ETHANEDIAMIDE, N-(2-ETHOXYPHENYL)-N'-2-ETHYLPHENYL-

(CAS #23949-66-8)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: August 28, 2023

Expiration Date: August 28, 2028

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GreenScreen® Executive Summary for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is used as a light stabilizer in polymers including polyvinyl chloride (soft and rigid), acrylonitrile butadiene styrene, polyamide, polycarbonate, and polysulfone. In the United States, it is approved as a food contact substance at concentrations up to 0.04% when used as a UV absorber in linear low-density polyethylene polymers not to be in contact with infant formula or human milk.

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is a white powder that is not volatile. It is slightly soluble in water and much more soluble in octanol.

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c
    - High Persistence-P + Moderate Group I Human Health Hazard (carcinogenicity-C)
    - High P + Very High Ecotoxicity (chronic aquatic-CA)
- Benchmark 2e
    - Moderate Group I Human Health Hazard (C)
- Benchmark 2f
    - Very High ecotoxicity (CA)

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

ToxServices' original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark U (BM-U) score. ToxServices changed the benchmark score to BM-2 with a version 1.4 update in the current assessment, due to availability of new data and updated modeling tools.

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

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

Type I (input data) uncertainties in ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s NAMs dataset include lack of, or insufficient experimental data for carcinogenicity, developmental toxicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation, and lack of validated test methods for respiratory sensitization. Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s Type II (extrapolation output) uncertainties include lack of defined applicability domains for a few models, limitations of *in vitro* genotoxicity data in mimicking *in vivo* metabolism and

their focusing on a few events in the genotoxicity process, and the lack of consideration of non-immunological mechanisms for respiratory sensitization. Some of ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl-

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**	DG	*L*	DG	**L**	**L**	**L**	*L*	DG	**L**	*L*	**L**	*L*	**L**	*vH*	*H*	*L*	*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 Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

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

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: November 19, 2014

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: November 20, 2014

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Megan B. Boylan, M.S.
Title: Toxicologist
Organization: ToxServices LLC
Date: July 12, 2023

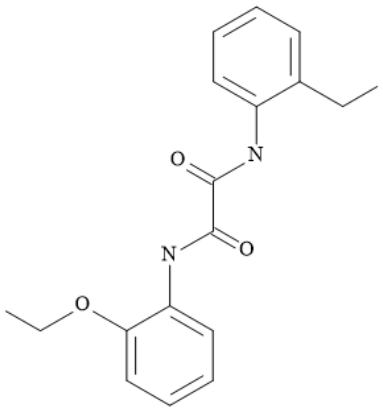
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: August 28, 2023

Expiration Date: August 28, 2028[2]

Chemical Name: Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-

CAS Number: 23949-66-8

Chemical Structure(s):

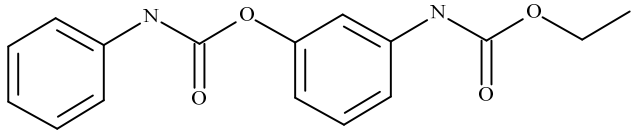


Also called:
N'-(2-ethoxyphenyl)-N-(2-ethylphenyl)oxamide; 2-Ethoxy-2'-ethyloxanilide; N-(2-Ethoxyphenyl)-N'-(4-ethylphenyl)-ethlyene diamide; N-(2-Ethoxyphenyl)-N'-(2-ethylphenyl)oxamide; Tinuvin 312; n1-(2-

[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).

ethoxyphenyl)-n2-(2-ethylphenyl)ethanediamide; Oxanilide, 2'-ethoxy-2"-ethyl-; Ethanediamide, N1-(2-ethoxyphenyl)-N2-(2-ethylphenyl)-; HOSTAVIN VSU; SANDUVOR VSU (PubChem 2023)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Several data gaps were identified for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl. However, no suitable surrogates with sufficient data were identified using the structural similarity search function of U.S. EPA's Analog Identification Methodology (AIM) software. The ECHA registration dossier used desmedipham (CAS #13684-56-5) as a surrogate for reproductive toxicity. However, the two compounds only share a maximum common substructure (MCS) Tanimoto coefficient ot 0.25, indicating poor structural similarity (ChemMine 2023). Therefore, ToxServices used modeling to address data gaps where feasible.



Discarded Surrogate: Desmedipham (CAS #13684-56-5)

Identify Applications/Functional Uses (PubChem 2023)**:**
UV/light stabilizer

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

GreenScreen® Summary Rating for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl-[3,4 5,6]:
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes"). This score is based on the following hazard score combinations:

- Benchmark 2c
  - High Persistence-P + Moderate Group I Human Health Hazard (carcinogenicity-C)
  - High P + Very High Ecotoxicity (chronic aquatic-CA)
- Benchmark 2e
  - Moderate Group I Human Health Hazard (C)
- Benchmark 2f
  - Very High ecotoxicity (CA)

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E, and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- meets the requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if

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

ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- were assigned a High score for the data gaps R, or E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl-

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

No transformation products were identified for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-. A GLP-compliant hydrolysis test conducted according to OECD Guideline 111 was performed with ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (as Hostavin VSU P, 99.23% purity) incubated at 20, 30, or 50°C and pH 4, 7, or 9 (ECHA 2023). While no hydrolysis occurred at pH of 4, slight hydrolysis was found at 20°C and 30°C at pHs of 7 and 9, and moderate hydrolysis occurred at 50°C at pHs of 7 and 9. The hydrolysis products were not identified. ToxServices used OECD QSAR Toolbox (OECD 2023) to predict the hydrolysis products of ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- under acidic, neutral, and basic conditions. No hydrolysis products were predicted for neutral conditions. The following hydrolysis products were identified under acidic and basic pH: 2-ethylaniline (CAS #578-54-1), [(2-ethylphenyl)amino](oxo)acetic acid (CAS #50740-38-0), o-phenetidine (CAS #94-70-2), 2-(2-ethoxyanilino)-2-oxo-acetic acid[7] (CAS #NA), and oxalic acid (CAS #144-62-7). Since normal rain has a slightly acidic pH of 5.6,[8] ToxServices concluded that these hydrolysis products are feasible and relevant. The hydrolysis products are LT-P1 chemicals or are not listed in the Pharos database. Therefore, the Benchmark Score for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not modified by the transformation products.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[9,10]
End	Hydrolysis	2-Ethylaniline	578-54-1	Yes	Yes	LT-P1

[7] SMILES: CCOc1ccccc1NC(=O)C(O)=O
[8] https://www.epa.gov/acidrain/what-acid-rain
[9] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[10] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

Table 1: Environmental Transformation Product Summary						
Life Cycle Stage	**Transformation Pathway**	**Environmental Transformation Product**	**CAS #**	**Feasible (Yes or No)**	**Relevant (Yes or No)**	**GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[9,10]**
End	Hydrolysis	[(2-Ethylphenyl)amino](oxo)acetic acid	50740-38-0	Yes	Yes	Not listed in Pharos database
End	Hydrolysis	o-Phenetidine	94-70-2	Yes	Yes	LT-P1
End	Hydrolysis	2-(2-Ethoxyanilino)-2-oxo-acetic acid	NA	Yes	Yes	Not listed in Pharos database
End	Hydrolysis	Oxalic acid	144-62-7	Yes	Yes	LT-P1

Introduction

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is used as a light stabilizer in polymers including polyvinyl chloride (soft and rigid), acrylonitrile butadiene styrene, polyamide, polycarbonate, and polysulfone (PubChem 2023). In the United States, it is approved as a food contact substance at up to 0.04% for use as UV absorber in linear low-density polyethylene polymers not to be in contact with infant formula and human milk (U.S. FDA 2023).

ToxServices assessed ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[11] 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 ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- can be found in Appendix C.

- Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not listed on the U.S. DOT list.

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

- Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is on the following lists for multiple endpoints. It is not present on any GreenScreen®-specified list for single endpoints.
    - EC – CEPA DSL: Inherently toxic in the environment
    - German FEA – Substances hazardous to waters: Class 1 – low hazard to waters

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-, as indicated in Table 2. General personal protective equipment (PPE) recommendations are presented in Table 3, below. No occupational exposure limits (OELs) were identified.

Table 2: GHS H Statements for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

H Statement	H Statement Details
No harmonized GHS H statements are reported by the European Chemicals Agency (ECHA). According to the notifications provided by companies to ECHA in REACH registrations, no hazards have been classified.	

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Eye: Safety goggles with side shields	ECHA 2023	None identified	
Hands: Chemical resistant protective gloves			
Respiratory: Particle filter with medium/high efficiency for solid particles			

Physicochemical Properties of Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-Ethylphenyl-

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is a white powder at room temperature. It has a low estimated vapor pressure and high measured boiling point, indicating that it is not likely to be very volatile. It is slightly soluble in water (0.3 mg/L). The partition coefficient suggests that it is more soluble in octanol than in water. The particle size of < 10 μm indicates that it is respirable.

Table 4: Physical and Chemical Properties of Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

Property	Value	Reference
Molecular formula	$C_{18}H_{20}N_2O_3$	PubChem 2023
SMILES Notation	CCC1=CC=CC=C1NC(=O)C(=O)NC2=CC=CC=C2OCC	PubChem 2023
Molecular weight	312.4 g/mol	PubChem 2023
Physical state	Solid	PubChem 2023
Appearance	White Dry powder	PubChem 2023, Clariant 2015
Melting point	126.9°C	ECHA 2023
Boiling point	283.4°C	ECHA 2023

Table 4: Physical and Chemical Properties of Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)		
Property	**Value**	**Reference**
Vapor pressure	0.000451 mm Hg at 25°C (estimated)	U.S. EPA 2017a
Water solubility	0.3 mg/L at 20°C	Clariant 2015, ECHA 2023
Dissociation constant	N/A	
Density/specific gravity	1.26 g/cm^3 at 23°C	ECHA 2023
Partition coefficient	Log K_{ow} = 4.9 at 25°C	ECHA 2023
Particle size	D10 = 1.28 µm D50 = 8.05 µm D90 = 24.84 µm	ECHA 2023
Bioavailability	See toxicokinetics section	

Toxicokinetics

There are no toxicokinetic data available for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-. Based on the physicochemical properties (small molecular weight, low water solubility, moderate partition coefficient, and low volatility), the ECHA dossier authors assume the extent of absorption to be 10%, < 10%, and 10% for oral, dermal, and inhalation routes of exposure. Following absorption, ECHA dossier authors state that it is most likely to be distributed to the liver and kidney (presumably because they serve as the major organs for xenobiotic metabolism and excretion), subjected to phase II metabolism, and excreted via bile and/or urine. No additional details were provided (ECHA 2023).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Moderate for carcinogenicity based on positive modeled carcinogenicity data by VEGA. Although it does not contain any structural alerts for genotoxic or nongenotoxic carcinogens, and OncoLogic predicted to be of low to marginal concern for carcinogenicity, the positive predictions of VEGA were in domain and could not be discounted. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited to marginal evidence of carcinogenicity (CPA 2018b). The confidence in the score is low as it is based on conflicting modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Toxtree 2018
  - Toxtree did not identify any structural alerts for genotoxic or nongenotoxic carcinogenicity (Appendix D).
- VEGA 2023
  - ToxServices used six VEGA models to predict the carcinogenicity of Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (Appendix E). If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70

indicate that the prediction has moderate or better predictivity (Gad 2016).
    - The CAESAR model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a carcinogen with low confidence. The global ADI is 0. Therefore, the results are not included in the weight of evidence.
    - The ISS model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a non-carcinogen with low confidence. The global ADI is 0. Therefore, the results are not included in the weight of evidence.
    - The IRFMN/Antares model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a carcinogen with moderate confidence. The global ADI = 0.745. However, the accuracy index (0.669) and concordance index (0.669) are < 0.7.
    - The IRFMN/ISSCAN-CGX model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a carcinogen with high confidence. The global ADI is 0.898.
    - The IRFMN oral carcinogenicity classification model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- to be an oral carcinogen with low reliability. The global ADI is 0. Therefore, the results are not included in the weight of evidence.
    - The IRFMN inhalation carcinogenicity classification model predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- to be an inhalation carcinogen with low reliability. The global ADI is 0. Therefore, the results are not included in the weight of evidence.
  - In summary, two of the six models produced reliable predictions with global ADIs > 0.7, and both of them predicted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a carcinogen. One of the two predictions, the one from IRFMN/ISSCAN-CGX model, was made with high confidence. Therefore, overall VEGA modeling results suggest a carcinogenic concern for the compound.
- U.S. EPA 2021
  - OncoLogic evaluated the ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a dicarbonyl. According to OncoLogic, dicarbonyls are direct-acting agents for carcinogenesis. The two substituents on the dicarbonyl group of ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- has a low baseline cancer concern. However, the inhalation route is more susceptible to direct-acting carcinogens. Therefore, the cancer concern for the oral and dermal routes are low, and for the inhalation route is marginal (Appendix F).

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for mutagenicity/genotoxicity based on negative results *in vitro* in a bacterial reverse mutation assay, a mammalian cell mutation assay, and a chromosomal aberration assay. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- 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 2023
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guideline 471. *Salmonella typhimurium* test strains TA98, TA100, TA1535, and TA1537, and *Escherichia coli* strain

WP2 *uvr*A were exposed to ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (trade name Hostavin VSU P, purity not specified) without a vehicle at 3-5,000 µg/plate with and without metabolic activation. S9 metabolic activation mix was derived from phenobarbital/beta-naphthoflavone induced rat liver. Positive controls of sodium azide, methylmethanesulfonate, 4-nitro-o-phenylene-diamine, and 2-aminoanthracene, as well as vehicle controls, were used. No cytotoxicity was observed and positive and vehicle controls were reported as valid. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restrictions).

- *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation assay conducted according to OECD Guideline 476/EU Method B.17. Chinese hamster lung fibroblasts (V79) were exposed to ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (99.23% purity) in dimethyl sulfoxide (DMSO) at 6.3-3,200 µg/mL with and without metabolic activation. S9 metabolic activation mix was derived from phenobarbital/beta-naphthoflavone induced rat liver. Positive controls of ethylmethanesulfonate and 7,12-dimethylbenzanthracene and vehicle controls were used. No cytotoxicity was observed and positive and vehicle controls were reported as valid. No increase in the mutation frequency was detected with treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restrictions).
- *In vitro*: Negative results for clastogenicity were obtained in a GLP-compliant chromosome aberration test conducted according to OECD Guideline 473/EU Method B.10. Human lymphocytes were exposed to (trade name Hostavin VSU P, purity not specified) in DMSO at up to 10 mM with and without metabolic activation. Positive controls of ethylmethanesulfonate and cyclophosphamide and vehicle controls were used. No cytotoxicity was observed and positive and vehicle controls were reported as valid. No increase in the frequency of chromosome aberrations was identified following treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restrictions).

Reproductive Toxicity (R) Score (H, M, or L): DG
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Data Gap for reproductive toxicity based on the lack of data identified for this endpoint.

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

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for developmental toxicity based on negative modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- DTU 2023
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is predicted to be negative and in domain by the Teratogenic Potential in Humans model battery, based on negative and in domain predictions by CASE Ultra, Leadscope, and SciQSAR models. It is out of domain for the developmental/reproductive toxicity library model (Appendix G).

Endocrine Activity (E) Score (H, M, or L): DG
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint. The negative prediction for estrogen activity is insufficient to determine its *in vivo* activity, and there are no data on its activity on the androgen and thyroid pathways.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is predicted to be inactive for estrogen agonism, antagonism, and binding (Appendix H).

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): L
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for acute toxicity based on an oral LD_{50} value greater than 2,000 mg/kg and a dermal LD_{50} greater than 5,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral*: $LD_{50} > 2{,}000$ mg/kg in male and female Wistar rats (GLP-compliant, OECD Guideline 423) (Klimisch 1, reliable without restrictions)
  - *Dermal*: $LD_{50} > 5{,}000$ mg/kg in male CFY rats (non-GLP compliant, similar to OECD Guideline 402) (Klimisch 2, reliable with restrictions)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): L
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for systemic toxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant following single exposures under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate and negative data and no GHS classifications are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral*: In the acute oral toxicity test conducted under GLP according to OECD Guideline 423 that identified an oral LD_{50} greater than 2,000 mg/kg in Wistar rats, animals (3/sex) received a single gavage dose of 2,000 mg/kg ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-, followed by an observation period of 14 days. No unscheduled mortality occurred. No

clinical signs of toxicity or treatment-related effects on body weights or gross pathological findings were detected (Klimisch 1, reliable without restrictions).
    - *Dermal*: In the acute dermal toxicity study (non-GLP, similar to OECD Guideline 402) that identified a dermal LD_{50} greater than 5,000 mg/kg in male CFY rats, animals (number and sex unspecified) received a single dose of 5,000 mg/kg ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a 40% suspension in aqueous gum tragacanth under occlusive conditions, followed by an observation period of 14 days. A control group was also included. No unscheduled mortality occurred. Slight erythema was detected at the application site during the first three days of the observation period. Slightly depressed body weight gains were detected in the treated animals during the first week of the observation period, but the values returned to normal during the second week. No treatment-related gross pathological alterations were detected at necropsy (Klimisch 2, reliable with restrictions).
- Based on the above results demonstrating a lack of systemic toxicity in the acute toxicity studies at doses equal to or higher than GHS classification cutoffs, ToxServices did not classify ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a specific target organ toxicant following single exposures under GHS criteria (UN 2021).

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated exposures under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - *Oral*: A pre-GLP subchronic repeated dose toxicity study conducted in a manner similar to OECD Guideline 408 was performed with Sprague-Dawley rats (20/sex/group) provided diets containing ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (trade name Sanduvor VSU, purity not specified) at 0, 1,600, 4,00, or 10,000 ppm for 13 weeks. The animals were evaluated for clinical signs of toxicity, body weight, food and water intake, hematology, clinical biochemistry, urinalysis, organ weights, gross pathology, and histopathology. No adverse treatment-related effects were identified on these parameters. Therefore, the study authors identified a NOAEL of 10,000 ppm in the diet (equivalent to 521 mg/kg/day for males and 663 mg/kg/day for females according to ECHA dossier authors) (Klimisch 2, reliable with restrictions).
- Based on the NOAEL of 521 mg/kg/day in the subchronic oral toxicity study in rats, ToxServices did not classify ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a specific target organ toxicant following repeated oral exposures under GHS criteria (UN 2021). GHS criteria define specific target organ toxicants following oral repeated exposures as chemicals that produce oral LOAELs no greater than 100 mg/kg/day in subchronic toxicity studies.

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for neurotoxicity toxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant based on

neurotoxicity following single exposures under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate and negative data and no GHS classifications are available (CPA 2018b). The confidence in the score is low as no specific neurobehavioral assessments were performed.

- 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 2023
  - *Oral*: In the previously described acute oral toxicity test conducted under GLP according to OECD Guideline 423 in Wistar rats, animals (3/sex) received a single gavage dose of 2,000 mg/kg ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-, followed by an observation period of 14 days. No unscheduled mortality occurred. No clinical signs of toxicity or treatment-related effects on body weights or gross pathological findings were detected (Klimisch 1, reliable without restrictions).
  - *Dermal*: In the previously described acute dermal toxicity study (non-GLP, similar to OECD Guideline 402) in male CFY rats, animals (number and sex unspecified) received a single dose of 5,000 mg/kg ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a 40% suspension in aqueous gum tragacanth under occlusive conditions, followed by an observation period of 14 days. A control group was also included. No unscheduled mortality occurred. Clinical signs were limited to the site of application and not indicative of neurotoxicity. No treatment-related gross pathological alterations were detected at necropsy (Klimisch 2, reliable with restrictions).
- Based on the above results demonstrating a lack of clinical signs and gross pathology findings indicative of neurotoxicity in the acute toxicity studies at doses equal to or higher than GHS classification cutoffs, ToxServices did not classify ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a specific target organ toxicant following single exposures for neurotoxicity under GHS criteria (UN 2021).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Data Gap for neurotoxicity (repeated dose) based on the lack of data identified for this endpoint.

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

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for skin sensitization based on the lack of dermal sensitization detected in mice. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- 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 2023
  - A GLP-compliant local lymph node assay (LLNA) conducted according to OECD Guideline 429/EU Method B.42 was performed with female CBA/CaOlaHsd mice (four/group)

administered topical applications of ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (trade name UV 312, purity not specified) in dimethylformamide at 1%, 2.5%, or 5% (w/w) to the dorsal surface of each ear on three consecutive days. The highest concentration tested was the highest non-irritating concentration. The stimulation indices (SIs) were 0.86, 0.94, and 0.94 for the 1%, 2.5%, and 5% solutions, respectively. Since the SIs did not exceed 3, the study authors concluded that ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was not sensitizing to the skin under the tested conditions (Klimisch 1, reliable without restriction).

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for respiratory sensitization based on extrapolation from the lack of dermal sensitization potential according to ECHA guidance (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (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 2023
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- does not contain any structural alerts for respiratory sensitization (Appendix I).
- Based on the weight of evidence and guidance from ECHA regarding assessment of respiratory sensitization potential, a score of Low was assigned. The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-, and as it does not contain any structural alerts for respiratory sensitization (OECD 2023), ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not expected to be a respiratory sensitizer.

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

Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for skin irritation/corrosivity based on the lack of dermal irritation seen in a rabbit study. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate negative data are available and there is no GHS classification (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - A pre-GLP dermal irritation test conducted according to 16 CFR §1500.41 was performed with albino rabbits (strain not specified, n=6) administered topical applications of 0.5 g 2-ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (purity not specified) in 0.5 mL

distilled water to abraded skin under occlusive dressing for 72 hours. The primary irritation score at 72 hours was 0/8. Scores of 0 to 0.5 indicate the chemical is a non-irritant. The study authors concluded that ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was not irritating to the skin under the conditions of this test (Klimisch 2, reliable with restrictions).

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *L*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for eye irritation/corrosivity based on minimal irritation seen in a rabbit study that does not warrant GHS classification. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate negative data are available and there is no GHS classification (CPA 2018b). The confidence in the score is low as the 21-day reversibility was not assessed.

- 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 2023
  - A pre-GLP ocular irritation test conducted according to 16 CFR §1500.41 was performed with albino rabbits (six total) administered ocular instillations of 75 mg undiluted ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (purity not specified). An observation period of seven days followed the instillation. The mean overall irritation scores were 0.8 after one day, 0.8 after two days, 0.8 after three days, and 0.7 after seven days (out of a maximum score of 110). The mean scores across 24, 48, and 72 hours were 0 for corneal opacity, iritis, and chemosis for all 6 animals. The mean scores across 24, 48, and 72 hours for conjunctival redness were 0, 0, 0, 1, 0.7, and 0.6 for each of the animals, respectively. The sole ocular effect was mild conjunctival inflammation detected in three rabbits, these effects were not fully reversible by the end of the 7-day observation period. The study authors concluded that ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was not irritating to the eyes under the conditions of this test (Klimisch 2, reliable with restrictions).
- Based on the weight of evidence, a score of Low was assigned. According to GHS criteria, the mean 24, 48 and 72 hours scores for corneal opacity ≥ 1, for iritis ≥ 1, for conjunctival redness ≥ 2, and/or for chemosis ≥ 2 in at least 2 out of 3 animals warrant classification to GHS Category 2A when the effects are reversible within 21 days, and to Category 2B when the effects are reversible within 7 days (UN 2021). The scores reported for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- do not warrant GHS classification. However, effects were not fully reversible within 7 days, and the 21-day reversibility was not determined due to the deviation of the study from the current OECD guidelines.

<u>Ecotoxicity (Ecotox)</u>

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for acute aquatic toxicity based on measured L/EC_{50} values >158 mg/L, >643 mg/L, and >100 mg/L in fish, daphnid, and algae, respectively. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when L/EC_{50} values are > 100 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for all three trophic levels.

- 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 2023
    - 96-hour LC_{50} > 158 mg/L and < 176 mg/L (*Cyprinus carpio*, carp, measured) (GLP-compliant, OECD Guideline 203/EU Method C.1) (Klimisch 1, reliable without restrictions)
    - 48-hour mobility EC_{50} > 643 mg/L (*Daphnia magna*, measured) (GLP-compliant, OECD Guideline/EU Method C.2) (Klimisch 1, reliable without restrictions) (GLP-compliant, OECD Guideline 202/EU Method C.2) (Klimisch 1, reliable without restrictions)
    - 72-hour growth rate EC_{50} >100 mg/L (*Desmodesmus subspicatus*, algae, nominal) (non-GLP-compliant, EU Method C.3) (Klimisch 2, reliable with restrictions)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *vH*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Very High for chronic aquatic toxicity based on estimated chronic aquatic toxicity value of 0.09 mg/L and 0.1 mg/L in fish and daphnid, respectively. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are no greater than 0.1 mg/L (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - 72-hour growth rate NOEC =100 mg/L (*D. subspicatus*, algae, nominal) (non-GLP-compliant, EU Method C.3) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2017b
    - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- belongs to the Neutral Organics ECOSAR chemical class (Appendix J). The most conservative predicted chronic values are 0.09 mg/L in fish, 0.1 mg/L in daphnia, and 0.51 mg/L in green algae. The predicted value in algae is higher than the measured water solubility of 0.3 mg/L, and therefore no effects at saturation is expected for the algae trophic level.
        - The prediction for algae is consistent with findings in the experimental algae study above.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *H*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of High for persistence based on an estimated half-life of 75 days in soil, its predicted dominant environmental compartment. GreenScreen® criteria classify chemicals as a High hazard for persistence when the half-life in soil is between 60 and 180 days (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
    - A GLP-compliant inherent biodegradability test conducted according to OECD Guideline 302C (modified MITI test) was performed with adapted domestic sewage exposed to ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- (purity not specified) at 30 mg/L for 28 days. At the end of the exposure period, no biodegradation was detected (Klimisch 1, reliable without restrictions).
- U.S. EPA 2017a

- The BIOWIN modeling Ready Biodegradable Predictor indicates that ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not expected to be readily biodegradable (Appendix K). Fugacity modeling predicts 74.4% will partition to soil with a half-life of 75 days, 25.6% will partition to water with a half-life of 37.5 days, and 0.0851% will partition to sediment with a half-life of 337.5 days.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for bioaccumulation based on an estimated BCF of 143.4. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when BCF values are between 100 and 500 (CPA 2018b). The confidence in the score is low as it is based on modeled data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017a
  - BCFBAF predicts a BCF of 794.4 using the regression-based model based on a measured log K_{ow} of 4.9, and a BC of 143.4 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix K).
    - As the value predicted using the Arnot-Gobas model considers metabolism, ToxServices selected this value over the value predicted by the regression-based model to score this endpoint.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for reactivity based on ToxServices not classifying it as being reactive following GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not classified for any of the reactivity sub endpoints following GHS criteria (CPA 2018b). The confidence in the score is low as it is not based on measured data or authoritative listing.

- 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 2023
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- does not contain functional groups associated with explosive or oxidizing properties.
- Clariant 2015
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not explosive.
  - Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- is not classified as oxidizing as it lacks organic peroxide groups.
- Based on the above information, ToxServices did not classify ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a reactive substance under GHS criteria (UN 2021).

Flammability (F) Score (vH, H, M, or L): L
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid following GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when the chemical is not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on 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 2023
    - In a non-GLP-compliant flammability test conducted according to EU Method A.10/VDI 2263, ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- did not ignite after two minutes of contact with a flame (Klimisch 1, reliable without restrictions).
- Based on the above data, ToxServices did not classify ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl- as a flammable solid under GHS criteria (UN 2021).

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

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

As shown in Table 5, Type I (input data) uncertainties in ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s NAMs dataset include lack of, or insufficient experimental data for carcinogenicity, developmental toxicity, endocrine activity, respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation, and lack of validated test methods for respiratory sensitization. Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s Type II (extrapolation output) uncertainties include lack of defined applicability domains for a few models, limitations of *in vitro* genotoxicity data in mimicking *in vivo* metabolism and their focusing on a few events in the genotoxicity process, and the lack of consideration of non-immunological mechanisms for respiratory sensitization. Some of ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-'s type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: No experimental data are available. **Developmental toxicity:** No experimental data are available. **Endocrine activity:** No experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Chronic aquatic toxicity:** No experimental data are available for the fish and aquatic invertebrate trophic levels. **Persistence:** No experimental data are available for environmental distribution and half-lives in dominant environmental compartments **Bioaccumulation:** No experimental BCF data are available and the experimental log K_{ow} suggests a bioaccumulation potential.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018).

[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).

	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]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[14] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[15]. **Endocrine activity**: The ToxCast models do not define applicability domains. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OncoLogic
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	Y	*In silico* modeling: Danish QSAR
Endocrine activity	Y	*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	

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

Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 302C Biodegradation test
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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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 Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

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	Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl)	23949-66-8	*M*	L	DG	*L*	DG	L	L	L	*L*	DG	L	*L*	L	*L*	L	*vH*	*H*	*L*	*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
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl)	2

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

Table 6

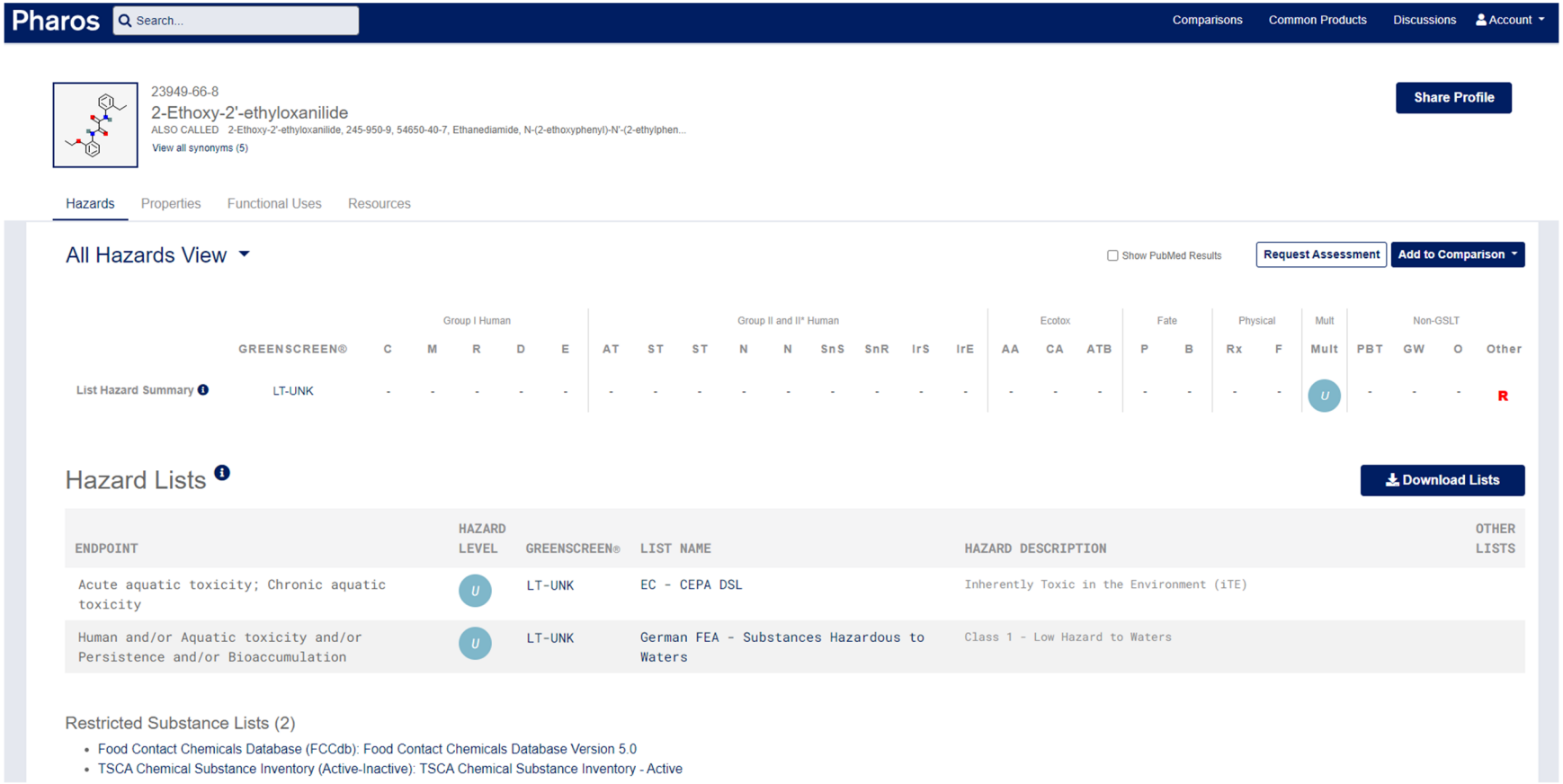
Chemical Name	Final GreenScreen® Benchmark Score
Ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl)	2

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

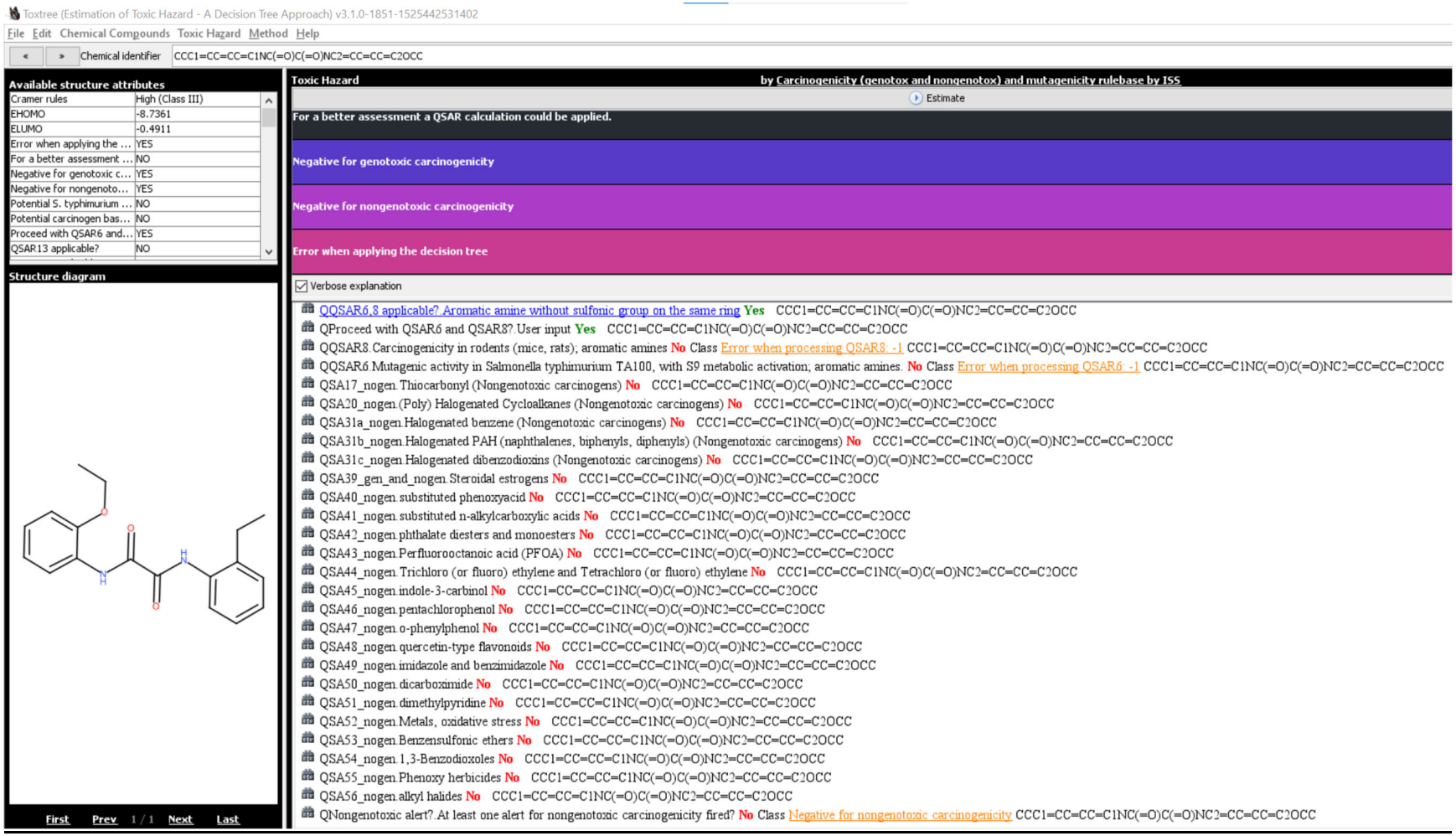
Table 5: Data Gap Assessment Table

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 Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)



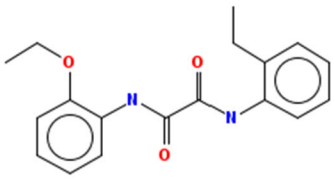
APPENDIX D: Toxtree Carcinogenicity Output for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)



APPENDIX E: VEGA Carcinogenicity Output for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

1. Prediction Summary

Prediction for compound Molecule 0

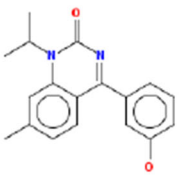


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- similar molecules found in the training set have experimental values that disagree with the predicted value
- model class assignment is uncertain
- predicted value disagrees with experimental values of training set compounds laying in the same neuron

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.502
P(NON-Carcinogen): 0.498
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

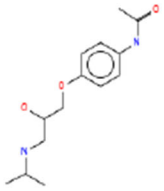
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 65765-07-3
Dataset id: 179 (Training set)
SMILES: O=C3N=C(c1cccc(O)c1)c2ccc(cc2N3C(C)C)C
Similarity: 0.825

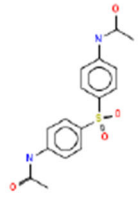
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 6673-35-4
Dataset id: 664 (Training set)
SMILES: O=C(Nc1ccc(OCC(O)CNC(C)C)cc1)C
Similarity: 0.813

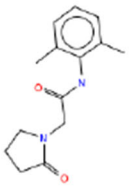
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 77-46-3
Dataset id: 714 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.813

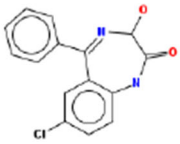
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 77191-36-7
Dataset id: 495 (Training set)
SMILES: O=C(Nc1c(cccc1C)C)CN2C(=O)CCC2
Similarity: 0.811

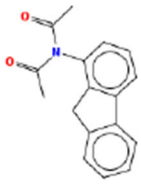
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 604-75-1
Dataset id: 620 (Training set)
SMILES: O=C1Nc3ccc(cc3(C(=NC1(O))c2ccccc2))Cl
Similarity: 0.807

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 63019-65-8
Dataset id: 203 (Training set)
SMILES: O=C(N(c3cccc2c1ccccc1Cc23)C(=O)C)C
Similarity: 0.799

Experimental value: Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.819 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.
✖	**Model class assignment reliability** Pos/Non-Pos difference = 0.003 Explanation: model class assignment is uncertain.
⚠	**Neural map neurons concordance** Neurons concordance = 0.75 Explanation: predicted value disagrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

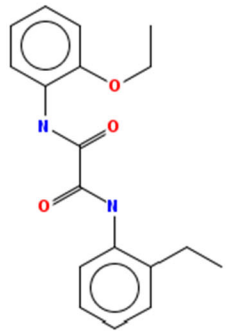
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

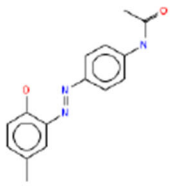


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural alerts: -
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

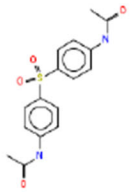


Compound #1

CAS: 2832-40-8
Dataset id: 44 (Training set)
SMILES: O=C(Nc2ccc(N=Nc1cc(ccc1(O))C)cc2)C
Similarity: 0.822

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA28ter Aromatic N-acyl amine; SA29 Aromatic diazo

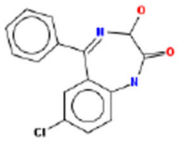


Compound #2

CAS: 77-46-3
Dataset id: 514 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.813

Experimental value: Carcinogen
Predicted value: Carcinogen

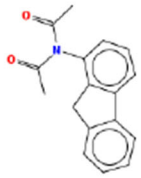
Alerts (not found in the target): SA28ter Aromatic N-acyl amine



Compound #3

CAS: 604-75-1
Dataset id: 693 (Training set)
SMILES: O=C1Nc3ccc(cc3(C(=NC1(O))c2ccccc2))Cl
Similarity: 0.807

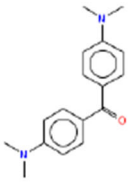
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 63019-65-8
Dataset id: 456 (Training set)
SMILES: O=C(N(c3cccc2c1ccccc1Cc23)C(=O)C)C
Similarity: 0.799

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

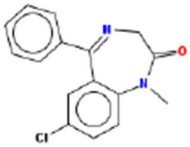


Compound #5

CAS: 90-94-8
Dataset id: 203 (Training set)
SMILES: O=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.796

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA28bis Aromatic mono- and dialkylamine



Compound #6

CAS: 439-14-5
Dataset id: 841 (Training set)
SMILES: O=C1N(c3ccc(cc3(C(=NC1)c2ccccc2))Cl)C
Similarity: 0.795

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.817
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

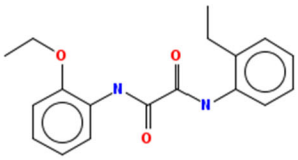
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0



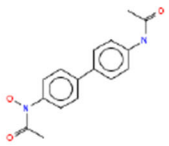
Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- accuracy of prediction for similar molecules found in the training set is not optimal
- some similar molecules found in the training set have experimental values that disagree with the predicted value
The following relevant fragments have been found: Carcinogenity alert no. 28; Carcinogenity alert no. 37; Carcinogenity alert no. 38

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 3
Structural alerts: Carcinogenity alert no. 28; Carcinogenity alert no. 37; Carcinogenity alert no. 38
Reliability: the predicted compound could be out of the Applicability Domain of the model
Remarks:
none

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values

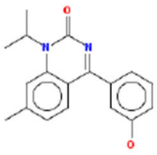


Compound #1

CAS: N.A.
Dataset id: 885 (Training set)
SMILES: O=C(Nc1ccc(cc1)c2ccc(cc2)N(O)C(=O)C)C
Similarity: 0.843

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 64



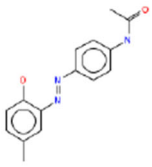
Compound #2

CAS: N.A.
Dataset id: 179 (Training set)
SMILES: O=C3N=C(c1cccc(O)c1)c2ccc(cc2N3C(C)C)C
Similarity: 0.825

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28

Alerts (not found in the target): Carcinogenity alert no. 33



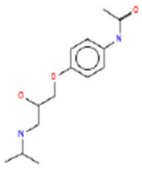
Compound #3

CAS: N.A.
Dataset id: 833 (Training set)
SMILES: O=C(Nc2ccc(N=Nc1cc(ccc1(O))C)cc2)C
Similarity: 0.822

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37

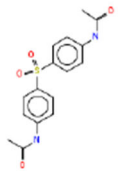
Alerts (not found in the target): Carcinogenity alert no. 33; Carcinogenity alert no. 36; Carcinogenity alert no. 71



Compound #4

CAS: N.A.
Dataset id: 674 (Training set)
SMILES: O=C(Nc1ccc(OCC(O)CNC(C)C)cc1)C
Similarity: 0.813

Experimental value: NON-Carcinogen
Predicted value: Possible NON-Carcinogen

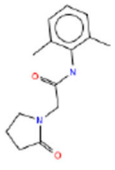


Compound #5

CAS: N.A.
Dataset id: 718 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.813

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 110



Compound #6

CAS: N.A.
Dataset id: 494 (Training set)
SMILES: O=C(Nc1c(cccc1C)C)CN2C(=O)CCC2
Similarity: 0.811

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	**Global AD Index** AD index = 0.745 Explanation: the predicted compound could be out of the Applicability Domain of the model.
✓	**Similar molecules with known experimental value** Similarity index = 0.83 Explanation: strongly similar compounds with known experimental value in the training set have been found.
⚠	**Accuracy of prediction for similar molecules** Accuracy index = 0.669 Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.
⚠	**Concordance for similar molecules** Concordance index = 0.669 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✓	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

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

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

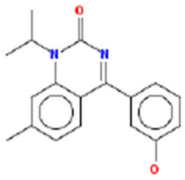
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 1 of 3:

Fragment found: Carcinogenity alert no. 28

Structural alert for carcinogenity defined by the SMARTS: Cc1ccccc1N

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

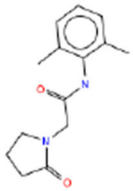


CAS: N.A.
Dataset id: 179 (Training set)
SMILES: O=C3N=C(c1cccc(O)c1)c2ccc(cc2N3C(C)C)C
Similarity: 0.825

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28

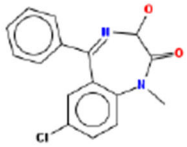
Alerts (not found in the target): Carcinogenity alert no. 33



CAS: N.A.
Dataset id: 494 (Training set)
SMILES: O=C(Nc1c(cccc1C)C)CN2C(=O)CCC2
Similarity: 0.811

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28



CAS: N.A.
Dataset id: 1482 (Training set)
SMILES: O=C1N(c3ccc(cc3(C(=NC1(O))c2ccccc2))Cl)C
Similarity: 0.809

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28

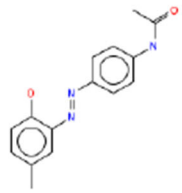
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 2 of 3:

Fragment found: Carcinogenity alert no. 37

Structural alert for carcinogenity defined by the SMARTS: Nc1ccccc1O

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

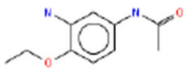


CAS: N.A.
Dataset id: 833 (Training set)
SMILES: O=C(Nc2ccc(N=Nc1cc(ccc1(O))C)cc2)C
Similarity: 0.822

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37

Alerts (not found in the target): Carcinogenity alert no. 33; Carcinogenity alert no. 36; Carcinogenity alert no. 71

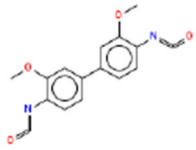


CAS: N.A.
Dataset id: 36 (Training set)
SMILES: O=C(Nc1ccc(OCC)c(N)c1)C
Similarity: 0.787

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37; Carcinogenity alert no. 38

Alerts (not found in the target): Carcinogenity alert no. 40



CAS: N.A.
Dataset id: 256 (Training set)
SMILES: O=C=Nc1ccc(cc1(OC))c2ccc(N=C=O)c(OC)c2
Similarity: 0.781

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37; Carcinogenity alert no. 38

Alerts (not found in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 65

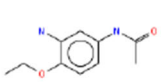
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts - 3 of 3:

Fragment found: Carcinogenity alert no. 38

Structural alert for carcinogenity defined by the SMARTS: COc1ccccc1N

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

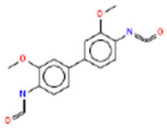


CAS: N.A.
Dataset id: 36 (Training set)
SMILES: O=C(Nc1ccc(OCC)c(N)c1)C
Similarity: 0.787

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37; Carcinogenity alert no. 38

Alerts (not found in the target): Carcinogenity alert no. 40

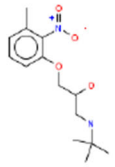


CAS: N.A.
Dataset id: 256 (Training set)
SMILES: O=C=Nc1ccc(cc1(OC))c2ccc(N=C=O)c(OC)c2
Similarity: 0.781

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 37; Carcinogenity alert no. 38

Alerts (not found in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 65



CAS: N.A.
Dataset id: 862 (Training set)
SMILES: O=[N+]([O-])c1c(OCC(O)CNC(C)(C)C)cccc1C
Similarity: 0.781

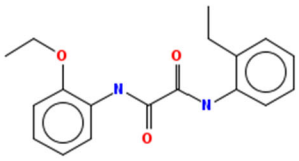
Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 28; Carcinogenity alert no. 37; Carcinogenity alert no. 38

Alerts (not found in the target): Carcinogenity alert no. 63; Carcinogenity alert no. 64

1. Prediction Summary

Prediction for compound Molecule 0

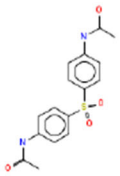


Prediction: Reliability:

Prediction is Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.
The following relevant fragments have been found: Carcinogenity alert no. 22; Carcinogenity alert no. 42

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 2
Structural alerts: Carcinogenity alert no. 22; Carcinogenity alert no. 42
Reliability: the predicted compound is into the Applicability Domain of the model
Remarks:
none

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

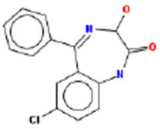


Compound #1

CAS: 77-46-3
Dataset id: 426 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.813

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

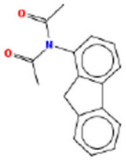


Compound #2

CAS: 604-75-1
Dataset id: 557 (Training set)
SMILES: O=C1Nc3ccc(cc3(C(=NC1(O))c2ccccc2))Cl
Similarity: 0.807

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

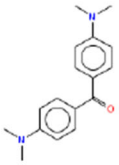


Compound #3

CAS: 63019-65-8
Dataset id: 379 (Training set)
SMILES: O=C(N(c3cccc2c1ccccc1Cc23)C(=O)C)C
Similarity: 0.799

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42



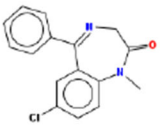
Compound #4

CAS: 90-94-8
Dataset id: 164 (Training set)
SMILES: O=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.796

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found in the target): Carcinogenity alert no. 41

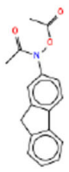


Compound #5

CAS: 439-14-5
Dataset id: 754 (Training set)
SMILES: O=C1N(c3ccc(cc3(C(=NC1)c2ccccc2))Cl)C
Similarity: 0.795

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42



Compound #6

CAS: 6098-44-8
Dataset id: 787 (Training set)
SMILES: O=C(ON(c2ccc3c1ccccc1Cc3(c2))C(=O)C)C
Similarity: 0.792

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

Alerts (not found in the target): Carcinogenity alert no. 36

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.898
Explanation: the predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.806
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 1
Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.

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

Symbols explanation:

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

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

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

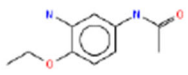
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 22

Structural alert for carcinogenity defined by the SMARTS: O(c1ccc(cc1N))C

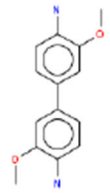
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 17026-81-2
Dataset id: 117 (Training set)
SMILES: O=C(Nc1ccc(OCC)c(N)c1)C
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen

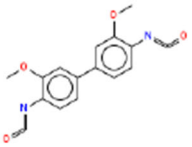
Alerts (found also in the target): Carcinogenity alert no. 22; Carcinogenity alert no. 42



CAS: 20325-40-0
Dataset id: 534 (Training set)
SMILES: O(c1cc(ccc1(N))c2ccc(N)c(OC)c2)C
Similarity: 0.785

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 22; Carcinogenity alert no. 42



CAS: 91-93-0
Dataset id: 148 (Training set)
SMILES: O=C=Nc1ccc(cc1(OC))c2ccc(N=C=O)c(OC)c2
Similarity: 0.781

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 22; Carcinogenity alert no. 42

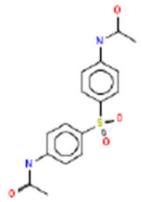
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 42

Structural alert for carcinogenity defined by the SMARTS: Nc1ccccc1

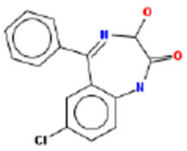
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 77-46-3
Dataset id: 426 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.813

Experimental value: Carcinogen
Predicted value: Carcinogen

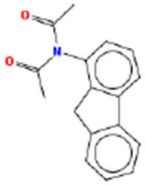
Alerts (found also in the target): Carcinogenity alert no. 42



CAS: 604-75-1
Dataset id: 557 (Training set)
SMILES: O=C1Nc3ccc(cc3(C(=NC1(O))c2ccccc2))Cl
Similarity: 0.807

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42



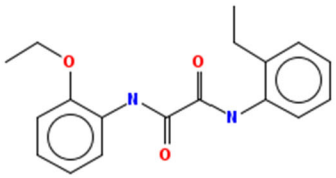
CAS: 63019-65-8
Dataset id: 379 (Training set)
SMILES: O=C(N(c3cccc2c1ccccc1Cc23)C(=O)C)C
Similarity: 0.799

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 42

1. Prediction Summary

Prediction for compound Molecule 0

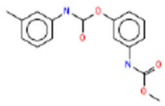


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Oral Carcinogenic class: Carcinogen
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

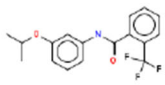
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 13684-63-4
Dataset id: 631 (Training set)
SMILES: O=C(Oc1cccc(c1)NC(=O)OC)Nc2cccc(c2)C
Similarity: 0.818

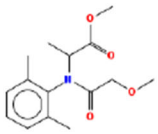
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 66332-96-5
Dataset id: 521 (Training set)
SMILES: O=C(Nc1cccc(OC(C)C)c1)c2ccccc2C(F)(F)F
Similarity: 0.81

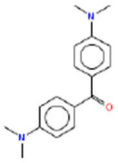
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 57837-19-1
Dataset id: 569 (Test set)
SMILES: O=C(OC)C(N(C(=O)COC)c1c(cccc1C)C)C
Similarity: 0.807

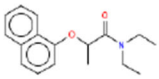
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 90-94-8
Dataset id: 206 (Training set)
SMILES: O=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.796

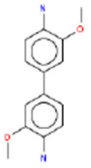
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 15299-99-7
Dataset id: 601 (Training set)
SMILES: O=C(N(CC)CC)C(Oc1cccc2ccccc12)C
Similarity: 0.794

Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #6

CAS: 119-90-4
Dataset id: 120 (Training set)
SMILES: O(c1cc(ccc1(N))c2ccc(N)c(OC)c2)C
Similarity: 0.785

Experimental value: Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0 Explanation: the predicted compound is outside the Applicability Domain of the model.
✔	**Similar molecules with known experimental value** Similarity index = 0.814 Explanation: strongly similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✖	**Concordance for similar molecules** Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

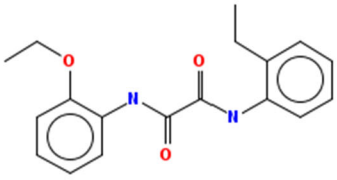
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0

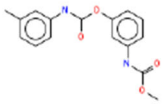


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc1ccccc1(OCC))C(=O)Nc2ccccc2CC
Experimental value: -
Predicted Inhalation Carcinogenic class: Carcinogen
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

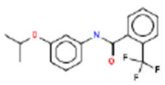
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 13684-63-4
Dataset id: 617 (Training set)
SMILES: O=C(Oc1cccc(c1)NC(=O)OC)Nc2cccc(c2)C
Similarity: 0.818

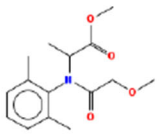
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 66332-96-5
Dataset id: 494 (Training set)
SMILES: O=C(Nc1cccc(OC(C)C)c1)c2ccccc2C(F)(F)F
Similarity: 0.81

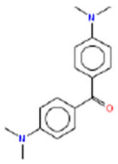
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 57837-19-1
Dataset id: 548 (Training set)
SMILES: O=C(OC)C(N(C(=O)COC)c1c(cccc1C)C)C
Similarity: 0.807

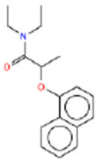
Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #4

CAS: 90-94-8
Dataset id: 173 (Test set)
SMILES: O=C(c1ccc(cc1)N(C)C)c2ccc(cc2)N(C)C
Similarity: 0.796

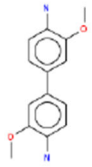
Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #5

CAS: 15299-99-7
Dataset id: 582 (Training set)
SMILES: O=C(N(CC)CC)C(Oc1cccc2ccccc12)C
Similarity: 0.794

Experimental value: NON-Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 119-90-4
Dataset id: 430 (Test set)
SMILES: O(c1cc(ccc1(N))c2ccc(N)c(OC)c2)C
Similarity: 0.785

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.814
Explanation: strongly similar compounds with known experimental value in the training set have been found.

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

Concordance for similar molecules
Concordance index = 0
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.

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

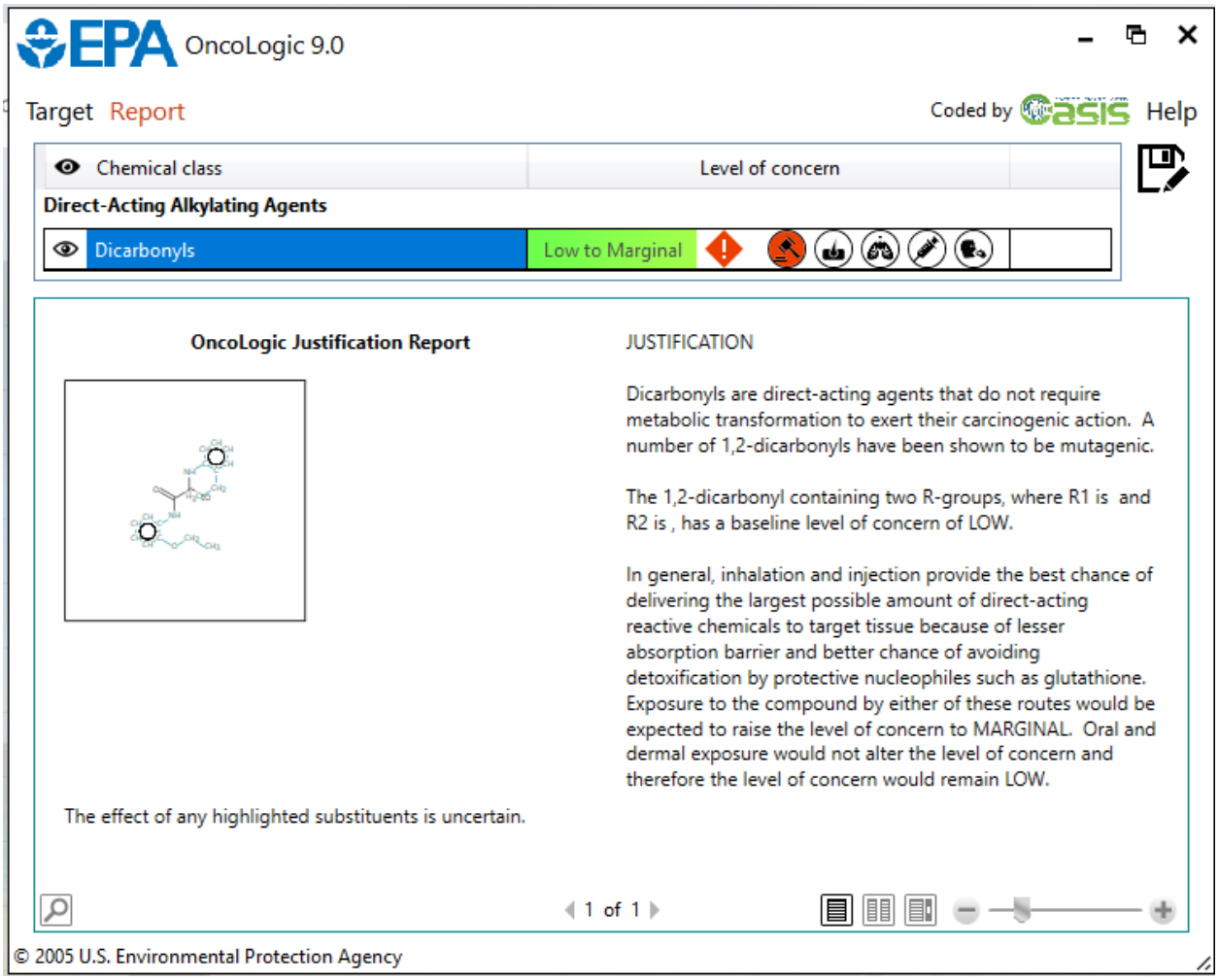
Symbols explanation:

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

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

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

APPENDIX F: OncoLogic Output for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

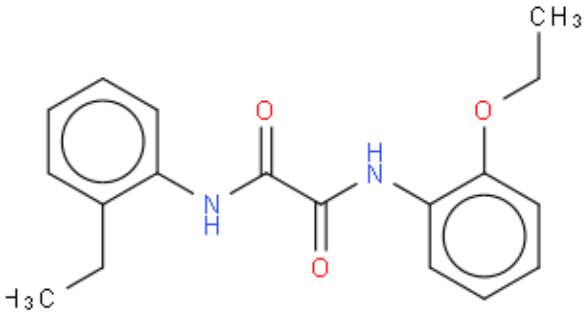


APPENDIX G: Danish QSAR Modeling Results for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

Danish (Q)SAR Database, https://qsar.food.dtu.dk Date: 14-07-2023

(Q)SAR predicted profile

Structure (as used for QSAR prediction):



SMILES (used for QSAR prediction): C(=O)(C(=O)Nc1c(CC)cccc1)Nc1c(OCC)cccc1

ID

Registry Number	23949-66-8	PubChem CID	
REACH EC Number (pre-registration, by 2013)	245-950-9	REACH EC Number (registration, 2019 or 2022)	245-950-9
REACH registration (2022)	Yes	REACH registration cumulated minimum annual tonnage (2022)	10
EU CLP Harmonized Classification*		DK-EPA / DTU QSAR-based CLP Advisory Classification	
EU Biocide active substances		EU Pesticide active substances	
EU EFSA Botanical substances		US TSCA (Oct. 2021)	Yes
Tox21 (2019)		ToxCast (Oct. 2021)	
Molecular Formula	C18 H20 N2 O3	Molecular weight (g/mole)	312.37
Chemical Name	N-(2-ethoxyphenyl)-N'-(2-ethylphenyl)oxamide		

(Annex VI to CLP up to and including the 9th ATP, and including Nordic Council of Minister SPIN list for group entries)

Developmental Toxicity

	Battery	CASE Ultra	Leadscope	SciQSAR
Teratogenic Potential in Humans	NEG_IN	NEG_IN	NEG_IN	NEG_IN

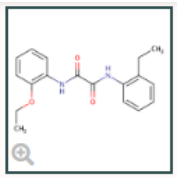
DTU-developed models based on commercial training set

.	Exp	Prediction_Domain
Developmental/Reproductive Toxicity library (PG) v1.1.2		NEG_low_OUT

VEGA model

Profiler-type of predictions to be used as supporting information together with relevant QSAR predictions

APPENDIX H: ToxCast Endocrine Modeling Results for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)



N-(2-Ethoxyphenyl)-N'-(2-ethylphenyl)oxa...

23949-66-8 | DTXSID1066944

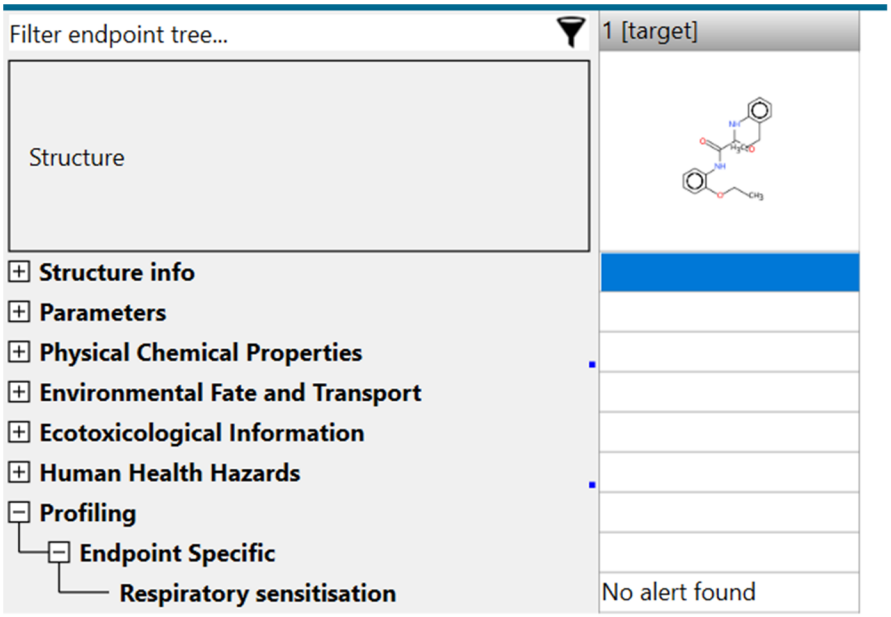
Searched by CASRN

Bioactivity - ToxCast: Models

ToxCast Model Predictions

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

APPENDIX I: OECD Toolbox Respiratory Sensitization Results for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)



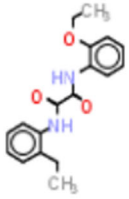
APPENDIX J: ECOSAR Modeling Results for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
23949668	Ethanediamide, N-(2-ethoxyphenyl)-N -(2-ethylphenyl)-	O=C(Nc(c(OCC)ccc1)c1)C(=O)Nc(c(ccc2)CC)c2

Structure



Details	
Mol Wt	312.37
Selected LogKow	4.9
Selected Water Solubility (mg/L)	0.3
Selected Melting Point (°C)	126.9
Estimated LogKow	3.69
Estimated Water Solubility (mg/L)	0.37
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	0.64	5	• 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
Daphnid	48h	LC50	0.47	5	• 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
Green Algae	96h	EC50	1.07	6.4	• 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
Fish		ChV	0.09	8	
Daphnid		ChV	0.1	8	
Green Algae		ChV	0.51	8	• 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
Fish (SW)	96h	LC50	0.82	5	• 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
Mysid	96h	LC50	0.09	5	

APPENDIX K: EPI Suite™ Modeling Results for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- (CAS #23949-66-8)

(Estimated values included in the GreenScreen® are highlighted and bolded)

CAS Number: 23949-66-8
SMILES : O=C(Nc(c(OCC)ccc1)c1)C(=O)Nc(c(ccc2)CC)c2
CHEM : Ethanediamide, N-(2-ethoxyphenyl)-N -(2-ethylphenyl)-
MOL FOR: C18 H20 N2 O3
MOL WT : 312.37
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 4.90
Boiling Point (deg C) : 283.40
Melting Point (deg C) : 126.90
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): 0.3
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 3.69

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 544.79 (Adapted Stein & Brown method)
Melting Pt (deg C): 233.52 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0.000451 (Modified Grain method)
VP (Pa, 25 deg C) : 0.0601 (Modified Grain method)
Subcooled liquid VP: 0.00469 mm Hg (25 deg C, Mod-Grain method)
: 0.625 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.3676
log Kow used: 4.90 (user entered)
melt pt used: 126.90 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 4.4383 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 5.58E-013 atm-m3/mole (5.65E-008 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: 6.179E-004 atm-m3/mole (6.261E+001 Pa-m3/mole)
VP: 0.000451 mm Hg (source: MPBPVP)
WS: 0.3 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 4.90 (user entered)
Log Kaw used: -10.642 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 15.542
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.2057
Biowin2 (Non-Linear Model) : 0.9989
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.2675 (weeks-months)
Biowin4 (Primary Survey Model) : 3.8165 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.3375
Biowin6 (MITI Non-Linear Model): 0.1000
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -1.1400
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): 0.625 Pa (0.00469 mm Hg)
Log Koa (Koawin est): 15.542
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 4.8E-006
Octanol/air (Koa) model: 855
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.000173
Mackay model : 0.000384
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 96.1450 E-12 cm3/molecule-sec
Half-Life = 0.111 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 1.335 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.000278 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 30.17 L/kg (MCI method)
Log Koc: 1.480 (MCI method)
Koc : 1547 L/kg (Kow method)
Log Koc: 3.190 (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 = 2.900 (BCF = 794.4 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.4604 days (HL = 0.3464 days)
Log BCF Arnot-Gobas method (upper trophic) = 2.156 (BCF = 143.4)
Log BAF Arnot-Gobas method (upper trophic) = 2.157 (BAF = 143.4)
log Kow used: 4.90 (user entered)

Volatilization from Water:
Henry LC: 5.58E-013 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 1.854E+009 hours (7.727E+007 days)
Half-Life from Model Lake : 2.023E+010 hours (8.429E+008 days)

Removal In Wastewater Treatment:
Total removal: 74.28 percent
Total biodegradation: 0.65 percent
Total sludge adsorption: 73.63 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**5.62e-006**	**2.67**	**1000**
Water	**25.6**	**900**	**1000**
Soil	**74.4**	**1.8e+003**	**1000**
Sediment	**0.0851**	**8.1e+003**	**0**

Persistence Time: 1.35e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	5.62e-006	2.67	1000
Water	25.6	900	1000
water	(25.5)		
biota	(0.101)		
suspended sediment	(0.00115)		
Soil	74.4	1.8e+003	1000
Sediment	0.0851	8.1e+003	0

Persistence Time: 1.35e+003 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.5e-006	2.67	1000
Water	8.6	900	1000
water	(8.17)		
biota	(0.0325)		
suspended sediment	(0.399)		
Soil	75.6	1.8e+003	1000
Sediment	15.8	8.1e+003	0

Persistence Time: 2.17e+003 hr

APPENDIX L: Change in Benchmark Score

Table 6 provides a summary of changes to ToxServices' GreenScreen® Benchmark™ for ethanediamide, N-(2-ethoxyphenyl)-N'-2-ethylphenyl-. The original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark U (BM-U) score. The benchmark score is changed to BM-2 with a version 1.4 update in the current assessment, due to availability of new data and updated modeling tools.

Table 6: Change in GreenScreen® Benchmark™ for Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl-

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
November 20, 2014	BM-U	v. 1.2	Original assessment
August 28, 2023	BM-2	v. 1.4	Benchmark updated to BM-2. The GreenScreen® assessment was updated with a v.1.4 template.

Licensed GreenScreen® Profilers

Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- GreenScreen® Evaluation (v.1.2) Prepared by:

SIGNATURE BLOCK

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- GreenScreen® Evaluation (v.1.2) QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC

Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- GreenScreen® Evaluation (v.1.4) Updated by:

SIGNATURE BLOCK

Megan B. Boylan, M.S.
Toxicologist
ToxServices LLC

Ethanediamide, N-(2-Ethoxyphenyl)-N'-2-ethylphenyl- GreenScreen® Evaluation (v.1.2) QC'd by:

SIGNATURE BLOCK

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