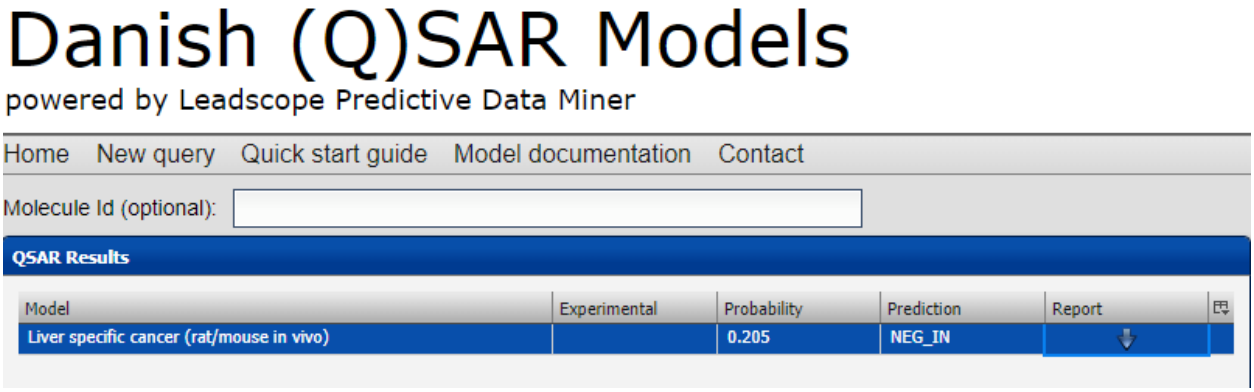
Fragment defined by the SMILES: CN(C)(C)C
The fragment has never been found in the model's training set

APPENDIX G: OncoLogic™ Carcinogenicity Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)



APPENDIX H: Danish (Q)SAR Database Carcinogenicity Output for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) (CAS #68187-69-9)





Model Features: Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk v1

Test Structure: A712C9FE6370DE64090ABDFD199000000

The following summarizes the overall contribution of the chemical features and other descriptors in the prediction.

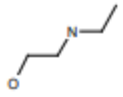
Model: Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk v1
# of Training Structures: 320
# of Features: 4 of 171 total
# of Property Descriptors: 7
Predicted Value: 0.205
% Matching Feature Contribution: 17.19%
% Non-Matching Feature Contribution: 44.43%
% Property Contribution: 38.38%

All Features | **Positive Features** | **Negative Features**

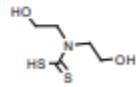
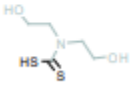
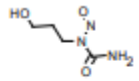
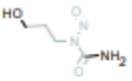
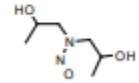
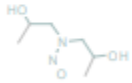
Feature Contribution: -0.0537 | **Feature Contribution: 0.0417** | **Feature Contribution: -0.0954**

Feature	Highlighted Structure	%Partial Property	Partial Property	Total Weight	Training Negatives	Training Positives	Actual Values
ALogP	ALogP	33.43	0.06852	0.257	211	109	
Scaffold 90	A712C9FE6370DE64090ABDFD199000000	20.37	0.04175	0.0477	4	5	
Rotatable Bonds	Rotatable Bonds	16.91	0.03466	0.0412	211	109	

Feature	Highlighted Structure	%Partial Property	Partial Property	Total Weight	Training Negatives	Training Positives	Actual Values
Parent Molecular Weight	Parent Molecular Weight	5.702	0.01169	0.0826	211	109	
Polar Surface Area	Polar Surface Area	4.049	0.0083	-0.136	211	109	
Lipinski Score	Lipinski Score	3.736	0.007658	0.0282	211	109	
Hydrogen Bond Acceptors	Hydrogen Bond Acceptors	1.303	0.002672	-0.119	211	109	
Hydrogen Bond Donors	Hydrogen Bond Donors	-6.644	-0.01362	-0.156	211	109	
Scaffold 56	A712C9FE6370DE64090AB DFD199000000	-11.93	-0.02447	-0.0442	14	3	
Scaffold 53	A712C9FE6370DE64090AB DFD199000000	-17.31	-0.03548	-0.0648	15	3	

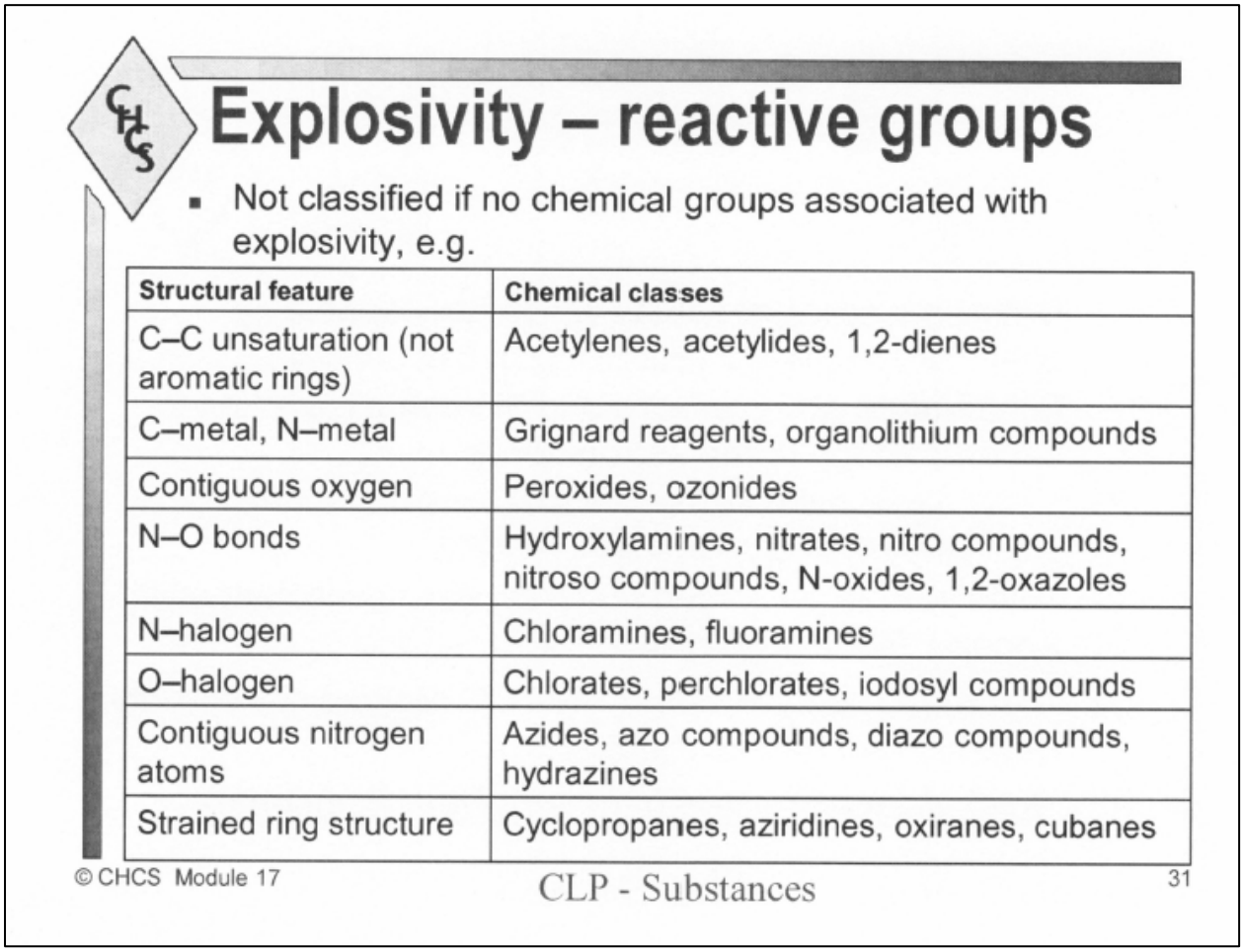
Feature	Highlighted Structure	%Partial Property	Partial Property	Total Weight	Training Negatives	Training Positives	Actual Values
 Scaffold 79	 A712C9FE6370DE84090ABDFD199000000	-17.32	-0.0355	-0.0502	9	2	L

Analog Structures from Model Training Set

Structure	Similarity	Experimental Value - Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk	Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk - Highlights	Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk - Call	Danish_QSAR_DB_Liver_specific_cancer_in_rat_or_mouse_in_vivo_QSARmodels.food.dtu.dk - Prob.
 DKDB_DNO_259	0.38	Negative	 DKDB_DNO_259	Negative	0.0434
 DKDB_DNO_303	0.35	Negative	 DKDB_DNO_303	Negative	0.0555
 DKDB_DNO_286	0.35	Negative	 DKDB_DNO_286	Negative	0.0614

APPENDIX I: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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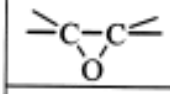
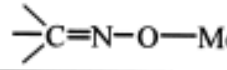
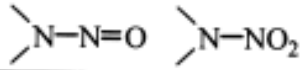
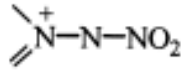
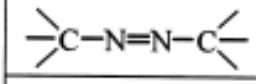
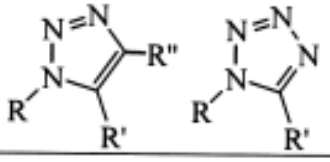
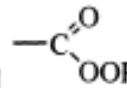
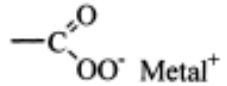
Explosivity – Full List

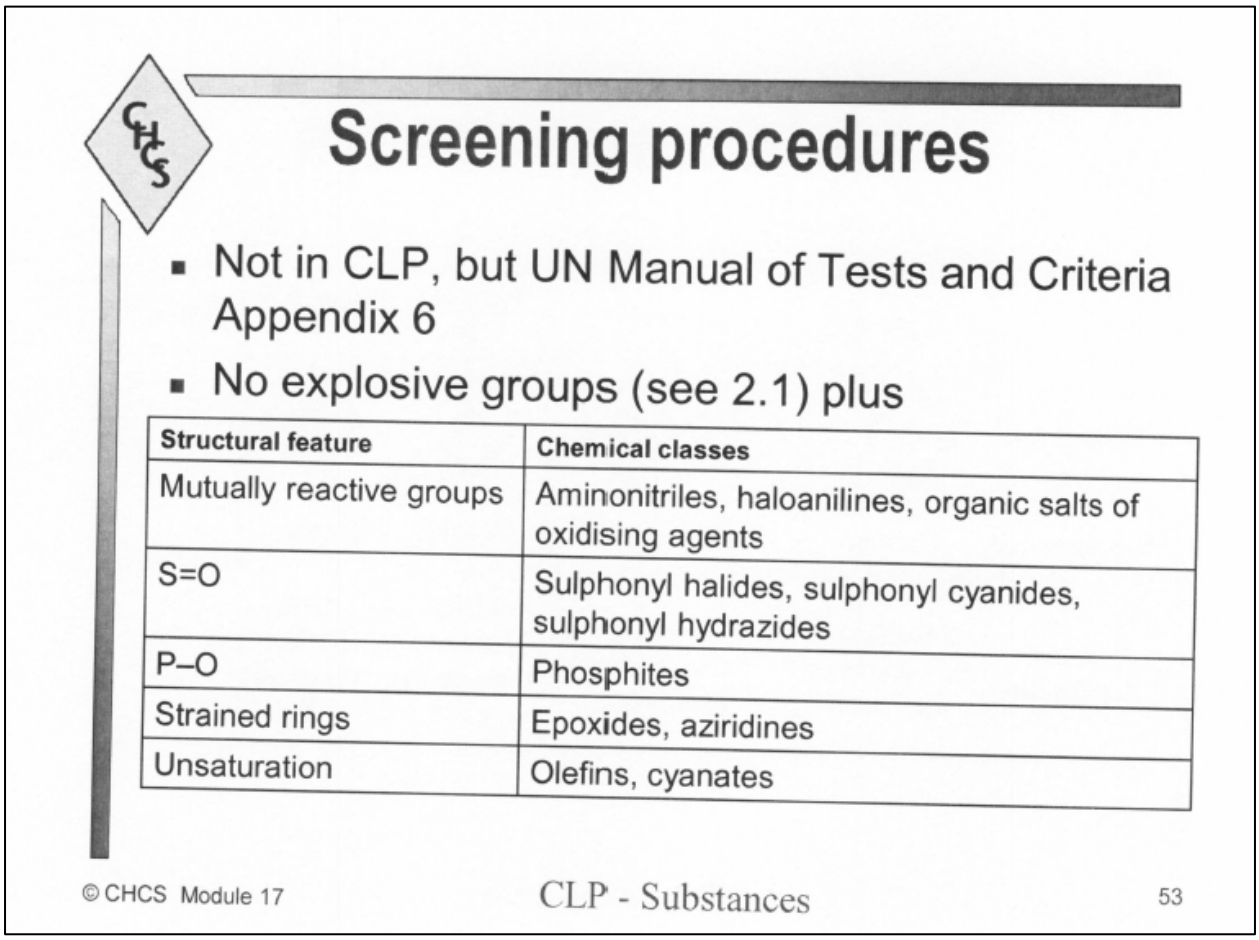
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



APPENDIX J: Change in Benchmark Score

Table 5 provides a summary of changes to ToxServices' GreenScreen® Benchmark™ for quaternary ammonium compounds, (hydrogenated tallow alkyl)bis(hydroxyethyl)methyl, ethoxylated, chlorides (15 EO). This is a new GreenScreen® assessment.

Table 5: Change in GreenScreen® Benchmark™ for Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)Bis(Hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO)

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
August 28, 2023	BM-2	v. 1.4	New assessment

Licensed GreenScreen® Profilers

Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)bis(hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Zach Guerrette, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC

Quaternary Ammonium Compounds, (Hydrogenated Tallow Alkyl)bis(hydroxyethyl)methyl, Ethoxylated, Chlorides (15 EO) GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC