2,2,4-TRIMETHYL-1,2-DIHYDROQUINOLINE (TMDHQ)

(CAS #147-47-7)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 4, 2021

Expiration Date: November 4, 2026

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GreenScreen® Executive Summary for 2,2,4-Trimethyl-1,2-Dihydroquinoline (TMDHQ) (CAS #147-47-7)

2,2,4-Trimethyl-1,2-dihydroquinoline, also called TMDHQ, is a derivative of quinoline that is used as an antioxidant (monomer) in styrene-butadiene and nitrile butadiene rubbers and latexes. It is described by some sources as a dark yellow liquid and by others as a tan powder. It has low volatility and water solubility and is non-flammable.

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

- Benchmark 2c
  - High Persistence (P) + Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental toxicity-D)
  - High Persistence (P) + Very High Group II Human Toxicity (systemic toxicity-single dose-STs)
  - High Persistence (P) + Moderate Group II Human Toxicity (acute mammalian toxicity-AT)
  - High Persistence (P) + High Group II* Human Toxicity (systemic toxicity-repeated dose-STr*)
  - High Persistence (P) + High Ecotoxicity (acute aquatic toxicity and chronic aquatic toxicity-CA)
- Benchmark 2e
  - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental toxicity-D)
- Benchmark 2f
  - High Group II* Human Toxicity (systemic toxicity-repeated dose-STr*)

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity, endocrine activity, and *in silico* models for respiratory sensitization, endocrine activity, chronic aquatic toxicity and persistence. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020b):

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

Type I (input data) uncertainties in TMDHQ's NAMs dataset include the experimental data for endocrine activity, respiratory sensitization, chronic aquatic toxicity, and persistence, and lack of validated test methods for respiratory sensitization. TMDHQ's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, the unknown *in vivo* relevance of EDSP Tox 21 screening assays and *in silico* modeling of receptor binding, and the lack of defined applicability domains in OECD Toolbox as well as ToxCast models. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries, and ECHA's decision framework and guidance to evaluate respiratory sensitization.

GreenScreen® Hazard Summary Table for TMDHQ

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*	*	*								
M	**L**	*M*	*M*	DG	**M**	**vH**	**H**	DG	DG	*L*	*L*	*L*	*L*	*H*	*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 2,2,4-Trimethyl-1,2-Dihydroquinoline (TMDHQ) (CAS #147-47-7)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Mouna Zachary, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: October 12, 2021, November 4, 2021

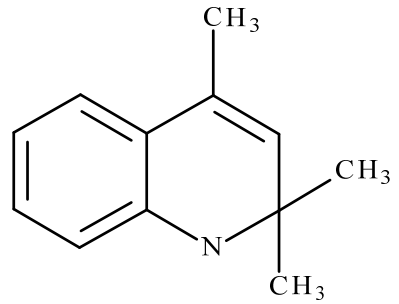
Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: October 21, 2021, November 4, 2021

Expiration Date: November 4, 2026[2]

Chemical Name: 2,2,4-Trimethyl-1,2-dihydroquinoline (TMDHQ)

CAS Number: 147-47-7

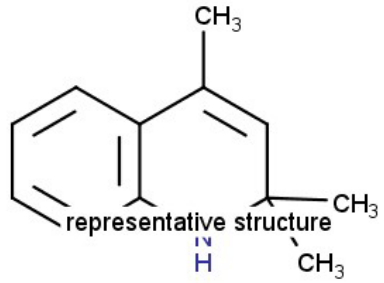
Chemical Structure(s):



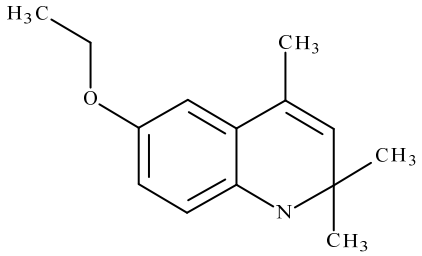
Also called: 1,2-Dihydro-2,2,4-trimethylquinoline (monomer), Flectol A, Flectol H, Flectol pastilles, Polnox R, Quinoline, 1,2-dihydro-2,2,4-trimethyl-, Trimethyl dihydroquinoline, Vulkanox HS/LG, Vulkanox HS/powder, Acetonanil (ChemIDplus 2021).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited toxicological data were identified for TMDHQ. Data were available for its oligomeric mixture (CAS #26780-96-1), which contains TMDHQ as one of its components as well as its dimer and trimers and other unidentified chemicals (ECHA 2021a). Therefore, ToxServices used data on this mixture to fill data gaps. When no data were available for the oligomeric mixture of TMDHQ or its data were insufficient, ToxServices identified ethoxyquin (CAS #91-53-2) as another surrogate and its data were evaluated. Ethoxyquin is also a 1,2-dihydro-2,2,4-trimethylquinoline derivative with a maximum common substructure (MCS) Tanimoto coefficient of 0.812 with TMDHQ, indicating appropriate structural resemblance (ChemMine 2021). However, it contains an ethoxy group at position 6 of the quinoline ring.

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



Surrogate: 1,2-Dihydro-2,2,4-trimethylquinoline, oligomers (TMDHQ, oligomers, CAS # 26780-96-1), a representative structure (ECHA 2021a)



Surrogate: Ethoxyquin (CAS #91-53-2)

Identify Applications/Functional Uses:

1- Antioxidant in styrene-butadiene and nitrile-butadiene rubbers and latexes (NTP 1997).
2- Monomer polymerized for use as a rubber antioxidant (PubChem 2021).

Known Impurities[3]:
The screen is performed on the theoretical pure substance.

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

- Benchmark 2c
  - High Persistence (P) + Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental toxicity-D)
  - High Persistence (P) + Very High Group II Human Toxicity (systemic toxicity-single dose-STs)
  - High Persistence (P) + Moderate Group II Human Toxicity (acute mammalian toxicity-AT)
  - High Persistence (P) + High Group II* Human Toxicity (systemic toxicity-repeated dose-STr*)

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

  - High Persistence (P) + High Ecotoxicity (acute aquatic toxicity and chronic aquatic toxicity-CA)
- Benchmark 2e
  - Moderate Group I Human Toxicity (carcinogenicity-C, reproductive toxicity-R, and developmental toxicity-D)
- Benchmark 2f
  - High Group II* Human Toxicity (systemic toxicity-repeated dose-STr*)

Data gaps (DG) exist for endocrine activity-E, single dose neurotoxicity-Ns, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis) (CPA 2018b), TMDHQ meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if TMDHQ 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 TMDHQ

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

Environmental Transformation Products

ToxServices did not identify any transformation products for TMDHQ. The OECD Toolbox (OECD 2021) predicted no hydrolysis is expected for TMDHQ (Appendix D). In addition, it undergoes minimal biodegradation and no biodegradation products have been reported (ECHA 2021a).

A GLP-compliant hydrolysis test conducted according to US EPA PAG 161-1 with the surrogate ethoxyquin indicated that it is unstable and undergoes appreciable and rapid hydrolytic degradation in buffered aqueous solutions at pH levels of 5, 7 and 9. Additionally, stability decreases as pH decreases with half-lives at 25°C of 3.6 days (pH 5), 6.7 days (pH 7), and 9.3 days (pH 9). The chemical identities of the hydrolysis products were not reported (ECHA 2021b). Therefore, their assessment using GreenScreen List Translator is not possible.

Introduction

2,2,4-Trimethyl-1,2-dihydroquinoline, also called TMDHQ is a monomer that is used as an antioxidant in styrene-butadiene and nitrile butadiene rubbers and latexes (NTP 1997). It is described by some sources as a dark yellow liquid and by others as a tan powder. It has low volatility and water solubility, and is non-flammable (CAMEO Chemicals Undated, HSDB 2003).

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

U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCP SCIL)

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). 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).

TMDHQ is not listed on the SCP 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 2021) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for TMDHQ can be found in Appendix C.

- TMDHQ is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- TMDHQ is not listed on the U.S. DOT list.
- TMDHQ is not present on any GreenScreen®-specified authoritative or screening lists.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for TMDHQ. However, it is associated with several hazard statements identified in its safety data sheet (SDS) as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for TMDHQ (CAS #147-47-7) (Santa Cruz Biotechnology 2016, PubChem 2021)

H Statement	H Statement Details
H302	Harmful if swallowed
H303	Causes skin irritation
H304	Causes serious eye irritation
H305	May cause damage to organs
H412	Harmful to aquatic life with long lasting effects (PubChem 2021)

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for TMDHQ (CAS #147-47-7)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Wear protective gloves/ eye protection/ face protection.	Santa Cruz Biotechnology 2016	OEL-RUSSIA short term exposure limit = 1 mg/m^3	NIOSH 2018

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

Physicochemical Properties of TMDHQ

TMDHQ is reported to be either a colorless to yellow liquid or a light tan powder that is insoluble in water. Its estimated vapor pressure of 0.0154 mmHg indicates that it is not highly volatile. It has slight water solubility, and the measured log K_{ow} of 2.93 suggests that it is not likely to bioaccumulate.

Table 3: Physical and Chemical Properties of TMDHQ (CAS #147-47-7)

Property	Value	Reference
Molecular formula	$C_{12}H_{15}N$	ChemIDplus 2021
SMILES Notation	CC1=CC(C)(C)Nc2ccccc12	ChemIDplus 2021
Molecular weight	173.25	ChemIDplus 2021
Physical state	Liquid Solid	CAMEO Chemicals Undated HSDB 2003
Appearance	Dark cloudy copper-colored or yellow liquid. Light tan powder	CAMEO Chemicals Undated HSDB 2003
Melting point	79 to 81°F 120°C	CAMEO Chemicals Undated HSDB 2003
Boiling point	491 to 500°F at 743 mm Hg	CAMEO Chemicals Undated
Vapor pressure	0.0154 mm Hg at 25°C (estimated)	U.S. EPA 2017a
Water solubility	less than 0.1 mg/mL (100 mg/L) at 66°F	CAMEO Chemicals Undated
Dissociation constant	Not identified	
Density/specific gravity	1.03 at 77°F 1.08 @ 25°C	CAMEO Chemicals Undated HSDB 2003
Partition coefficient	log K_{ow} = 2.93 (measured)	U.S. EPA 2021b

Toxicokinetics

- Absorption and Excretion.
  - NTP 1997, Ioannou, et al. 1987
    - *Oral*: TMDHQ was well absorbed from the gastrointestinal tract of male Fischer 344/N rats following oral administration at doses of 11.5, 115, or 1,150 µmol/kg. Absorption, distribution, metabolism, and excretion were not significantly affected by the dose. TMDHQ -derived radioactivity was excreted primarily in urine (60- 70%) and feces (20-30%) within 3 days after administration.
    - *Dermal:* TMDHQ was also well absorbed through the skin. Topical application of radiolabeled TMDHQ to shaved male F344 rats showed that approximately 80% of the dose had been absorbed after 24 hours. Similarly, in another study, 50% of the material had been absorbed within 6 hours after topical administration,
- Distribution
  - NTP 1997
    - *Dermal:* Topical application of 14C-l.2-dihydro-2,2,4-trimethylquinoline at 20 µg in 20 mg/kg to shaved male F344 rats resulted in accumulation of 14C in urine, feces, skin (site of application and nonapplication site), liver, fat. and kidney.

        - Following iv administration, the greatest amounts of TMDHQ -derived radioactivity were present in high volume tissues, including muscle, adipose, skin, liver, and blood.
- Metabolism
    - NTP 1997
        - Greater than 99% of TMDHQ excreted in urine and feces was in the form of metabolites. The two most abundant metabolites in the urine were the O-sulfate of 1,2-dihydro-6-hydroxy, 2,2,4-trimethylquinoline and the mono-O- sulfate of 1,2-dihydro-3,6-dihydroxy-2,2,4-trimethylquinoline. NTP proposed a metabolic pathway involving hydroxylation by mixed function oxidases followed by sulfate, glucuronide, and/or glutathione conjugation.
- In summary, TMDHQ is well absorbed following oral and dermal exposures with approximate absorption rates of up to 70% following oral exposure and 80% following dermal exposure. Following oral, and dermal administration in rats, TMDHQ is extensively distributed, and the highest concentrations were found in the liver. TMDHQ is expected to undergo ring hydroxylation followed by sulfate, glucuronide, and/or glutathione. The main excretion pathways are urine and feces.

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): M
TMDHQ was assigned a score of Moderate for carcinogenicity based on some evidence of carcinogenic activity seen in male rats in 2-year NTP dermal carcinogenicity study. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is or limited or marginal evidence of carcinogenicity in animals (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1997
    - *Dermal*: In 2-year carcinogenicity studies conducted by the National Toxicology Program (NTP), groups of 60 male and 60 female F344/N rats or B6C3F1 mice were topically administered 0, 36, 60, or 100 mg/kg/day and 0, 3.6, 6, or 10 mg/kg/day TMDHQ (> 90% purity) in acetone, respectively, 5 days per week for 103 (males) or 104 (females) weeks. Nine or ten animals per group were evaluated after 15 months of treatment. In rats, treatment caused several non-neoplastic skin lesions at the site of application in the mid and high dose groups, such acanthosis in males and females and hyperkeratosis in females. In addition, absolute and relative right kidney weights of 60 and 100 mg/kg/day male rats were significantly greater than those of the controls at the 15-month interim evaluation. Incidences of renal tubule adenoma and adenoma or carcinoma (combined) in all treated groups of males were significantly/greater than those in the controls. These incidences exceeded the range from the historical controls in 2-year NTP feed studies. An extended (step section) evaluation of the kidneys of male rats did not reveal an additional increase in neoplastic response because additional adenomas and hyperplasias were observed in the controls as well as in treated groups. Based on increased incidences of renal tubule adenoma

and adenoma or carcinoma (combined)[9], the NTP concluded that there was some evidence of carcinogenic activity of TMDHQ in male F344/N rats but not in females. In mice, there was no evidence of carcinogenic activity, and no non-neoplastic lesions were observed in male or female mice attributed to treatment with TMDHQ.

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

TMDHQ was assigned a score of Low for mutagenicity/genotoxicity based on the weight of evidence from numerous well conducted *in vitro* and *in vivo* tests for mutagenicity and clastogenicity that were consistently negative. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative results for mutagenicity and clastogenicity and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1997
  - *In vitro*: TMDHQ (>90% purity) was negative for mutagenicity when tested in a *Salmonella typhimurium* microsome preincubation assay according to the NTP guideline using four strains (TA98, TA100, TA1535, and TA1537) at doses of 0, 1, 3.3, 10, 33, 100, and 220 µg/plate (high dose limited by cytotoxicity) in the presence and absence of metabolic activation.
  - *In vitro*: In a sister chromatid exchange assay conducted according to an acceptable NTP guideline, Chinese hamster ovary (CHO) cells were exposed to TMDHQ (>90% purity) at 40-120 µg/mL with or without metabolic activation. Treatment caused produced marked cell cycle delay at all concentrations in the absence of metabolic activation. In the presence of S9, occasional cell cycle delay was noted at higher doses, and culture times were adjusted accordingly. TMDHQ induced a moderate increase in sister chromatid exchanges at a single dose level in the first trial conducted with S9; this increase was not reproduced in either of two subsequent trials, and the overall response in the presence of S9 was considered to be negative.
  - *In vitro*: In a chromosomal aberrations test conducted according to an acceptable NTP guideline, cultured CHO cells were exposed to TMDHQ (>90% purity) at 70-100 µg/mL with or without metabolic activation. There was no increase in the frequency of chromosomal aberrations.
  - *In vivo*: In a mouse peripheral blood micronucleus test conducted according to an acceptable NTP guideline, male and female B6C3F1 mice were exposed topically to 2.5-50 mg/kg /day TMDHQ (>90% purity) for 13 weeks. No increases in the frequency of micronucleated erythrocytes were observed in peripheral blood samples obtained from treated animals.

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

TMDHQ was assigned a score of Moderate for reproductive toxicity based on decreased number of litters per pair and increased gestation length in a 2-generation reproductive toxicity study in rats with the surrogate ethoxyquin at a LOAEL of 300 mg/kg/day, in the presence of maternal systemic toxicity. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2018b). (CPA 2018b). The confidence in the score is low as effects may be secondary to maternal toxicity.

[9] NTP interprets some evidence of carcinogenicity as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- NTP 1997
    - *Dermal:* In 13-week repeated dose toxicity studies conducted by the NTP, male and female F344/N rats (10/sex/dose) or B6C3F1 mice (10/sex/dose) were topically administered TMDHQ (>90% purity) in acetone at doses of 0, 5, 20, 50, 100, or 200 mg/kg/day, and 0, 2.5, 5, 10, 20, or 50 mg/kg/day, respectively, for 13 weeks. Doses were applied to clipped, interscapular skin five times per week. Male animals were evaluated for sperm morphology, count, and motility. The right testis and right epididymis were isolated and weighed. Female animals were evaluated for vaginal cytology (frequency of estrous stages and estrous cycle length). Histopathology evaluations were performed on seminal vesicles and testis with epididymis in the control and high dose groups and on the uterus in all dose groups. Treatment did not cause any significant differences in reproductive tissue parameters or estrous cycle characterization between treated and control groups.
- ECHA 2021b
    - <u>*Surrogate: Ethoxyquin (CAS #91-53-2)*</u>: *Oral:* In a non-GLP, non-guideline (peer-reviewed) two-generation reproductive toxicity study that included developmental endpoints, male and female beagle dogs (F0: 5 males and 10 females/treatment group; F1: 8 males and 13 female pups/treatment group) were fed diets containing 0, 100, or 225 ppm ethoxyquin (purity not specified) (approximately 2.5 and 5.6 mg/kg/day, respectively) for a minimum of 82 days before pairing. For the F1 matings, 8 male and 13 female pups were fed diets containing 0, 100, or 225 ppm ethoxyquin from weaning until breeding at an age of 10-30 months (and the 2nd estrus cycle in females). Routine physical examinations were performed, and animals were regularly observed. Semen samples were collected during the first week of treatment and at the time of mating in order to record volume, sperm count, motility, velocity, and morphology. Urine and blood samples were collected for hematology, clinical chemistry, and urinalysis from fasted adults before treatment and at the end of the F0 phase, at weeks 10, 23, 36, 49 and 62, and at the end of the F1 growth phase, and at the conclusion of the F1 mating phase. Ophthalmological examinations were carried out at the beginning and end of the F1 growth and matin phases. Mating, birth (whelping), and lactation indices were recorded. F1 adults and pups showing signs of toxicity were necropsied and tissues (not specified) from controls and F1 animals were evaluated histologically, as well as tissues (not specified) from F2 pups showing signs of toxicity. Livers and gall bladders of F1 adults at the low dose and adrenal glands and spleens from F1 adult females at the low dose were analyzed. Macroscopic and microscopic evaluations were carried out on F0 and F1 animals that died or were sacrificed due to clinical signs of toxicity. A statistically significant increase in serum alkaline phosphatase activity was measured in F0 males in the high dose group and in F0 females in the low and high dose groups. Two pregnant females in the high dose group did not give birth. There were no differences between treated and control animals in terms of mating performance, labor, birth, or weaning indices, semen parameters, or clinical signs, as well as no differences in litter size, pup survival, and pup weight and growth. A NOAEL ≥ 5.6 mg/kg/day was estimated for reproductive performance for the first parental generation (P0). In the second parental generation (P1), at 225 ppm (approximately 5.6 mg/kg/day), there was an increase in the number of both male and female pups with a raw or red anus, dehydration, nasal discharge, excessive lachrymation, thinness, and pale gums. Nasal discharge and excessive lachrymation were also observed in the low dose group. Treatment related reductions in

erythrocyte count, hematocrit, and hemoglobin were observed, and partial thromboplastin time were reduced in treated females. Serum activities of alkaline phosphatase, gamma-glutamyl transferase (GT), and alanine aminotransferase were increased in animals in the high dose group, indicating impaired liver function. In the F1 high dose mating group, statistically significant reductions in glucose, cholesterol, protein, albumin, and albumin:globulin ratio were observed, along with increases in total bilirubin concentration and in gamma-GT, alkaline phosphatase, and alanine aminotransferase activities. Increases in the absolute weights of the spleen and testes and both organs relative to brain weight were observed in treated males. Lesions in the liver of one high dose male and in the cervical lymph nodes of two high dose females were noted. Pigment protoporphyrin IX was observed in livers of 7/13 females at the low dose, 2/7 males at the high dose, and 10/11 females at the high dose. Fibrosis and hemorrhage frequencies were increased in the spleens of females in the high dose and there was also an increase in the incidence of pituitary cysts in animals in the high dose group. There were no treatment-related effects on reproductive performance, in terms of semen analyses or mating, gestation, whelping, or weaning indices; therefore, a NOAEL ≥ 5.6 mg/kg/day was estimated for reproductive performance for P1 animals. In the F1 generation, signs of clinical toxicity were observed in treated animals, including raw or red anus, dehydration, nasal discharge, and excessive lachrymation. A systemic toxicity LOAEL of 2.5 mg/kg/day was assigned due to clinical signs of parental toxicity, including excessive lachrymation and dehydration, and changes in clinical chemistry and pigment deposition in the liver of treated animals at the low dose in both the F0 and F1 generations (Klimisch score 2 – reliable with restrictions).

- EC 2008b
    - *Surrogate: Ethoxyquin (CAS #91-53-2): Oral:* In a two-generation study with limited reporting from an abstract, ethoxyquin was tested at 0, 75, 150 or 300 mg/kg/day in by gavage in rats (strain unspecified, 20/sex/group) following a continuous breeding protocol. Animals were individually housed for one week followed by cohabitation in breeding pairs for 16 weeks. Litters were terminated after evaluation on PND 1 during this period. Litters born after week 17 were reared until weaning on PND 21. Selected weanlings (F1) were reared to PND 81, then mated within groups to produce F2 generation, and sacrificed after delivery of the second generation litters. Parental systemic toxicity LOAEL was established by study authors at the lowest dose, 75 mg/kg/day, based on kidney and liver effects (increased weights by 13-56%). Study authors identified a reproductive toxicity NOAEL of 150 mg/kg/day and LOAEL of 300 mg/kg/day based on decreased number of litters per pair (by 22%), decreased number of live pups per litter (by 22%), increased gestation length and decreased live pup weight for the F0 generation evaluation. Crossover mating indicated that these effects were female-mediated. Study authors identified a developmental toxicity LOAEL of 75 mg/kg/day without statement of basis. No additional details were available.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
TMDHQ was assigned a score of Moderate for developmental toxicity based on fetal morphological effects (such as cleft palate, and skeletal variations) in prenatal developmental toxicity studies in rats performed with the target chemical and its oligomeric mixture. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity in animal studies and when they are classified to GHS Category 2 (CPA 2018b). The confidence in the score is low as the effects may be secondary to maternal systemic toxicity.

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

  - *Screening:* Not present on any screening lists for this endpoint.
- Sitarek and Sapota 2003, NIOSH 2018
  - *Oral*: In a prenatal developmental toxicity study, female rats (number and strain not reported) were exposed orally to unlabeled TMDHQ (trade name Polnoks R) during gestation days (GD) 6-15 at doses of 50 to 400 mg/kg/day to assess prenatal toxicity and to radiolabeled ^{14}C TMDHQ at a dose 210 mg/kg to evaluate tissue distribution. Treatment produced several teratogenic effects in pups of the 100 mg/kg/day dose group and higher. These included cleft palate, wavy ribs, kyphoscoliosis, exencephaly, external hydrocephalus, hydronephrosis, and renal hypoplasia. Peak ^{14}C-radioactivity was found in mothers' plasma about 10 hr after administration of the test substance at dose 210 mg/kg. Study authors concluded that TMDHQ is teratogenic in rats and it can penetrate into placenta to the fetus.
- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In a reliable prenatal developmental toxicity study, pregnant Sprague-Dawley rats (25/dose) were administered the test substance (purity not reported) in corn oil via gavage at doses of 0, 20, 120, and 300 mg/kg/day from GD 6 to 15. Fetuses were individually weighted, sexed and examined for external, visceral and skeletal abnormalities. No effect on maternal survival and pregnancy status was observed. Body weight gain was statistically reduced during gestation days 6 -9 in the high dose group and food consumption was reduced at some time points in the mid and high dose group. Clinical signs of toxicity were observed in treated females at 120 mg/kg/day and above. In addition, maternal liver weight was dose related and statistically significantly increased in the same dose groups (120 and 300 mg/kg). In terms of fetotoxicity, treatment also caused fetal morphological effects in the litters of high dose group. These included increases in the number of litters with kinked tail, rib anomalies, and vertebral abnormalities with or without associated rib anomalies, a statistically significant increase in the number of litters with various developmental variations (malaligned sternebra(e), 14th rudimentary rib, 7th cervical rib, and 27 presacral vertebrae). Additional observations in the high dose group, although not statistically significant, comprised: descendent urethra(s), renal papilla(e) not developed, and 14th full rib. Based on this study authors assigned a NOAEL of 20 mg/kg/day for maternal toxicity. The NOAEL for developmental toxicity was 120 mg/kg/day (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Moderate was assigned. Developmental effects, such as increased number of fetuses with variations in vertebrae and cleft plate, and congenital defect internal hydrocephalus, were reported in prenatal developmental toxicity studies performed with the target chemical and its oligomeric mixture at doses as low as 100 mg/kg/day. No details on the maternal toxicity were reported in the studies with the target chemical. For the oligomeric mixture, the developmental effects observed in the study occurred at maternally toxic doses and therefore they could be secondary to maternal toxicity. As it is not clear whether the developmental effects seen with TMDHQ are due to the maternal toxicity or a direct action of the chemical, ToxServices assumed that TMDHQ has some direct capacity to cause developmental toxicity and classified it as a GHS Category 2 developmental toxicant. GHS Category 2 developmental toxicants are defined as having limited or marginal evidence of reproductive toxicity in animals (UN 2021).

Endocrine Activity (E) Score (H, M, or L): DG
TMDHQ was assigned a score of Data Gap for endocrine activity due to lack of sufficient data. Although *in vitro* high throughput assays for the surrogate do not indicate a concern for endocrine effects, no *in vivo* data are available.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2021b
  - TMDHQ was inactive in 6 out of 6 assays of estrogen agonism and antagonism, inactive in 8 out of 8 assays for androgen receptor agonism or antagonism, inactive in 6 out of 6 assays for thyroid receptor activity, and inactive in 2 out of 2 assays for steroidogenesis, of the Tox 21 high throughput *in vitro* assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program in the 21st Century (EDSP21) (Appendix E).
  - TMDHQ was predicted to be inactive for estrogen agonism, antagonism and binding according to the CERAPP Potency Level models (Consensus and from literature). It was also predicted to be inactive for androgen receptor agonism, antagonism and binding according to the COMPARA (Consensus) model (Appendix F).

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

TMDHQ was assigned a score of Moderate for acute toxicity based on an oral LD_{50} value of 1,450 mg/kg in mice supported by data on its surrogate, ethoxyquin. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are >300 – 2,000 mg/kg and when they are classified to GHS Category 4 (CPA 2018b). The confidence in the score is high as it is based on measured data for the target chemical and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ChemIDplus 2021
  - *Oral:* LD_{50} (mouse, sex and strain not specified) = 1,450 mg/kg.
  - *Oral:* LD_{50} (rat, sex and strain not specified) >2,000 mg/kg.
  - *Oral:* LD_{50} (rabbit, sex and strain not specified) >2,000 mg/kg.
- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):*
    - *Oral:* LD_{50} (male and female Albino rats) greater than 2,730 mg/kg but less than 3,720 (Klimisch 2, reliable with restrictions).
    - *Dermal:* LD_{50} (male and female New Zealand White rabbits) > 5,100 mg/kg (Klimisch 2, reliable with restrictions).
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):*
    - *Oral:* LD_{50} (Albino rats) = 1,779 mg/kg in males, 1,675 mg/kg in females and 1,726 mg/kg combined (GLP-compliant, EPA OPP 81-1) (Klimisch 2, reliable with restrictions).
    - *Inhalation:* 4-hr LC_{50} (male and female rat) > 1.97 mg/L (GLP-compliant, EPA OPP 81-3) (Klimisch 2, reliable with restrictions).
    - *Dermal:* LD_{50} (male and female Albino rats) > 2,000 mg/kg (GLP-compliant, EPA OPP 81-2) (Klimisch 2, reliable with restrictions).

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

TMDHQ was assigned a score of Very High for systemic toxicity (single dose) based on its surrogate having a LOAEL of 100 mg/kg in an acute oral toxicity study in dogs . GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity (single dose) when animal studies identify oral LOAEL values of ≤ 300 mg/kg (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality 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.
- Santa Cruz Biotechnology 2016
  - A safety data sheet (SDS) for TMDHQ states that is classified to GHS Category 2 for systemic toxicity following single exposure with a hazard statement of H371: - May cause damage to organs. No further details were reported.
- ECHA 2021a
  - <u>*Surrogate: TMDHQ, oligomers (CAS #26780-96-1)*</u>*: Oral:* In a non-GLP acute oral toxicity test conducted according to a standard guideline, male and female Albino rats (5/sex/group) were administered gavage doses of the test substance (purity not reported) in propylene glycol at 2,160, 2,580, 3,090, 3,720, and 4,470 mg/kg. Clinical signs as sluggishness were reported to start 48 h after dosing; deaths occurred during the second to fourth day after treatment thereafter the surviving animals recovered from clinical signs. Macroscopic examination of the survivors revealed white necrotic spots on the kidney of several rats. Authors assigned an oral LD_{50} of 3,190 mg/kg (Klimisch Score 2, reliable with restrictions).
    - *As no data were provided on the doses that caused the microscopic findings in the kidney, ToxServices conservatively assigned a LOAEL of 2,160 mg/kg for systemic toxicity in this study. The LOAEL of 2,160 mg/kg is above the GHS Category 2 Guidance value of 2,000 mg/kg for systemic toxicity following single oral exposure. Therefore, TMDHQ, oligomers is most likely not classified per GHS. However, as no NOAEL is determined, there is insufficient information to concluded that adverse effects do not occur at the threshold of 2,000 mg/kg.*
  - <u>*Surrogate: TMDHQ, oligomers (CAS #26780-96-1)*</u>*: Dermal:* In a non-GLP acute dermal toxicity test conducted according to a standard guideline, male and female New Zealand White rabbits (1/sex/dose) were administered topical applications of the test substance (purity not reported) in corn oil at 5,010 and 7,940 mg/kg for 24 hours. An observation period of 14 days followed the exposure period. One female in the 5,010 mg/kg survived; in the high dose group (7,940 mg/kg) one male rabbit survived and one female rabbit died after 4 days. Clinical signs such as reduced appetite and activity were noted for all animals and gross autopsy of the survivors indicated hemorrhagic areas of the lung, discoloration of liver, spleen, and kidney, and inflammation of the gastrointestinal tract. Authors assigned a dermal LD_{50} of > 5,010 (Klimisch Score 2, reliable with restrictions).
    - *Based on the microscopic findings, ToxServices assigned a LOAEL of 5,010 mg/kg for systemic toxicity in this study. This LOAEL is above the GHS Category 2 Guidance value of 2,000 mg/kg for systemic toxicity following single dermal exposure. Therefore, TMDHQ, oligomers is most likely not classified per GHS. However, as no NOAEL is determined, there is insufficient information to concluded that adverse effects do not occur at the threshold of 2,000 mg/kg.*
- ECHA 2021b

- *Surrogate: Ethoxyquin (CAS #91-53-2): Oral:* Ethoxyquin (purity not specified) was evaluated for acute oral toxicity in a GLP-compliant study conducted in a manner similar to OECD Guideline 401. Albino rats (Crl:CD®BR) (5/sex/dose) were orally exposed by gavage to the test substance at 1,500, 1,950, and 2,535 mg/kg, followed by a 14-day observation period. Deaths of treated animals occurred withing 3 days of dosing, with the following mortalities: 2/10, 9/10, and 8/10 for the 1,500, 1,950, and 2,535 mg/kg dose groups, respectively. Clinical indicators of toxicity included ataxia in 24 animals, hypoactivity (21 animals), ocular discharge (16 animals), urogenital staining, hypothermia (cool to the touch, 13 animals), dried red material around the eyes, forelimbs, and nose, labored breathing (11 animals), prostrate positioning (10 rats), abnormal excretion (5 rats), and dried yellow material around the mouth. Surviving animals appeared normal, aside from the observation of dried yellow material around the mouth. There was no treatment-related effect on body weight. Histopathological examination revealed irritation in the gastrointestinal tract, and three animals exhibited hemorrhagic thymus glands. Dark red lungs and red fluid in the urinary bladder were observed in two rats. Enlarged cervical lymph nodes were noted in one animal and eye opacity in another animal. No other gross necropsy findings were observed in the animals that survived to planned euthanization. An oral LD_{50}s of 1,779, 1,675, and 1,726 mg/kg were calculated for males, females, and combined, respectively (Klimisch score 2 – reliable with restrictions).
- *Surrogate: Ethoxyquin (CAS #91-53-2): Inhalation*: Ethoxyquin was evaluated for acute inhalation toxicity in a GLP-compliant study conducted in a manner similar to OECD Guideline 403. Crl:CD®BR rats (5/sex/dose) were exposed whole body to an aerosol of 1.97 mg/L ethoxyquin (purity not specified) (100 % of the particles < 10 microns and 13.4 % < 1.18 microns) for 4 hours, with a 14-day post administration observation period. One animal was sacrificed on Day 1 for humane reasons, while all other animals survived the dosing and observation periods. Clinical observations included salivation during dosing, wet and/or dried yellow material on external body surfaces, dried red material around the nose, and dried yellow material around the eyes. There were no other significant clinical observations or effects on body weight during the study; however, the study authors suggest that tremors in 6/10 animals following treatment might indicate neurotoxic potential of ethoxyquin. A LC_{50} > 1.97 mg/L was assigned (Klimisch score 2 – reliable with restrictions).
- *Surrogate: Ethoxyquin (CAS #91-53-2): Dermal*: Ethoxyquin was evaluated for acute dermal toxicity in a GLP-compliant study conducted in a manner similar to OECD Guideline 402. Crl:CD®BR albino rats (5/sex/dose) were exposed to 2,000 mg/kg (1.98 mL/kg) ethoxyquin (purity not specified) on clipped, intact skin under semi-occlusive conditions for 24 hours, with a 14-day post-exposure observation period. There was no mortality and there were no treatment-related clinical observations, including effects on body weights, in this study. The test substance induced very slight to slight erythema on 8 animals and 10 sites had signs of desquamation. No edema or other treatment-related findings were observed. Dermal irritation was reversible by Day 12 or earlier, except in two females with observed desquamation. A dermal LD_{50} > 2,000 mg/kg was estimated (Klimisch score 2 – reliable with restrictions).

- JMPR 2005
  - *Surrogate: Ethoxyquin (CAS #91-53-2): Oral:* In a GLP-compliant acute toxicity study, Beagle dogs (6/sex) received a single oral dose of ethoxyquin (purity 98.93%) in capsules at 0, 50, 100 or 200 mg/kg. Four animals/sex were sacrificed 24 hours afterwards, and the remaining 2/sex were observed for 14 days before sacrifice. Examinations included clinical observation, body weight, food consumption, hematology, serum chemistry, urinalysis,

ophthalmology, gross pathology and histopathology. All dosed male groups and two highest dose female groups had increased mean serum alkaline phosphatase and alanine aminotransferase levels at the end of the 2-week recovery period. All dosed groups had higher total serum bilirubin concentrations and all dosed females had lower urea nitrogen at 24 hours post dosing. All dosed animals also had higher incidences of bilirubin in the urine. The effects on bilirubin were reversible, and decreased urea nitrogen was attributed to slight hepatic insufficiency by study authors. Histopathology findings at 24 hours post dosing included minimal to mild bile stasis in the liver in all dosed groups, which correlated with increased total bilirubin in serum. High dose animals had depleted hepatocellular glycogen, and one male had increased leukocytes in intrahepatic blood vessels and altered hepatocellular cytoplasm. Minimal bile stasis in the liver was also observed in recovery group in all dosed male groups and the two highest dose female groups. Study authors stated that the serum biochemistry changes indicative of liver effects measured at 50 mg/kg were minimal to mild in severity, and hence the toxicological significance was equivocal. JMPR did not consider these effects observed at 50 mg/kg to be toxicologically significant and assigned a NOAEL of 50 mg/kg and LOAEL of 100 mg/kg for this study.

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

TMDHQ was assigned a score of High for systemic toxicity (repeated dose) based on ToxServices classifying it to GHS Category 1 for systemic toxicity following dermal repeated exposure based on a dermal LOAEL of 14.2 mg/kg/day established in a 90-day study with the liver identified as the target organ. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when animal studies identify dermal LOAEL values ≤ 20 mg/kg/day, and when they are classified to GHS Category 1 (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NIOSH 2018
  - *Oral*: In a repeated dose toxicity study with very limited details, oral administration of TMDHQ to rats caused effects on the liver (liver function tests impaired) and the lowest published toxic dose was reported to be 12 mg/kg/30 days. This is equivalent to 0.4 mg/kg/day (12 mg/kg / 30 days). No further details were provided. *Due to the limited details on this study, ToxServices considered the study insufficient for GHS classification purposes.*
  - *Inhalation*: In a repeated dose toxicity study with very limited details, administration of TMDHQ to rats via inhalation exposure caused effects on the kidney, ureter, and bladder: other changes in urine composition. Further, there were changes in serum composition (e.g. TP, bilirubin, cholesterol) as well as weight loss or decrease in weight gain. No additional details were provided. The lowest published toxic dose was reported to be 12,500 µg/m^3/4h/21week. This is equivalent to 0.0125 mg/L/4h/21week (12,500 µg/m^3 / 10^{-6}). No further details were provided. *Due to the limited details on this study, ToxServices considered the study insufficient for GHS classification purposes.*
- NTP 1997
  - *Dermal:* In a 13-week repeated dose toxicity study conducted by the NTP, male and female F344/N rats (10/sex/dose) were topically administered TMDHQ (>90% purity) in acetone at doses of 0, 5, 20, 50, 100, or 200 mg/kg/day(rats) for 13 weeks. Doses were applied to

clipped, interscapular skin five times per week. Animals were evaluated for clinical observations, body weight, hematology, clinical chemistry, sperm morphology (males), vaginal cytology evaluations (females), gross pathology, and histopathology. No mortalities were seen. Treatment caused skin irritation including acanthosis, and hyperkeratosis at the site of application in 100 and 200 mg/kg/day rats. Most of these lesions were considered within the range of minimal to mild in severity. Males at 200 mg/kg/day had lower mean body weight gain (5%) when compared to the control group. In addition, absolute and relative liver weights of 200 mg/kg/day males and absolute liver weights of 100 and 200 mg/kg/day females were significantly greater than those of the vehicle controls. Absolute thymus weights of 20, 50, 100, and 200 mg/kg/day males were significantly lower than those of the vehicle controls. Histopathological examination showed cytoplasmic vacuolization of hepatocytes in the livers of 200 mg/kg/day males. There were no treatment related effects on other parameters measured in this study. Based on the decrease of absolute thymus weights in males at 20 mg/kg/day, ToxServices assigned a NOAEL of 5 mg/kg for systemic toxicity in this study.

- *The LOAEL of 20 mg/kg, equivalent to 14.2 mg/kg/day[10], is below the GHS Guidance cut-off value of 20 mg/kg/day for Category 1 in a 90-day dermal study. Therefore, TMDHQ is classified to GHS Category 1 for systemic toxicity following dermal repeated exposure.*

- *Dermal:* In another 13-week repeated dose toxicity study conducted by the NTP, male and female B6C3F1 mice (10/sex/dose) were topically administered TMDHQ (>90% purity) in acetone at doses of 0, 2.5, 5, 10, 20, or 50 mg/kg/day for 13 weeks. Doses were applied to clipped, interscapular skin five times per week. Animals were evaluated for clinical observations, body weight, hematology, clinical chemistry, sperm morphology (males), vaginal cytology evaluations (females), gross pathology, and histopathology. All mice except one 2.5 mg/kg/day female survived to the end of the study. Treatment caused skin irritation including acanthosis and hyperkeratosis at the site of application in 5, 10, 20, and 50 mg/kg/day mice. There were no treatment related effects on any of the parameters measured in this study. Accordingly, ToxServices assigned a NOAEL of 50 mg/kg/day for systemic toxicity, which was the highest dose tested. The NOAEL for local effects is 2.5 mg/kg.

- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1): Oral:* In a GLP-compliant combined repeated dose and carcinogenicity study conducted in a manner similar to OECD Guideline 453, male and female Sprague-Dawley rats (60/sex/dose) were administered the test substance (100% purity) at doses of 0, 50, 250, and 1,000 ppm in the diet for 2 years; these doses were reported to be equivalent to 2.3, 11.8, and 48 mg/kg/day in males and 3.1, 15.3, and 63 mg/kg/day in females. Treatment caused a significant decrease on the body weight of females in the high dose group, histopathologic effects on adrenals in the high dose males, and effects on liver weight (increases) and liver histopathology in the high dose males and in the mid and high dose females. Based on this study authors established systemic toxicity NOAELs of 250 ppm in males and 50 ppm in females (Klimisch Score 2, reliable with restrictions).
    - *The NOAEL of 50 ppm in females, equivalent to 15.3 mg/kg/day, is above the duration adjusted GHS Guidance cut-off value of 12.5 mg/kg/day2[11] for Category 2 for a 2-year study. Therefore, TMDHQ is not classified per GHS.*

[10] Converting exposure period 5days/week to daily = 20 mg/kg x 5 / 7(days) = 14.2 mg/kg/day0020
[11] 100 mg/kg/day x 13 weeks /104 weeks =12.5 mg/kg/day.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): DG
TMDHQ was assigned a score of Data Gap for neurotoxicity (single dose) based on insufficient data identified. Ataxia and hypoactivity that were reversible were observed at 1,500 – 2,535 mg/kg in an acute oral toxicity study with the surrogate ethoxyquin at doses that caused deaths of some animals. Tremors were observed at an aerosol concentration of 1.97 mg/L which also caused sacrifice of one animal *in extremis.* Therefore, it is unclear if the observed effects are specific neurotoxicity or secondary to the acute general toxicity of the test compound. Additionally, the effects such as tremors are not consistent with transient narcotic effects (i.e., central nervous system depression), which warrant GHS Category 3 classification.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- NIOSH 2018
  - *Oral*: In acute oral toxicity studies with very limited details, rats and mice administered single doses of TMDHQ exhibited clinical signs of neurotoxicity such as general depressed activity. No further details were reported.
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2): Oral:* In the previously described GLP-compliant acute oral toxicity test conducted according to EPA OPP 81-1, male and female albino rats (5/sex/group) were administered gavage doses of undiluted test substance (purity not reported) at 1,500, 1,950 and 2,535 mg/kg. An observation period of 14 days followed the dosing. Deaths of treated animals occurred withing 3 days of dosing, with the following mortalities: 2/10, 9/10, and 8/10 for the 1,500, 1,950, and 2,535 mg/kg dose groups, respectively. Treatment caused clinical signs of neurotoxicity such as ataxia in 24 animals, and hypoactivity in 21 rats. These signs disappeared by day 7 or earlier (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: Ethoxyquin (CAS #91-53-2): Inhalation:* In the previously described GLP-compliant acute inhalation toxicity study conducted according to EPA OPP 81-3, male and female Crl:CD®BR rats (5/sex/dose) were exposed to the test substance (purity not reported) aerosol via whole body inhalation for 4 hours at a concentration of 1.97 mg/L. Treatment caused tremors in 6 of 10 animals following inhalation exposure. Study authors stated that this might suggest a neurotoxic potential and is considered to be in line with the frequent observation of ataxia in the acute oral toxicity study. However due to the study design (whole-body exposure), the toxic signs might be also (at least partly) due to oral intake of traces of the test substance from the fur and it cannot be certainly stated that they were exclusively caused by inhalation (Klimisch Score 2, reliable with restrictions).
- Based on the weight of evidence, a Data Gap was assigned. Ataxia and hypoactivity that were reversible were observed at 1,500 – 2,535 mg/kg in an acute oral toxicity study with the surrogate ethoxyquin at doses that caused deaths of some animals. Tremors were observed at an aerosol concentration of 1.97 mg/L which also caused sacrifice of one animal *in extremis.* Therefore, it is unclear if the observed effects are specific neurotoxicity or secondary to the acute general toxicity of the test compound. Additionally, the effects such as tremors are not consistent with transient narcotic effects, which warrant GHS Category 3 classification. However, available data are insufficient to determine if Category 1 or 2 classification is warranted.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
TMDHQ was assigned a score of Data Gap for neurotoxicity (repeated dose) due to lack of data.

- Authoritative and Screening Lists

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

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *L*
TMDHQ was assigned a score of Low for skin sensitization based on the lack of dermal sensitization reactions observed in guinea pig studies performed with the surrogate TMDHQ, oligomers. GreenScreen® criteria classify chemicals as a Low for skin sensitization when adequate data are available and negative, and they are not classified per GHS (CPA 2018b). The confidence in the score is low due to conflicting data for 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 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In a GLP-compliant guinea pig maximization test (GPMT) conducted according to OECD Guideline 406, female guinea pigs (n =10) were intradermally and epicutaneously induced with 5 and 50% solutions of the test substance (purity not reported) in polyethylene glycol, respectively and challenged with 12% test substance. The challenge led to no skin effects in the animals of the treatment group or of the control group. TMDHQ, oligomers was not dermally sensitizing under the conditions of this assay (Klimisch Score 1, reliable without restriction).
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):* Ethoxyquin (purity not specified) was tested in a GLP-compliant modified Buehler method dermal sensitization study in a manner similar to OECD Guideline 406. Male and female Dunkin-Hartley guinea pigs (6/sex/dose) were topically induced with the undiluted test substance, once per week for 3 weeks for a total of 3 induction exposures. The exposure periods each lasted 6 hours. Two weeks after the last induction exposure, animals were challenged with a topical application of test substance at a concentration of 50% and followed by another challenge at a concentration of 50%. Reactions to challenge and re-challenge were evaluated at 24 and 48 hours after exposure. Body weights and clinical observations were recorded before dosing and at the end of the study. A positive control group was induced and challenged with dinitrochlorobenzene (DNCB). No mortality, clinical findings, or body weight changes were observed in the study. Undiluted ethoxyquin induced 7 very slight reactions in the treated group following both the first and second induction doses. The 50% concentration of the test substance induced 10 very slight reactions at 24 hours in the treated group following the challenge dosing. After 48 hours, irritation included 9 sites with very slight reactions and 1 with a slight (grade 1) reaction. After the rechallenge with 50% test substance, there were 12 very slight reactions and by 48 hours, dermal irritation included 11 very slight reactions and 1 site with a slight (grade 1) reaction. Focal eschar was observed for one site at 24 and 48 hours. Four animals had desquamation at 48 hours after dosing. A "Sensitization Incidence Index" was calculated as 8% or 1/12 for the treated group following challenge dosing, and "Irritation Severity Indices" of 0.4 and 0.5 at 24 and 48 hours, respectively, were recorded. The Sensitization Incidence Index for the positive control was calculated to be 100% or 6/6 following challenge dosing with 0.1% DNCB, with Irritation Severity Indices of 1.8 and 1.5 at 24 and 48 hours, respectively. The authors of this study indicated that GHS criteria have not been met and ethoxyquin is not a skin sensitizer (Klimisch score 2 – reliable with restrictions).

        - EC report authors concluded that ethoxyquin may be a weak skin sensitizer based on the results of this study, but the severity of the responses does not warrant classification. However, the results were obscured by the difficulties in distinguishing irritation and sensitization reactions, and skin sensitization reactions may be underestimated due to very slight patchy erythema being described as equivocal (EC 2008b).
- EC 2008b
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* Dermal sensitization reactions were reported in workers handling fruit or animal diets containing ethoxyquin. Therefore, ethoxyquin is considered a human sensitizer.
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* In a GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406, Hartley albino guinea pigs (20 total) were induced with six intradermal injections of an unspecified concentration of ethoxyquin (presumably unchanged 52% tradename product of ethoxyquin) and one week later induced epicutaneously with 52% ethoxyquin. Two weeks later, animals were epicutaneously challenged with 6% (highest non-irritating concentration) for 24 hours. Seven days later, animals were rechallenged epicutaneously with 3% or 1% ethoxyquin. 16/20 and 15/20 positive responses were recorded at 24 hours and 48 hours after the first challenge, respectively. 15/20 and 8/20 positive responses were recorded at 24 hours and 48 hours after the second challenge with 3% ethoxyquin, respectively. 2/20 positive reactions were recorded at both 24 hours and 48 hours after the second challenge with 1% ethoxyquin. The sham control animals had 3/10 and 1/10 positive responses 24 hours and 48 hours after the challenge, respectively. Study authors concluded that ethoxyquin was a dermal sensitizer.
        - Per GHS criteria (UN 2021), ≥30% responding at >1% intradermal induction dose corresponds to GHS Category 1B.
- Based on the weight of evidence, a low confidence score of Low was assigned. Although the surrogate ethoxyquin showed some evidence of weak sensitization, the surrogate TMDHQ, oligomers, which contains the target chemical as a constituent, was negative in a well conducted guinea pig maximization test. Therefore, ToxServices assigned a Low based on reliable data on the more similar surrogate, but confidence is reduced due to conflicting data between surrogates.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
TMDHQ was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential and according to 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). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2021
    - TMDHQ does not contain any structural alerts for respiratory sensitization using the OECD QSAR Toolbox v4.5 (see Appendix D).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based

on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). TMDHQ is not expected to be sensitizing to the skin based on data on the most similar surrogate (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by TMDHQ, and as TMDHQ does not contain any structural alerts for respiratory sensitization (OECD 2021).

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

TMDHQ was assigned a score of Low for skin irritation/corrosivity based on negative results in dermal irritation tests conducted with surrogates. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, and they are not classified per GHS (CPA 2018b). The confidence in the score is low due to lack of measured data on the target chemical as it is reported in secondary sources to be irritating to the skin.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Santa Cruz Biotechnology 2016
  - A safety data sheet (SDS) for TMDHQ states that is irritating to the skin and is classified to GHS Category 2. No further details were reported.
- Bibra 1998
  - An abstract on the toxicity profile of TMDHQ reported that it produced irritation of the skin when tested in laboratory animals. *ToxServices did not have access to the full report and is therefore unable to evaluate the corresponding studies and conduct a GHS classification.*
- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In a non-GLP acute dermal irritation test conducted in a manner similar to OECD Guideline 404, New Zealand White rabbits (n=6, sex not specified) were administered 500 mg of the test substance (purity not reported) to the skin for 24 hours. The type of coverage was not reported. The mean (24, 48, and 72 hour) erythema and edema scores were both 0. The test substance was not dermally irritating under the conditions of this assay (Klimisch Score 2, reliable with restrictions).
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):* Ethoxyquin (purity not specified) induced slight erythema on the clipped skin of New Zealand White rabbits in a GLP-compliant study conducted in a manner similar to OECD Guideline 404. Six animals were administered on clipped skin a dressing containing 0.5 mL test substance, under semiocclusive conditions, for 4 hours. Treated skin was examined 30-60 minutes, 24, 48, and 72 hours, and then daily through Day 7, after removal of the test substance for signs of erythema and edema. The test substance induced very slight erythema (a score of 0.33/1) on 5 animals which was reversible by Day 4 or earlier. The mean scores across 24, 48 and 72 hours for each of the 6 animals tested were 0, 0.33, 0.66, 0, 1 and 0, respectively. No edema or other dermal findings were recorded. Desquamation was noted on two sites (Klimisch score 2 – reliable with restrictions).
    - The effects observed in this study are not sufficient to classify ethoxyquin as a Category 3 skin irritant. The criteria for a GHS Category 3 skin irritant are mean value $\geqslant$ 1.5 - < 2.3 for erythema/eschar or for edema in at least 2 of 3 animals tested at 24, 48, and 72 hours after patch removal (UN 2021).
- EC 2008b

  - *Surrogate: Ethoxyquin (CAS #91-53-2):* Ethoxyquin (52% purity) was not irritating in a GLP-compliant skin irritation study conducted in New Zealand white rabbits exposed to 0.5 mL on the intact skin for 4 hours. The mean 24, 48, and 72 hours erythema/edema scores were 0.67, 0.33 and 0.67 for each of the three animals tested. Therefore, the severity does not warrant GHS classification.
- Based on the weight of evidence, a score of Low was assigned. TMDHQ was reported to be irritating to the skin in its SDS and literature. However, experimental data supporting this classification were lacking. Dermal irritation tests of high quality were available for the surrogates TMDHQ, oligomers and ethoxyquin, which indicted no irritation potential. Therefore, ToxServices relied on the measured data for the surrogates and assigned a score of Low for this endpoint.

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

TMDHQ was assigned a score of Low for eye irritation/corrosivity based on negative results in ocular irritation tests conducted with surrogates. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative, and they are not classified per GHS (CPA 2018b). The confidence in the score is low due to lack of measured data on the target chemical as it is reported in secondary sources to be irritating to the eye.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Santa Cruz Biotechnology 2016
  - A safety data sheet for TMDHQ states that is irritating to the eye and is classified to GHS Category 2A. No further details were reported.
- Bibra 1998
  - An abstract on the toxicity profile of TMDHQ reported that in laboratory animals, TMDHQ produced irritation of the eye. *ToxServices did not have access to the full report and is therefore unable to evaluate the corresponding studies and conduct a GHS classification.*
- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In a non-GLP acute ocular irritation test conducted in a manner similar to OECD Guideline 405, one eye of New Zealand white rabbits (n=6, sex not specified) was instilled with 0.1 mL unchanged test substance (purity not reported) for 24 hours. Treatment caused slight discomfort immediate after dosing to 10 min after dosing. The mean scores (48, 72, 120, and 168 hour) for corneal opacity, iris, conjunctivae were 0. The study authors concluded that the test substance is not irritating to the eye (Klimisch Score 2, reliable with restrictions).
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):* A GLP-compliant ocular irritation test conducted according to EPA OPP 81-4 was performed with New Zealand white rabbits (6 animals; sex not specified) administered 0.1 mL of undiluted ethoxyquin (purity not specified) for 96 hours without rinsing. Ocular reactions were recorded and scored 1, 24, 48, and 72 hours, followed by observations up to Day 4 in the absence of a reaction. The mean conjunctivae score was 0.444/2 and the effects were fully reversible within 96 hours. The mean chemosis score was 0.167/1 and the effects were fully reversible within 72 hours. There was no evidence of damage or a treatment-related effect on the iris or the cornea (Klimisch score 2 – reliable with restrictions).
    - The effects observed in this study are not sufficient to classify ethoxyquin as a GHS Category 2 eye irritant. The criteria for a GHS Category 2 eye irritant are as

follows: corneal opacity ≥ 1, and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or chemosis ≥ 2 (UN 2021).
        - chemosis ≥ 2 (UN 2021).
- EC 2008b
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* In a GLP-compliant ocular irritation study conducted according to OECD Guideline 405, New Zealand white rabbits received 0.1 mL 52% ethoxyquin in one eye without rinsing. The eyes were scored at 1, 24, 48, and 72 hours post-instillation. The scores for corneal opacity and iritis were 0 across all time points in all animals. The mean 24, 48, and 72 hour scores for conjunctival redness were 0.67, 1, and 1 for each of the 3 animals, and the mean scores for chemosis were 0. Study authors concluded that the test material was slightly irritating to the eye but did not warrant GHS classification.
        - The effects observed in this study are not sufficient to classify ethoxyquin as a GHS Category 2 eye irritant. The criteria for a GHS Category 2 eye irritant are as follows: corneal opacity ≥ 1, and/or iritis ≥ 1, and/or conjunctival redness ≥ 2, and/or chemosis ≥ 2 (UN 2021).
- Based on the weight of evidence, a score of Low was assigned. TMDHQ was reported to be irritating to the eye in its SDS and literature. However experimental data supporting this classification were lacking. Ocular irritation tests of high quality were available for the surrogates TMDHQ, oligomers and ethoxyquin, which indicted no irritation potential. Therefore, ToxServices relied on the measured data of high quality for the surrogates and assigned a score of Low for this endpoint.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): *H*
TMDHQ was assigned a score of High for acute aquatic toxicity based on experimental L/EC_{50} values as low as 2 mg/L in daphnia for a surrogate. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when acute aquatic toxicity values are > 1 to 10 mg/L (CPA 2018b). The confidence in the score is low due to mixed data for the 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 2021a
    - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):*
        - Based on the weight-of evidence from three water solubility studies conducted with TMDHQ oligomers, its water solubility is estimated to be around or below 1 mg/L. Only a small portion (less than 0.1 %) of the substance is considered to be soluble in water.
        - 96-hour mortality LL_{10} (*Danio rerio*, fish) > 100 mg/L (purity not reported, GLP-compliant, and EU Method C.1), the effective loading (EL) was determined upon water accommodated fraction (WAF) without chemical analysis (Klimisch Score 2, reliable with restrictions).
        - 48-hour mobility EL_{50} (*Daphnia magna*, invertebrate) = 56 mg/L (purity not reported, GLP-compliant and EU Method C.2), the effective loading (EL) was determined upon water accommodated fraction (WAF) without chemical analysis (Klimisch Score 2, reliable with restrictions).

        - 72-hour EL_0 (*Desmodesmus subspicatus*, green algae) >100 mg/L for growth rate (purity not reported, GLP-compliant and EU Method C.3), the effective loading (EL) was determined upon water accommodated fraction (WAF) without chemical analysis (Klimisch Score 2, reliable with restrictions).
- ECHA 2021b
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 18 mg/L (GLP-compliant, OECD 203) (Klimisch score 2 – reliable with restrictions)
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 96-hour NOEC (clinical signs) (*O. mykiss*, rainbow trout) = 3.5 mg/L (GLP-compliant, OECD 203) (Klimisch score 2 – reliable with restriction)
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 24-hour mortality EC_{50} (*Daphnia magna*) > 2.9 mg/L (GLP-compliant, OECD II A 8.3.1) (Klimisch score 2 – reliable with restrictions)
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 48-hour mortality EC_{50} (*D. magna*) = 2 mg/L (GLP-compliant, OECD II A 8.3.1) (Klimisch score 2 – reliable with restriction)
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 72-hour growth rate and biomass EC_{50} (*Pseudokirchneriella subcapitata*, green algae) (GLP-compliant, OECD 201) (Klimisch score 2 – reliable with restrictions):
        - 72-hour - EC_{50} – growth rate: > 16 mg/L
        - 72-hour - EC_{50} – biomass: 6.1 mg/L
        - 72-hour NOEC – biomass and growth rate: 2.3 mg/L
- U.S. EPA 2017b
    - TMDHQ is designated to the neutral organics ECOSAR chemical class. The predicted acute aquatic values are 20.8 mg/L in fish (96-hour LC_{50}), 12.87 mg/L in *daphnia* (48-hour EC_{50}), 10.42 mg/L in Mysid, and 13.67 mg/L in green algae (96-hour EC_{50}).
- Based on the weight of evidence, a score of High was assigned. Data on the surrogates are mixed, but ToxServices relied on data on ethoxyquin as its water solubility, which is highly relevant to aquatic toxicity potential, is more similar to the target. In addition, the modeled data on the target indicate it has higher aquatic toxicity than the surrogate oligomeric mixture.

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

TMDHQ was assigned a score of High for chronic aquatic toxicity based on the predicted ChV value of 0.68 mg/L in the marine invertebrate mysid shrimp. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when the most conservative chronic aquatic toxicity value is > 0.1 to 1 mg/L (CPA 2018b). The confidence in the score is low as it is based on predicted data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021b
    - *Surrogate: Ethoxyquin (CAS #91-53-2):* 72-hour growth rate and biomass NOEC (*P. subcapitata*, green algae) (GLP-compliant, OECD 201) (Klimisch score 2 – reliable with restriction):
        - 72-hour NOEC – biomass and growth rate: 2.3 mg/L
- U.S. EPA 2017b
    - TMDHQ is designated to the neutral organics ECOSAR chemical class. The most conservative predicted chronic aquatic values (ChV) values are 2.25 mg/L in fish, 1.59 mg/L in *Daphnia*, 0.68 mg/L in *Mysid*, and 4.34 mg/L in green algae (Appendix G).
- GHS criteria state data on mysid can be used for classification as it represents a crustacean species other than daphnia. Based on this, ToxServices considered mysid shrimp as the most sensitive species and relied on its predicted ChV value to assigned a score of High.

Environmental Fate (Fate)

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

TMDHQ was assigned a score of High for persistence based on a predication that it is not readily biodegradable with a half-life value of 75 days in soil, the predominant partitioning compartment supported by data on its oligomeric mixture. GreenScreen® criteria classify chemicals as a High hazard for persistence when soil is the dominant environmental compartment and the half-life in soil is greater than 60 to 180 days (CPA 2018b). The confidence in the score is low due to lack of measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021a
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In a GLP-compliant ready biodegradability test conducted according to EU Method C.4-E (Closed Bottle), domestic, activated, and non-adapted sludge were exposed to the test substance (purity not reported) at 2.5 mg/L for 28 days. No degradation was observed at the end of exposure period. Study authors concluded that TMDHQ, oligomers is not readily biodegradable (Klimisch Score 2, reliable with restrictions).
  - *Surrogate: TMDHQ, oligomers (CAS #26780-96-1):* In an inherent biodegradability test, only 1% biodegradation of the test substance was observed during 35 days of exposure to acclimated bacterial inoculum. Accordingly, study authors concluded that TMDHQ, oligomers is not inherently biodegradable (Klimisch Score 2, reliable with restrictions).
- U.S. EPA 2017a
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that TMDHQ is expected to be not readily biodegradable. Fugacity modeling (MCI method) predicts 80.7% will partition to soil with a half-life of 75 days (1,800 hours / 24 hours), 18.1% will partition to water with a half-life of 37.5 days (900 hours / 24 hours), and 1.1% will partition to sediment with a half-life of 337.5 days (Appendix H).

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

TMDHQ was assigned a score of Very Low for bioaccumulation based on a measured a log K_{ow} value of 2.93 and an estimated BCF value of 82.05. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are ≤ 4 and BCF / BAF values are ≤ 100 (CPA 2018b). The confidence in the score is high as it is based on a measured log K_{ow} 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.
- U.S EPA 2021b
  - TMDHQ has a measured log K_{ow} of 2.93. No further details were reported.
- U.S. EPA 2017a
  - BCFBAF (v3.01) predicts a BCF of 39.83 L/kg wet-wt for TMDHQ from a regression-based method and a BCF of 82.05 for the upper trophic level using the Arnot-Gobas method, both based on a measured log K_{ow} of 2.93 (Appendix H).

Physical Hazards (Physical)

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

TMDHQ was assigned a score of Low for reactivity based on its surrogate not being explosive when tested according to EU Method A.14, supported by lack of structural alerts for oxidizing and explosive properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2018b). The confidence in the score is low due to lack of measured data on the oxidizing properties.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of TMDHQ. These procedures are listed in the GHS (UN 2021).
  - TMDHQ is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix I).
  - TMDHQ 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.
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):* In a GLP-compliant test conducted according to EU Method A.14, the test substance (99.2% purity) has no explosive properties when exposed to intense heat (thermal sensitivity) or when exposed to shock or friction (mechanical sensitivity) (Klimisch Score 2, reliable with restrictions).

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

TMDHQ was assigned a score of Low for flammability based on not being classified as a flammable liquid per GHS supported by data on its surrogate. GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not classified per GHS as flammable liquids or solids (CPA 2018b). The confidence in the score is high as it is based on a measured flash point for the target chemical and a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CAMEO Chemicals Undated
  - TMDHQ (purity not reported) has a measured flash point of 214 °F. This is equivalent to 101°C [(214°F − 32) × 5/9]. *According to GHS criteria, the flash point of 101°C is above the GHS Guidance value for Category 4 flammable liquid (93ºC). Therefore, TMDHQ is not classified per GHS.*
- ECHA 2021b
  - *Surrogate: Ethoxyquin (CAS #91-53-2):* Ethoxyquin (98.6% purity) has a measured flash point of >= 148 - <= 152 °C obtained from a GLP-complaint closed cup method test conducted according to EU Method A.9 (Klimisch Score 2, reliable with restrictions). *According to GHS criteria, this flash point is above the GHS Guidance value for Category 4 flammable liquid (93ºC). Therefore, ethoxyquin is not classified per GHS.*

Use of New Approach Methodologies (NAMs)[12] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity, endocrine activity, and *in silico* models for respiratory sensitization, endocrine activity, chronic aquatic toxicity and persistence. NAMs are non-animal alternative that can be used alone or in combination to provide information for safety assessment (Madden et al. 2020). At present, there is not a uniformly accepted framework on how to report and apply individual NAMs (U.S. EPA 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 2020b):

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

As shown in Table 4, Type I (input data) uncertainties in TMDHQ's NAMs dataset include the experimental data for endocrine activity, respiratory sensitization, chronic aquatic toxicity, and persistence, and lack of validated test methods for respiratory sensitization. TMDHQ's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, the unknown *in vivo* relevance of EDSP Tox 21 screening assays and *in silico* modeling of receptor binding, and the lack of defined applicability domains in OECD Toolbox as well as ToxCast models. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries, and ECHA's decision framework and guidance to evaluate respiratory sensitization.

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

Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Respiratory sensitization**: No experimental data or human data are available. In addition, there are no formally recognized and validated animal or *in vitro* tests. **Endocrine activity:** No *in vivo* experimental data or human data are available. **Chronic aquatic toxicity:** Experimental data are only available for one trophic level. **Persistence:** No measured data are available.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[13].

[12] 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).

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

	The *in vitro* SCE assay (as defined in OECD 479, a guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[14]. The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. **Endocrine activity:** ToxCast models don't define applicability domain; the *in vivo* relevance of EDSP Tox 21 screening assays and *in silico* modeling of receptor binding is unknown due to lack of consideration of metabolism and other toxicokinetic factors. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* micronucleus test
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* high throughput data: EDSP Tox 21 screening assays *In silico* modeling: ToxCast models
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	Y	*In silico:* ECOSAR
Chronic aquatic toxicity	Y	*In silico:* ECOSAR
Persistence	Y	*In silico:* EPI Suite™
Bioaccumulation	Y	*In silico:* EPI Suite™

[14] https://www.oecd.org/env/ehs/testing/Draft_Intro_Genotoxicity%20TGs%20September%202014.pdf

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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 TMDHQ (CAS #147-47-7)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / TMDHQ / 147-47-7	M	L	*M*	*M*	DG	M	vH	H	DG	DG	*L*	*L*	*L*	*L*	*H*	*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	Yes	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
TMDHQ	2

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

Table 6

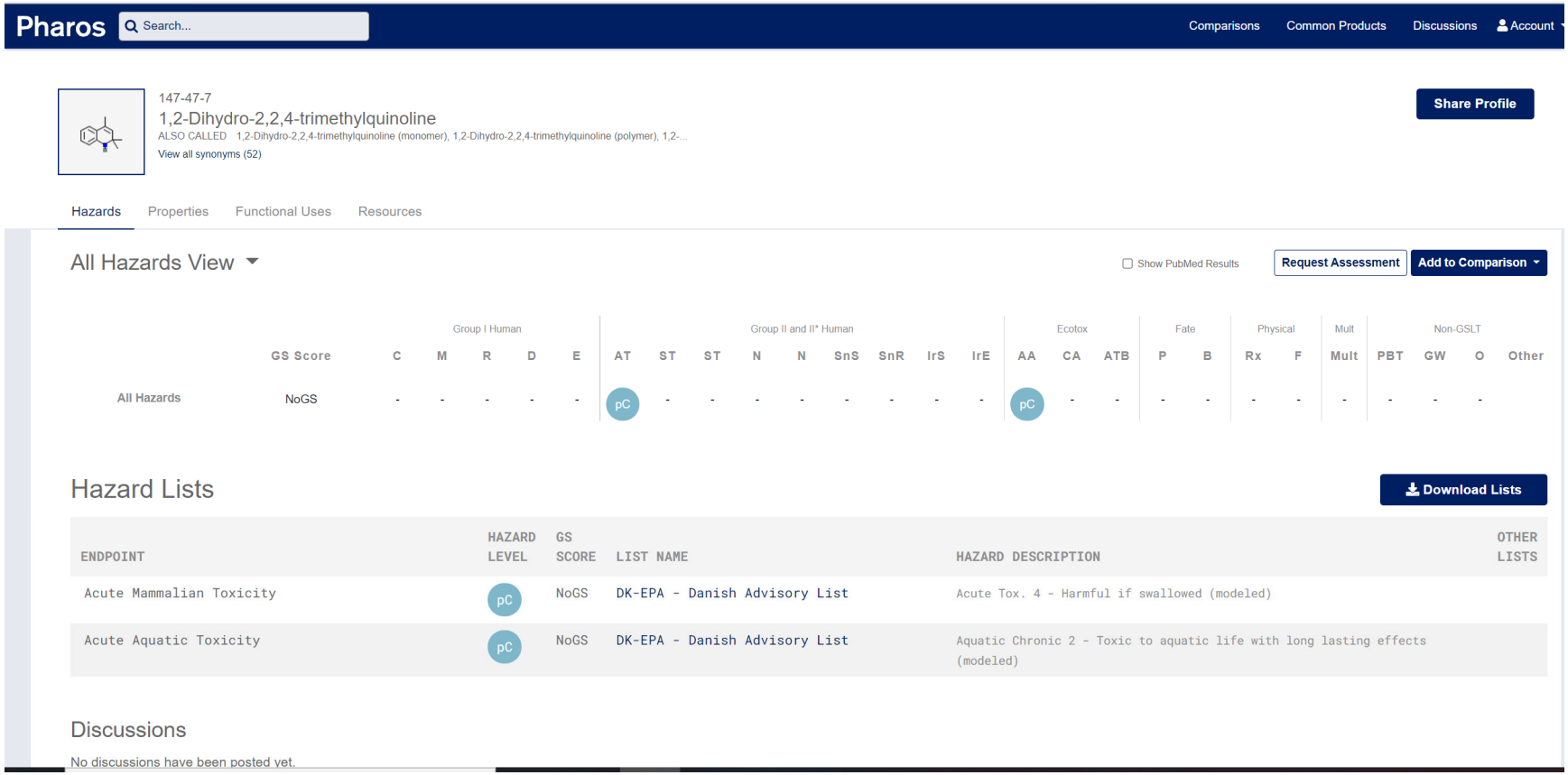
Chemical Name	Final GreenScreen® Benchmark Score
TMDHQ	2

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

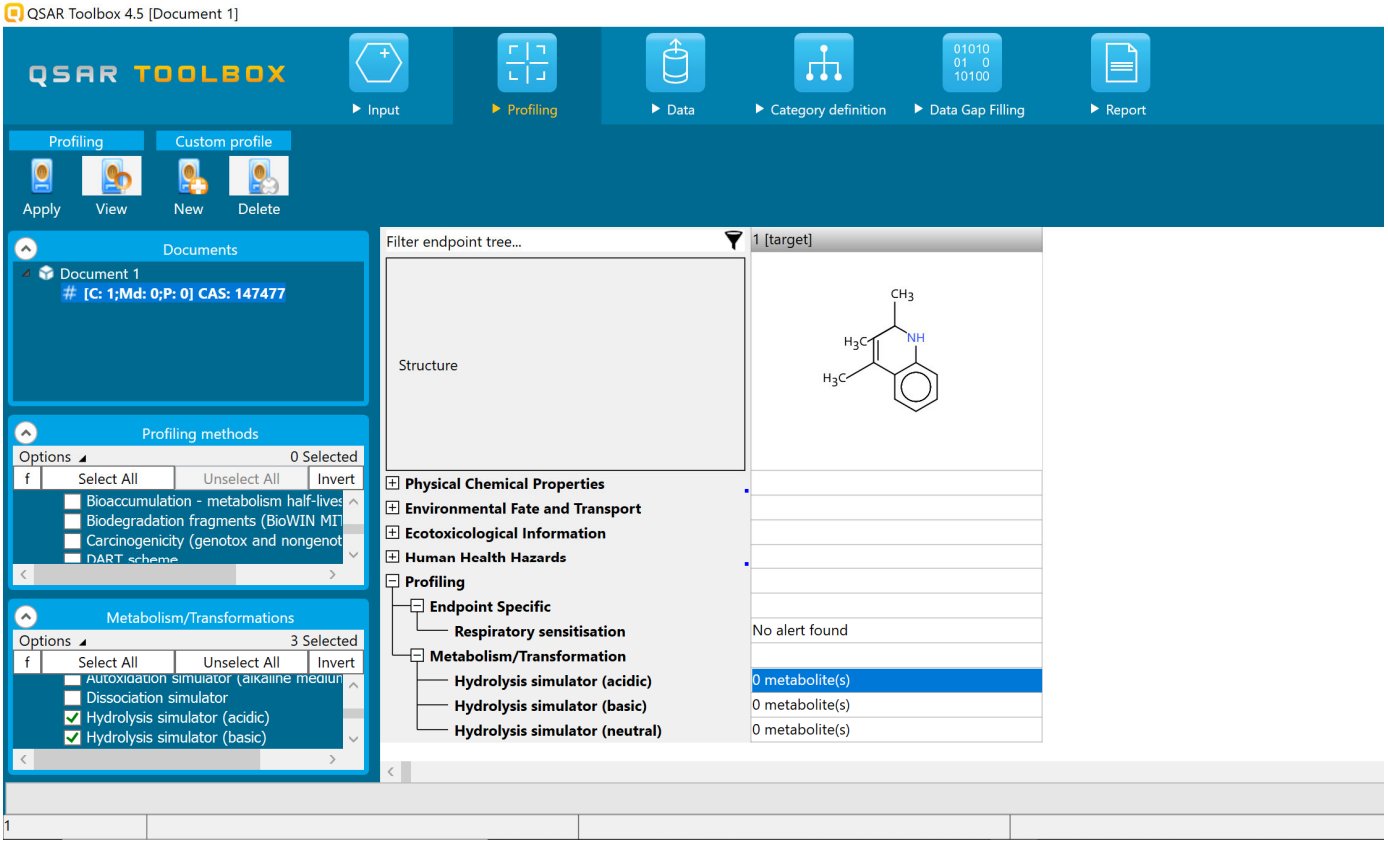
Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

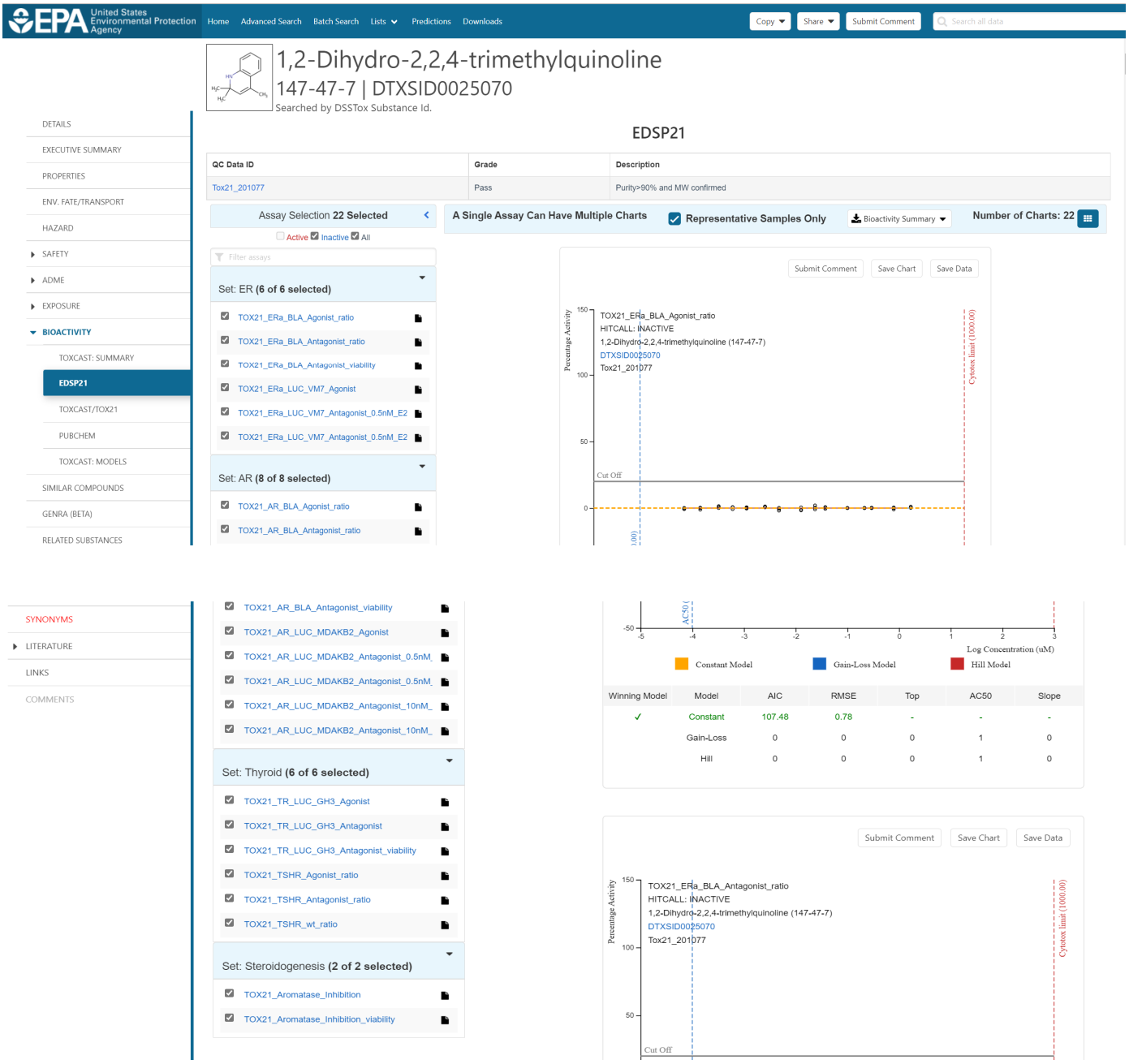
APPENDIX C: Pharos Output for TMDHQ (CAS #147-47-7)



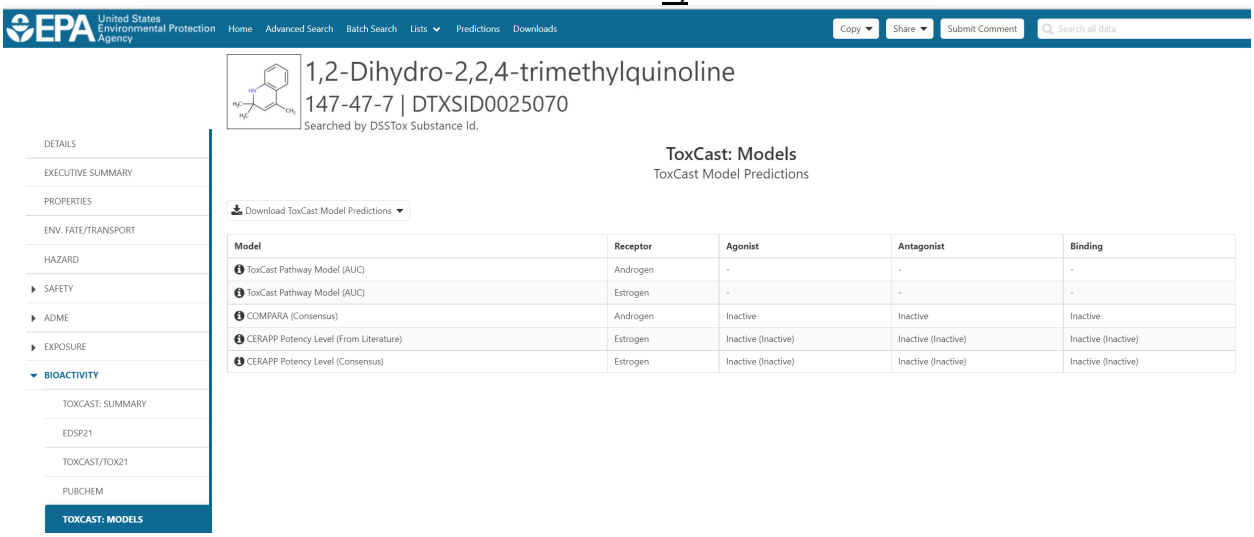
APPENDIX D: OECD Toolbox Profile and Hydrolysis Results for TMDHQ (CAS #147-47-7)



APPENDIX E: U.S. EPA Bioactivity (EDSP21) Summary for TMDHQ (CAS #147-47-7)



APPENDIX F: U.S. EPA Bioactivity (ToxCast Models) Summary for TMDHQ (CAS #147-47-7)



Model	Receptor	Agonist	Antagonist	Binding
ToxCast Pathway Model (AUC)	Androgen	-	-	-
ToxCast Pathway Model (AUC)	Estrogen	-	-	-
COMPARA (Consensus)	Androgen	Inactive	Inactive	Inactive
CERAPP Potency Level (From Literature)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)
CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Inactive (Inactive)

APPENDIX G: ECOSAR Modeling Results for TMDHQ (CAS #147-47-7)

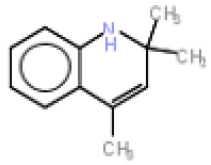
Created on Oct 20, 2021 3:19:03 AM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
147477	Quinoline, 1,2-dihydro-2,2,4-trimethyl-	N(c(c(C(=C1)C)ccc2)c2)C1(C)C

Structure



Details	
Mol Wt	173.26
Selected LogKow	2.93
Selected Water Solubility (mg/L)	100
Selected Melting Point (°C)	26.5
Estimated LogKow	3.3
Estimated Water Solubility (mg/L)	363.97
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	26.5

Class Results:	

Neutral Organics

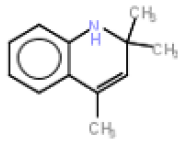
Created on Oct 20, 2021 3:19:03 AM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
147477	Quinoline, 1,2-dihydro-2,2,4-trimethyl-	N(c(c(C(=C1)C)ccc2)c2)C1(C)C

Structure



Details	
Mol Wt	173.26
Selected LogKow	2.93
Selected Water Solubility (mg/L)	100
Selected Melting Point (°C)	26.5
Estimated LogKow	3.3
Estimated Water Solubility (mg/L)	363.97
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	26.5

Class Results:	

Neutral Organics

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)	96h	LC50	26.33	5	
Mysid	96h	LC50	10.42	5	
Fish (SW)		ChV	5.04	8	
Mysid (SW)		ChV	0.68	8	
Earthworm	14d	LC50	241.24	6	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

APPENDIX H: EPI Suite™ Modeling Results for TMDHQ (CAS #147-47-7)

(Estimations Used for Hazard Classification Are Highlighted and Bolded)

CAS Number: 147-47-7
SMILES: N(c(c(C(=C1)C)ccc2)c2)C1(C)C
CHEM: Quinoline, 1,2-dihydro-2,2,4-trimethyl-
MOL FOR: C12 H15 N1
MOL WT: 173.26
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.93
Boiling Point (deg C) : 260.00
Melting Point (deg C) : 26.50
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 100
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 3.30

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 271.31 (Adapted Stein & Brown method)
Melting Pt (deg C): 70.42 (Mean or Weighted MP)
VP (mm Hg,25 deg C): 0.0154 (Modified Grain method)
VP (Pa, 25 deg C): 2.05 (Modified Grain method)
MP (exp database): 26.5 deg C
BP (exp database): 260 deg C
Subcooled liquid VP: 0.0159 mm Hg (25 deg C, Mod-Grain method)
: 2.12 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 364
log Kow used: 2.93 (user entered)
melt pt used: 26.50 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 117.24 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.08E-006 atm-m3/mole (3.12E-001 Pa-m3/mole)
Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 3.511E-005 atm-m3/mole (3.557E+000 Pa-m3/mole)
VP: 0.0154 mm Hg (source: MPBPVP)
WS: 100 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.93 (user entered)
Log Kaw used: -3.900 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 6.830
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.2474
Biowin2 (Non-Linear Model) : 0.0439
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.4692 (weeks-months)
Biowin4 (Primary Survey Model) : 3.3359 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.1493
Biowin6 (MITI Non-Linear Model): 0.0356
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.4699
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 2.12 Pa (0.0159 mm Hg)
Log Koa (Koawin est): 6.830
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.42E-006
Octanol/air (Koa) model: 1.66E-006
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 5.11E-005
Mackay model : 0.000113
Octanol/air (Koa) model: 0.000133

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 127.4757 E-12 cm3/molecule-sec
Half-Life = 0.084 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 1.007 Hrs
Ozone Reaction:
OVERALL Ozone Rate Constant = 13.650000 E-17 cm3/molecule-sec
Half-Life = 0.084 Days (at 7E11 mol/cm3)
Half-Life = 2.015 Hrs
Fraction sorbed to airborne particulates (phi):
8.22E-005 (Junge-Pankow, Mackay avg)
0.000133 (Koa method)

Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1087 L/kg (MCI method)
Log Koc: 3.036 (MCI method)
Koc : 318 L/kg (Kow method)
Log Koc: 2.502 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.600 (BCF = 39.83 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.3012 days (HL = 2.001 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.914 (BCF = 82.05)
Log BAF Arnot-Gobas method (upper trophic) = 1.914 (BAF = 82.07)
log Kow used: 2.93 (user entered)

Volatilization from Water:
Henry LC: 3.08E-006 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 251.6 hours (10.48 days)
Half-Life from Model Lake : 2855 hours (118.9 days)

Removal In Wastewater Treatment:
Total removal: 5.30 percent
Total biodegradation: 0.12 percent
Total sludge adsorption: 5.01 percent
Total to Air: 0.17 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0468	1.01	1000
Water	18.1	900	1000
Soil	80.7	1.8e+003	1000
Sediment	1.1	8.1e+003	0

Persistence Time: 1.04e+003 hr

Level III Fugacity Model: (MCI Method with Water percents)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0468	1.01	1000
Water	18.1	900	1000
water	(18.1)		
biota	(0.000771)		
suspended sediment	(0.0295)		
Soil	80.7	1.8e+003	1000
Sediment	1.1	8.1e+003	0

Persistence Time: 1.04e+003 hr

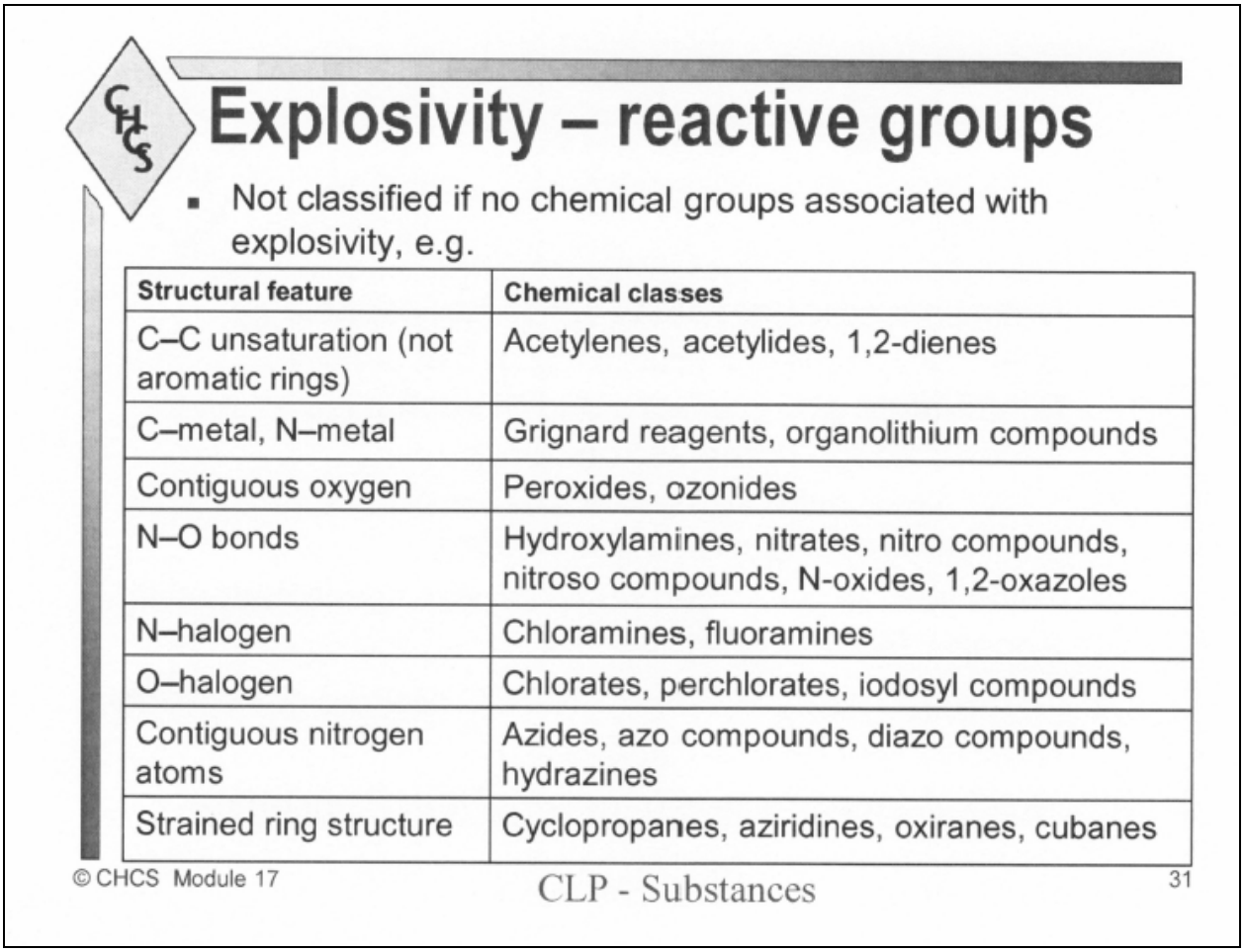
Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.0496	1.01	1000
Water	19.9	900	1000
water	(19.9)		
biota	(0.000845)		
suspended sediment	(0.0104)		
Soil	79.7	1.8e+003	1000
Sediment	0.388	8.1e+003	0

Persistence Time: 995 hr

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

APPENDIX J: Change in Benchmark Score

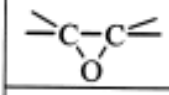
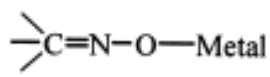
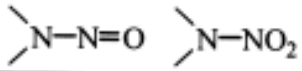
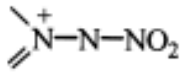
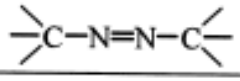
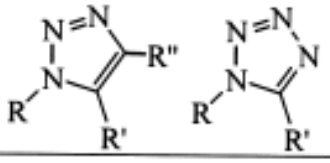
Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for TMDHQ. This GreenScreen® assessment has undergone one round of updates which does not affect the benchmark score.

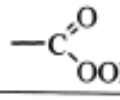
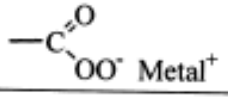
Table 5: Change in GreenScreen® Benchmark™ for TMDHQ (CAS #147-47-7)

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
October 6, 2021	BM-2	v. 1.4	New assessment
November 4, 2021	BM-2	v. 1.4	Minor updates in response to Ecology's comments

Explosivity – Full List

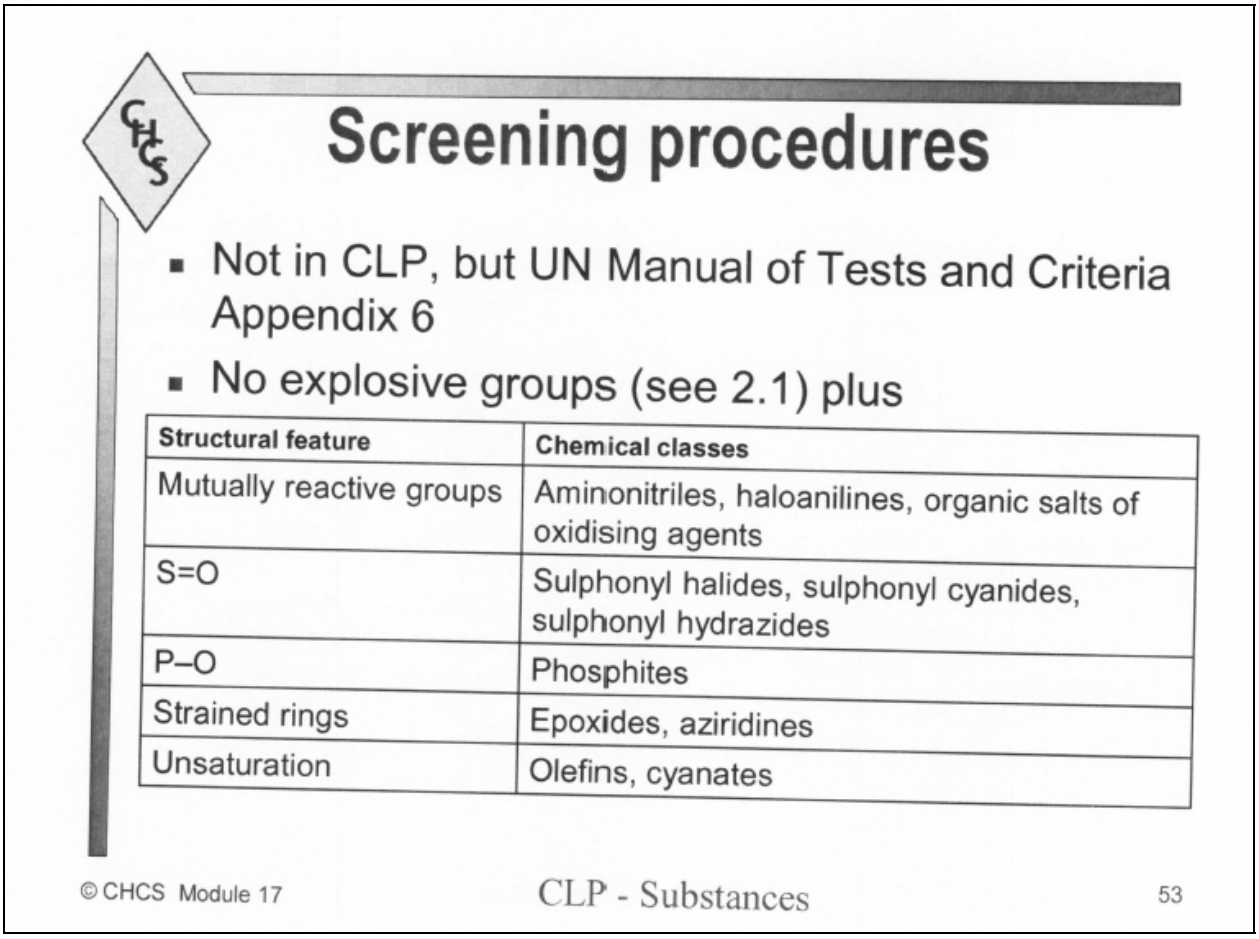
Table R.7.1-28 Chemical groups associated with explosive properties

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

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

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

Self-Reactive Substances



Licensed GreenScreen® Profilers

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