BENZENESULFONAMIDE, 4-METHYL-N-[[[3-[[(4-METHYLPHENYL)SULFONYL]OXY]PHENYL] AMINO]CARBONYL]-)

(CAS #232938-43-1)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: June 1, 2020

Expiration Date: June 1, 2025

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GreenScreen® Executive Summary for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is a white powder under standard temperature and pressure. It is slightly soluble in water, non-volatile and non-flammable. Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is used as a fixing and coloring agent, is used in the manufacture of paper, pulp, and paper products, and has been identified as a replacement for bisphenol A that is used as a color developer in thermal receipts.

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) 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 + High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)
  - High P + Moderate Group I Human Health Hazard (carcinogenicity-C, reproductive toxicity-R and developmental toxicity-D)
  - High P + Moderate Group II* Human Health Hazard (repeated dose systemic toxicity-STr*)
- Benchmark 2e
  - Moderate Group I Human Health Hazard (C, R and D)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Hazard Summary Table for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-)

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
						single	repeat*	single	repeat*										
M	L	*M*	*M*	DG	L	L	M	*L*	L	L	*L*	L	L	H	H	*H*	vL	L	L

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

GreenScreen® Chemical Assessment for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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Title: Senior Toxicologist
Organization: ToxServices LLC
Date: April 20, 2020

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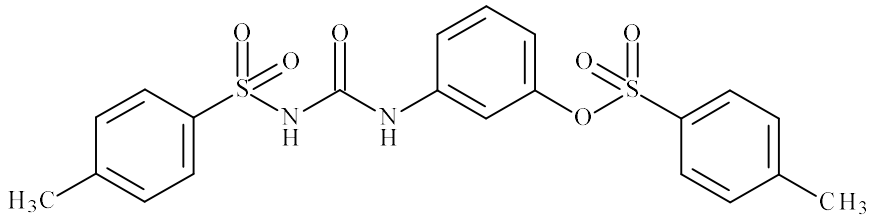
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: June 1, 2020

Expiration Date: June 1, 2025[2]

Chemical Name: Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-)

CAS Number: 232938-43-1

Chemical Structure(s):



Also called:
EC 432-520-2; 3-((((4-Methylphenyl)sulfonyl)carbamoyl)amino)phenyl 4-methylbenzenesulfonate (ChemIDplus 2020); Pergafast 201; 3-(3-Tosylureido)phenyl p-toluenesulfonate; DTXSID90872910; N-(p-Toluolsulfonyl)-N'-(3-(p-toluolsulfonyloxy)phenyl)harnstoff; 3-({[(4-methylphenyl)sulfonyl]carbamoyl}amino)phenyl 4-methylbenzenesulfonate (PubChem 2020)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A sufficiently complete toxicological database was available to assign a Benchmark Score for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-). The United States Environmental Protection Agency (U.S. EPA) Comptox dashboard identifies CAS #276693-33-5 as a similar compound with 99% similarity but no data were identified for this compound. Therefore, no surrogates were used in this assessment.

Identify Applications/Functional Uses:
1. Fixing and coloring agent and in the manufacture of paper, pulp, and paper products (U.S. EPA 2020).

[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).

2. Replacement for bisphenol A used as a color developer in thermal receipts (DEPA 2014, Björnsdotter et al. 2017a, NTP 2017).

Known Impurities[3]:
No information is available. The screen is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-)[4,5 6,7]: Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

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

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Summary Table for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-)

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
						single	repeat*	single	repeat*										
M	**L**	*M*	*M*	DG	**L**	**L**	**M**	*L*	**L**	**L**	*L*	**L**	**L**	**H**	**H**	*H*	**vL**	**L**	**L**

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

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

Environmental Transformation Products

The hydrolysis half-life of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy] phenyl] amino]carbonyl]-) was estimated to be greater than one year at 25°C and pH 7 based on the results of a GLP-compliant OECD Guideline 111/EU Method C.7 hydrolysis test (ECHA 2020a). No hydrolysis products were identified in this study. ToxServices predicted the hydrolysis products of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) under acidic, neutral, and basic conditions using OECD QSAR Toolbox (OECD 2020). Under acidic and basic conditions, toluene-4-sulphonamide (CAS #70-55-3) and [3-(p-tolylsulfonyloxy)phenyl]carbamic acid (CAS #NA)[8] were identified as hydrolysis products. Under neutral conditions, carbon dioxide (CAS #124-38-9) and p-toluenesulfonic acid 3-aminophenyl ester (CAS #3865-15-4) were identified in addition to toluene-4-sulphonamide and [3-(p-tolylsulfonyloxy)phenyl]carbamic acid.

ToxServices considered all four of these hydrolysis products to be feasible hydrolysis products because they are predicted to be formed under neutral pH, but carbon dioxide is not relevant since it is one of the ultimate biodegradation/mineralization products per Section 11.4.3 of the GreenScreen® Guidance (CPA 2018b). ToxServices considers the remaining three hydrolysis products to be relevant. Because none of these three hydrolysis products are LT-1 chemicals, ToxServices did not modify the Benchmark Score for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) based on 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	Toluene-4-sulphonamide	70-55-3	Yes	Yes	LT-UNK
End	Hydrolysis	[3-(p-Tolylsulfonyloxy) phenyl]carbamic acid	N/A	Yes	Yes	Not listed in Pharos database
End	Hydrolysis	Carbon dioxide	124-38-9	Yes	No	LT-UNK
End	Hydrolysis	p-Toluenesulfonic acid 3-aminophenyl ester	3865-15-4	Yes	Yes	Not listed in Pharos database

Introduction

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is used as a fixing and coloring agent and in the manufacture of paper, pulp, and paper products (U.S. EPA 2020). It has been identified as a replacement for bisphenol A used as a color developer in thermal receipts (DEPA 2014, Björnsdotter et al. 2017a, NTP 2017).

ToxServices assessed benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

[8] SMILES: Cc1ccc(cc1)S(=O)(=O)Oc1cccc(NC(O)=O)c1.
[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 2020) 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).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2020). 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 2015a).

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not listed on the SCP SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2020) 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 Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) can be found in Appendix C.

- Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not listed on the U.S. DOT list.
- Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not on any lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

A harmonized EU GHS classification is available for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-); it is classified as a GHS Category 2 chronic aquatic toxicant (H411) (ECHA 2020b).

Table 2: H Statements for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1) (ECHA 2020b)

H Statement	H Statement Details
H411	Toxic to aquatic life with long lasting effects

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-Methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (CAS #232938-43-1)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, safety glasses, protective clothing, particle filter	BASF 2017 SCBT 2019	OSHA PEL, 8-hour TWA: 2.1 mg/m^3	BASF 2017

OSHA: Occupational Safety and Health Administration
PEL: Permissible Exposure Limit
TWA: Time Weighted Average

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

Physicochemical Properties of Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl] oxy]phenyl] Amino]carbonyl]-)

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is a white, powdery solid under standard temperature and pressure. It has a low vapor pressure (1.01 x 10^{-14} mm Hg) indicating that it exists mostly in the solid phase. It is slightly soluble in water (34.7 mg/L), and is more soluble in octanol than in water (log K_{ow} = 2.6). Its log K_{ow} of 2.6 suggests it does not have significant bioaccumulation potential.

Table 4: Physical and Chemical Properties of Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

Property	Value	Reference
Molecular formula	$C_{21}H_{20}N_2O_6S_2$	PubChem 2020
SMILES Notation	CC1=CC=C(C=C1)S(=O)(=O)NC(=O)NC2=CC(=CC=C2)OS(=O)(=O)C3=CC=C(C=C3)C	PubChem 2020
Molecular weight	460.5 g/mol	PubChem 2020
Physical state	Solid	ECHA 2020a
Appearance	White powder	ECHA 2020a
Melting point	157.7°C (OECD 102)	ECHA 2020a
Boiling point	Decomposes > 200 to > 210°C without boiling (DIN 51007, OECD 103)	ECHA 2020a
Vapor pressure	1.35 x 10^{-12} Pa (1.01 x 10^{-14} mm Hg) at 25°C (OECD 104)	ECHA 2020a
Water solubility	34.7 mg/L at 20°C (OECD 105)	ECHA 2020a
Dissociation constant	No dissociation detected (OECD 112) pKa1 = 5.3 pKa2 = -3.8 pKa3 = -13.6	ECHA 2020a Björnsdotter et al. 2017a
Density/specific gravity	1,412 kg/m^3 at 20.9°C (OECD 109)	ECHA 2020a
Partition coefficient	Log K_{ow} = 2.6 at 20°C (OECD 117)	ECHA 2020a

Toxicokinetics

A GLP-compliant dermal absorption test conducted according to OECD Guideline 428 was performed with human split thickness skin preparations (five/group) exposed to single topical applications of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) at 10 or 5,000 µg/cm^2 for eight hours (ECHA 2020a). The carrier for the low dose group was an aqueous suspension of 0.5% carboxymethyl cellulose (CMC), and the carrier for the high dose group was acidified water meant to simulate a mixture of sweat and the test substance on the surface of the skin. At the end of the treatment period, 1.33% and 0.05% of the low and high doses were absorbed into or through the skin (Klimisch 1, reliable without restriction).

No measured data on distribution, metabolism, or elimination/excretion were identified for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-). Using OECD QSAR Toolbox (OECD 2020), the following metabolites are predicted for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-):

- *In vivo* rat metabolism simulator
    - [2-Hydroxy-5-(p-tolylsulfonylcarbamoylamino)phenyl] 4-methylbenzenesulfonate (CAS #NA)[12]
    - 1-(3-Hydroxyphenyl)-3-(4-methylphenyl)sulfonylurea (CAS #NA)[13]
    - p-Toluenesulfonic acid (CAS #104-15-4)
    - 4-[(3-hydroxyphenyl)carbamoylsulfamoyl]benzoic acid (CAS #NA)[14]
    - 1-[4-(hydroxymethyl)phenyl]sulfonyl-3-(3-hydroxyphenyl)urea (CAS #NA)[15]
    - 1-(4-formylphenyl)sulfonyl-3-(3-hydroxyphenyl)urea (CAS #NA)[16]
- Rat liver S9 metabolism simulator
    - 1-(3-Hydroxyphenyl)-3-(4-methylphenyl)sulfonylurea (CAS #NA)
    - p-Toluenesulfonic acid (CAS #104-15-4)
    - 1-[4-(hydroxymethyl)phenyl]sulfonyl-3-(3-hydroxyphenyl)urea (CAS #NA)
    - 1-(4-formylphenyl)sulfonyl-3-(3-hydroxyphenyl)urea (CAS #NA)
- Skin metabolism simulator
    - [2-Hydroxy-5-(p-tolylsulfonylcarbamoylamino)phenyl] 4-methylbenzenesulfonate (CAS #NA)
    - [3-(p-Tolylsulfonylcarbamoylamino)phenyl] 4-(hydroxymethyl)benzenesulfonate (CAS #NA)[17]
    - [3-[[4-(hydroxymethyl)phenyl]sulfonylcarbamoylamino]phenyl] 4-methylbenzenesulfonate[18]

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *M*
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Moderate for carcinogenicity based on the presence of structural alerts for non-genotoxic carcinogenicity and no measured carcinogenicity data. Toxtree identified two structural alerts. One of the alerts was not reliable based on the ISS modeling in VEGA, which also identified this structural alert and determined that the compound is outside its applicability model. However, the carcinogenic potential of the other structural alert could not be ruled out. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when limited or marginal evidence of carcinogenicity is available (CPA 2018b). The confidence in the score is low as it is based on modeling.

- 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
    - Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) contains structural alerts for non-genotoxic carcinogenicity ("Aromatic amine without sulfonic group on the same ring" and "Benzenesulfonic ethers"). It does not contain structural alerts for genotoxic carcinogenicity. See Appendix D.

[12] Cc1ccc(cc1)S(=O)(=O)NC(=O)Nc1ccc(O)c(OS(=O)(=O)c2ccc(C)cc2)c1
[13] Cc1ccc(cc1)S(=O)(=O)NC(=O)Nc1cccc(O)c1
[14] OC(=O)c1ccc(cc1)S(=O)(=O)NC(=O)Nc1cccc(O)c1
[15] OCc1ccc(cc1)S(=O)(=O)NC(=O)Nc1cccc(O)c1
[16] Oc1cccc(NC(=O)NS(=O)(=O)c2ccc(C=O)cc2)c1
[17] Cc1ccc(cc1)S(=O)(=O)NC(=O)Nc1cccc(OS(=O)(=O)c2ccc(CO)cc2)c1
[18] Cc1ccc(cc1)S(=O)(=O)Oc1cccc(NC(=O)NS(=O)(=O)c2ccc(CO)cc2)c1

- VEGA 2019
    - ToxServices attempted to model the carcinogenic potential of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) using the following VEGA models: CAESAR v2.1.9, ISS v1.0.2, IRFMN/Antares v1.0.0, IRFMN/ISSCAN-CGX v1.0.0, IRFMN oral classification model v1.0.0, and IRFMN inhalation classification model v1.0.0. However, the chemical was not in the applicability domain (AD) of the six models (global AD index < 0.7). Therefore, the model results were not used to evaluate the carcinogenicity of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-). Specifically, for the ISS model, which is built upon the Toxtree carcinogenicity model, the following alert for carcinogenicity was identified: benzenesulfonic ethers. The low confidence level from the ISS model indicates that this structure alert in Toxtree does not adequately predicts the carcinogenicity outcome. See Appendix E.
- U.S. EPA 2013
    - ToxServices attempted to model the carcinogenic potential of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) using Oncologic. However, benzenesulfonate esters[19] are not specific organic subsystems including in the Oncologic program. As the structure did not match any of the specific organic subsystems, Oncologic could not be used to predict the carcinogenic potential of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-).

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for mutagenicity/genotoxicity based on the lack of mutagenicity *in vitro* and lack of clastogenicity *in vivo*. 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 measured data from high quality studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
    - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant OECD Guideline 471/EU Method B.13/14. *Salmonella typhimurium* TA 1535, TA 1537, TA 98 and TA 100 and Escherichia coli strain WP_2 *uvr* A were exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in dimethyl sulfoxide (DMSO) at 33-5,000 µg/plate with and without exogenous metabolic activation (unspecified S9 mix). The positive controls were sodium azide, 4-nitro-o-phenylene-diamine, methyl methane sulfonate, and 2-aminoanthracene. No evidence of cytotoxicity was identified following exposure to the test substance. No statistically significant increase in the mutation frequency was detected following treatment in the presence or absence of metabolic activation. The vehicle and positive controls performed as expected (Klimisch 1, reliable without restriction).
    - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation test conducted in a manner similar to OECD Guideline 476. Chinese

[19] Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is classified as a benzenesulfonate ester in the Classyfire database (http://classyfire.wishartlab.com/entities/HEVGMYPGMWZOBU-UHFFFAOYSA-N).

hamster ovary (CHO) cells exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in DMSO at 3.1-200 µL/mL without metabolic activation and 3.1-300 µL/mL with metabolic activation (unspecified S9). The positive controls were ethyl methanesulfonate and methylcholanthrene. No statistically significant increase in the mutation frequency was detected following treatment in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction).

- *In vitro*: Ambiguous results for clastogenicity were obtained in a GLP-compliant chromosome aberration assay conducted according to OECD Guideline 473/EU Method B.10 test. Chinese hamster lung fibroblasts (V79) were exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in DMSO at 18.8-300 µg/mL without metabolic activation and 18.8-250 µg/mL with metabolic activation (unspecified S9 mix). The positive controls were ethylmethanesulphonate (without metabolic activation) and cyclophosphamide (with metabolic activation. A statistically significant increase in the frequency of chromosome aberrations was detected at 150 µg/mL without metabolic activation and at 18.8 and 75 µg/mL, but not at 37.5 µg/mL, with metabolic activation. Increased clastogenicity coincided with high cytotoxicity at 150 µg/mL without metabolic activation (19.1% mitotic index) and 75 µg/mL with metabolic activation (28.6% mitotic index). The vehicle and positive controls performed as expected (Klimisch 1, reliable without restriction).
- *In vivo*: Negative results for clastogenicity were obtained in a GLP-compliant OECD Guideline 474 micronucleus test. NMRI mice (12/sex for high dose group; 6/sex for other groups) were administered single gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in corn oil at 200, 670, or 2,000 mg/kg. The animals were sacrificed 24 hours or 48 hours (high dose only) after dose administration and bone marrow samples were isolated for assessment of micronuclei. Cyclophosphamide was used as the positive control. No increase in the mean number of normochromatic erythrocytes was detected following treatment with benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) indicating a lack of bone marrow cytotoxicity. However, the study design included the limit dose of 2,000 mg/kg/day for exposures less than 14 days.[20] No statistically significant increase in the frequency of micronuclei was detected with treatment. The vehicle and positive controls performed as expected (Klimisch 1, reliable without restriction).

- In summary, benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not mutagenic in a bacterial reverse mutation assay and a mammalian cell gene mutation test, but was clastogenic in an *in vitro* chromosome aberration assay in the presence of significant cytotoxicity. However, no evidence of clastogenicity was identified in a micronucleus test in mice exposed up to the limit dose specified by OECD Guideline 474. Based on the lack of mutagenicity *in vitro* and lack of clastogenicity *in vivo*, ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a genotoxicants under GHS criteria (UN 2019).

Reproductive Toxicity (R) Score (H, M, or L): *M*
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Moderate for reproductive toxicity based on irreversible degeneration of the germinal epithelium in the testes in male rats exposed by gavage for 28 days at 750 mg/kg/day.

[20] https://www.oecd-ilibrary.org/environment/test-no-474-mammalian-erythrocyte-micronucleus-test_9789264264762-en

Although there is a lack of adverse treatment-related effects detected in a reproduction / developmental toxicity screening test up to the highest dose tested (200 mg/kg/day), reproductive effects at higher doses than 200 mg/kg/day could not be ruled out in the absence of reproductive performance data. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2018b). The confidence in the score is low as the score is based on data from a screening test and a repeated dose toxicity study with an effect at a high dose.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- BASF 2011, ECHA 2020a
  - A GLP-compliant reproduction / developmental toxicity screening test conducted in a manner similar to OECD Guideline 421 was performed with Crl:WI(Han) (outbred, SPF-quality) rats (40/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as Pergafast 201, purity not specified) in propylene glycol at 0, 50, 100, or 200 mg/kg/day. Males were treated for 29 days encompassing the two-week premating period, mating period, and up to termination. Females were dosed for 42-46 days including the two-week pre-mating period, mating period, gestation, and at least four days during the lactation period. The adults were evaluated for clinical signs of toxicity, body weight, reproductive indices (mating, fertility, conception, and gestation), sperm parameters (testis and epididymis weights and stage of spermatogenesis), and ovarian/uterine content (number of corpora lutea and implantation sites). No treatment-related effects were identified on reproductive indices, reproductive organs, or sperm parameters. The REACH registration dossier authors identified a reproductive toxicity NOAEL of 200 mg/kg/day for this study based on the lack of adverse effects on reproduction detected at up to the highest dose tested (Klimisch 1, reliable without restriction).
    - Note: US. EPA (2015b) noted that a non-statistically significant decrease in the number of implantation sites was identified in high dose dams.
    - Note: See the repeated dose systemic toxicity section below for a discussion of the treatment-related effects on non-reproductive organ systems.
- BASF 2011, ECHA 2020a
  - A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407 was performed with Wistar rats (5/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in polyethylene glycol at 0, 30, 150, or 750 mg/kg/day for 28 days. Additional animals were administered 0 or 750 mg/kg/day for 28 days and then maintained for an additional 14 days without treatment (recovery groups). The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. Bilateral degeneration of the germinal testicular epithelium was detected in high dose males that was not reversible after the recovery period.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Moderate for developmental toxicity based on reduced pup weights during the lactation period. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when limited or marginal evidence of developmental toxicity is identified in animal studies

(CPA 2018b). The confidence in the score is low as it is based on data from a screening test. Additionally, it is not clear if the reduced pup weights are a direct developmental effect or occur secondary to maternal toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- BASF 2011, ECHA 2020a
  - A GLP-compliant reproduction / developmental toxicity screening test conducted in a manner similar to OECD Guideline 421 was performed with Crl:WI(Han) (outbred, SPF-quality) rats (40/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as Pergafast 201, purity not specified) in propylene glycol at 0, 50, 100, or 200 mg/kg/day. Females were dosed for 42-46 days including the two-week pre-mating period, mating period, gestation, and at least four days during the lactation period. The offspring were evaluated for clinical signs of toxicity, viability, body weight, and gross pathological changes. Two, five, six, and two pups were found dead or were missing (presumed to cannibalized) in the control, low, mid, and high dose groups respectively. Since the mortality incidence did not show a significant dose-related trend and was within the normal historical range, the REACH registration dossier authors did not consider this finding to be treatment-related. Clinical signs of toxicity included incidental observations of small size and missing tail in the mid and high dose group. However, the REACH registration dossier authors did not consider these findings to be treatment-related since the incidences were within the range considered normal for pups of this age. Statistically-significant reductions in body weight (12-15% less than controls) were detected for male and female pups at 200 mg/kg/day on lactation days 1 and 4, and for female pups at 50 and 100 mg/kg/day on lactation day 1 but the reductions in the low and mid dose groups were slight and were within the normal range of historical controls according to the REACH registration dossier authors. Therefore, the REACH registration dossier authors did not consider the body weight changes at 50 and 100 mg/kg/day to be toxicologically relevant and identified a developmental toxicity NOAEL of 100 mg/kg/day based on reduced body weights identified for pups in the 200 mg/kg/day group (Klimisch 1, reliable without restriction).
    - Note: The reduced pup body weights in the high dose group coincided with maternal liver and kidney toxicity (see the repeated dose systemic toxicity section below).
    - Note: The U.S. EPA (2015b) identified a developmental toxicity NOAEL of 50 mg/kg/day based on reduced pup weights at 100 and 200 mg/kg/day and a maternal toxicity NOAEL of 50 mg/kg/day based on the renal and hepatic toxicity.

Endocrine Activity (E) Score (H, M, or L): DG
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Data Gap for endocrine activity based on the lack of thyroid signaling 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 2020a
  - A non-GLP-compliant test conducted in a manner similar to OECD Guideline 455 (stably transfected human estrogen receptor-α transcriptional activation assay for detection of estrogenic agonist-activity of chemicals) was performed with human breast carcinoma MCF-

7 cells stably transfected with an estrogen receptor-controlled luciferase reporter gene construct exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) at 0.065-6,500 µM continuously for three days. Increased luciferase activity is used as a marker for estrogen receptor-alpha induction. The positive controls were 17-beta-estradiol (E2; 0.5-150 pM) and nonyl phenol (0.5-50,000 nM). Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) treatment slightly increased the luciferase activity at concentrations near its solubility limit; at ≥ 65 µM, the luciferase activity was 115-123 % of the negative control. In contrast, E2 treatment at 1.5-150 pM resulted in luciferase activity that was 113-282% of the negative control. The relative potency of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was approximately 10^7-fold less than E2 (Klimisch 2, reliable with restrictions, OECD Guideline 455 specifies transfected hERα-HeLa-9903 cells, limited data on cytotoxicity, and discrepancies between study protocol and raw data (E2 concentrations specified as 0-300 pM but raw data indicated 0-150 pM).

- Goldinger et al. 2015, ECHA 2020a
    - A GLP-compliant steroidogenesis assay conducted according OECD Guideline 456 was performed with the H295R human adrenocortical carcinoma 257 cell line exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as Pergafast 201, purity not specified) at 0.1-100 µM for 48 hours. Cell viability was significantly decreased only at the highest concentration (100 µM). No statistically significant changes to E2 or free testosterone levels were detected with treatment (Klimisch 2, reliable with restrictions, "limitations in HPRC analysis").
- Keminer et al. 2020
    - The study authors evaluated the endocrine activity of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) in a fluorescence polarization ligand binding assay at 10 µM. Inhibition of ligand binding to the androgen receptor (AR), estrogen receptor alpha (ERα), and estrogen receptor beta (ERβ) were 21.55%, -1.36%, and 127.66%, respectively. A follow-up competition test using a fluorescence polarization assay incorporating multiple concentrations was performed with the ERβ. However, benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not active in the fluorescence polarization assay. Therefore, the authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) exhibited "no endocrine concern."
- Björnsdotter et al. 2017b
    - Extracts of thermal paper products (cash receipts, boarding passes, luggage tags, and cinema tickets) were screened for the presence of color developers, including Pergafast 201, using direct probe ambient mass spectrometry. Additionally, selected extracts were evaluated for estrogenicity using "LC-nanofractionation platform in combination with cell-based bioassay testing." The preliminary results indicate that Pergafast 201 has no to very low estrogenic activity relative to bisphenol A (BPA) and bisphenol S (BPS).
- In summary, the available data suggest that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) does not disrupt androgenic or estrogenic signaling. However, Section A2.2.2.1 of the GreenScreen® criteria (CPA 2018b) specifies that adequate and negative data for androgenicity, anti-androgenicity, thyroid effects, estrogenicity, and anti-estrogenicity are required to assign a Low score for the endocrine activity endpoint. Based on the lack of thyroid signaling data, ToxServices assigned a Data Gap for this endpoint.

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values greater than 2,000 mg/kg in rats. 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 data from high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: LD_{50} (Wistar rats) > 2,000 mg/kg (OECD Guideline 423/EU Method B.1) (Klimisch 1, reliable without restriction).
  - *Dermal*: LD_{50} (Wistar rats) > 2,000 mg/kg (OECD Guideline 402/EU Method B.3) (Klimisch 1, reliable without restriction).

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for systemic toxicity (single dose) based on the lack of systemic toxicity detected following single oral or dermal doses in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - *Oral*: In the acute oral toxicity test that identified an oral LD_{50} >2,000 mg/kg in Wistar rats, clinical signs of toxicity were limited to ruffled fur in one male on day 3 of the observation period. No treatment-related effects were identified on body weights or gross pathological findings (Klimisch 1, reliable without restriction).
  - *Dermal*: In the acute dermal toxicity test that identified a dermal LD_{50} > 2,000 mg/kg in Wistar rats, no clinical signs of toxicity, body weight effects, or changes to gross pathological findings were detected with treatment (Klimisch 1, reliable without restriction).

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Moderate for systemic toxicity (repeated dose) based on ToxServices classifying it as a Category 2 specific target organ toxicant following repeated oral doses under GHS criteria. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (repeated dose) when they are classified as GHS Category 2 specific target organ toxicants following repeated oral

doses (CPA 2018b). The confidence in the score is high as it is based on measured data from high quality studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- BASF 2011, ECHA 2020a
    - *Oral*: A GLP-compliant reproduction / developmental toxicity screening test conducted in a manner similar to OECD Guideline 421 was performed with Crl:WI(Han) (outbred, SPF-quality) rats (40/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as Pergafast 201, purity not specified) in propylene glycol at 0, 50, 100, or 200 mg/kg/day. Males were treated for 29 days encompassing the two-week premating period, mating period, and up to termination. Females were dosed for 42-46 days including the two-week pre-mating period, mating period, gestation, and at least four days during the lactation period. The adults were evaluated for clinical signs of toxicity, body weight and body weight gain, food consumption, hematology, clinical chemistry, organ weights, gross pathology, and histopathology. No treatment-related effects were identified on clinical signs of toxicity, body weight or body weight changes, or food consumption. Relative to the concurrent controls, decreased relative monocyte counts and hemoglobin levels were detected in high dose females, decreased hematocrit levels were detected in mid and high dose females, and decreased red blood cell counts and increased red blood cell distributions were detected in females of all dose groups. Statistically significantly increased reticulocyte counts were detected in the low and mid dose group females but not the high dose group females. High dose females also exhibited increased serum glucose, potassium, total bilirubin, alkaline phosphatase (ALP) and alanine aminotransferase (ALT) levels. High dose males also exhibited increased glucose levels. At necropsy, two mid dose females and two high dose females exhibited an accentuated lobular pattern of the liver. Upon microscopic examination, the lobular pattern correlated with slight vacuolation of periportal hepatocytes or hypertrophy of centrilobular hepatocytes in the mid dose females and congestion or minimal hypertrophy of centrilobular hepatocytes in the high dose females. Statistically significant treatment-related changes to organ weights were detected in females only and included increased relative kidney weights in the low, mid, and high dose groups, increased relative liver weights in the mid and high dose groups, and increased absolute liver and kidney weights in the high dose group. Hypertrophy of centrilobular hepatocytes was detected in 7/10 males and 6/10 females in the high dose group. The incidence and severity (minimal to slight) of this effect was statistically significantly greater than the concurrent control group. In the high dose group, 5/10 females exhibited minimal to slight vacuolation of the proximal tubule epithelium. The REACH registration dossier authors identified a systemic toxicity NOAEL of 100 mg/kg/day for this study based on the treatment-related effects detected on clinical chemistry and hematology parameters, organ weights, and histopathological findings at 200 mg/kg/day (Klimisch 1, reliable without restriction).
    - *Oral*: A GLP-compliant subchronic repeated dose toxicity study conducted according to OECD Guideline 408 was performed with Wistar rats (10/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in polyethylene glycol at 0, 12.5, 25, 50, or 150 mg/kg/day for 91-92 days. Additional groups of 5 animals/sex/group were administered 0 or 150 mg/kg/day for 91-92 days and then maintained for four weeks without treatment (recovery group). The animals were evaluated for clinical signs of toxicity, body weight,

food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. No treatment-related effects were detected on clinical signs of toxicity, body weight, body weight changes, food consumption, ophthalmological parameters, or gross pathological findings. High dose males and females exhibited statistically significantly decreased red blood cell counts and hemoglobin and hematocrit levels and increased red cell distribution width, indicative of slight anemia according to the REACH registration dossier authors. High dose males and females also exhibited significant increases in absolute and relative reticulocyte counts and a concomitant fluorescence shift towards high fluorescence in the reticulocyte fluorescence ratios, effects were "considered to be compensatory changes to the anemia." High dose females also exhibited a significantly higher number of large unstained cells; the toxicological significance of this finding is unknown. Other effects on hematology parameters were not considered to be treatment-related by the REACH registration dossier authors as they did not exhibit dose responses, were considered incidental, or were within the historical control range. Treatment-related effects on clinical chemistry parameters were limited to the high dose group and included statistically significantly increased inorganic phosphate and absolute and relative beta globulin levels in males at the end of the treatment and recovery periods, increased total bilirubin levels, absolute and relative alpha globulins in females, and reduced relative albumin levels and albumin/globulin ratio in females. Additional changes to clinical chemistry parameters were not considered to be treatment-related by the REACH registration dossier authors since they were detected only after the recovery period, were within the range for historical control values, were not dose dependent, or differed from unusually low or high concurrent control values.

The only treatment-related effect on urinalysis parameters was a statistically significantly increased urine output by high dose males at the end of the treatment period, but this effect was fully reversible at the end of the recovery period. Statistically significant effects on organ weights included increased relative (to body weight) liver weights at the end of the treatment period (reversible in recovery group) and increased absolute kidney weights in high dose males at the end of the recovery period, increased relative kidney weights in high dose females at the end of the treatment period (reversible in recovery group), and increased relative and absolute liver weights in females dosed with 12.5, 50, and 150 mg/kg/day at the end of the treatment period (reversible in recovery group). As no significant changes to liver weights were detected at 25 mg/kg/day and values in the 12.5 and 50 mg/kg/day groups were similar to each other (i.e. no dose response), the REACH registration dossier authors concluded that the differences in liver weights detected in females of the 12.5 and 50 mg/kg/day groups were not likely to be treatment related. When compared to brain weights, the relative liver weights for high dose females and relative kidney weight in high dose males exceeded the control values at the end of the recovery period. Treatment-related changes in histopathological findings included increased incidence and severity (minimal or slight) of cortical coarse vacuolation of adrenal glands detected in high dose males (9/10) and females (10/10), minimal or slight hypertrophy of centrilobular hepatocytes in 3/10 females at 50 mg/kg/day and 9/10 males and 10/10 females in the high dose group which correlated with the increased liver weights detected in these dose groups, and an increased incidence of extramedullary hematopoiesis of the spleen in high dose males (7/10) and females (7/10). After the recovery period, histopathological findings did not differ from controls in the liver and spleen, but 2/5 males and 2/5 females exhibited increased cortical coarse vacuolation of the adrenal glands compared to 0/5 controls of each sex. The REACH registration dossier authors identified a NOAEL and LOAEL of 50 and 150 mg/kg/day for

this study based on histopathological changes detected in both sexes in the high dose groups; the hepatic hypertrophy detected in the 50 mg/kg/day group was not considered to be the critical effect as it was only detected in females (Klimisch 1, reliable without restriction).

- Note: U.S. EPA (2015b) identified the NOAEL and LOAEL as 25 and 50 mg/kg/day, respectively, for females based on the increased liver weights and histopathological changes, while NTP (2017) identified the LOAEL as 12.5 mg/kg/day based on increased liver weights in females. Based on the correlation between liver weight and histopathological changes in the two highest dose groups, ToxServices agrees with U.S. EPA's selection of 25 mg/kg/day as the NOAEL for this study.

- *Oral*: A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407 was performed with Wistar rats (5/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in polyethylene glycol at 0, 30, 150, or 750 mg/kg/day for 28 days. Additional animals were administered 0 or 750 mg/kg/day for 28 days and then maintained for an additional 14 days without treatment (recovery groups). The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology. No mortalities occurred in the low or mid dose groups. One male and seven females (three dying during blood sampling) in the high dose group died prior to the scheduled sacrifice and one high dose female was sacrificed in moribund condition prior to the end of the exposure period. Clinical signs of toxicity included salivation in one female at 150 mg/kg/day and males and females in the high dose group and increased incidences of piloerection and hardened abdomen in high dose females.

  Although not statistically significant, mean body weights and mean body weight gains for high dose males and females were less than the concurrent control values beginning on day 8. No treatment-related effects were identified on food consumption during the treatment period. Decreased food consumption detected in females during the recovery period was not considered to be treatment-related by the REACH registration dossier authors. Treatment-related effects on hematology parameters included decreased red blood cell count, plasma hemoglobin, and hematocrit levels and increased mean cell volume and shift towards high fluorescence reticulocytes in mid dose males and females, and decreased red blood cell and lymphocyte counts, mean cell hemoglobin concentration, plasma hemoglobin, and hematocrit and increased mean cell volume, reticulocyte counts with shift towards high fluorescence reticulocytes and higher normoblast counts, methemoglobin concentration, white blood cell counts, segmented leukocyte counts, and polychromatophilia in high dose group animals. After the recovery period, high dose animals still exhibited decreased red blood cell counts, increased relative reticulocyte counts, and a shift toward low fluorescence reticulocytes indicating incomplete recovery. Treatment-related effects on clinical chemistry parameters included decreased phospholipids in mid dose males, increased gamma glutamyl transferase activity in mid dose males and females (not statistically significant), increased creatinine levels and decreased cholesterol, phospholipids and sodium levels in high dose males, increased creatinine kinase activity, calcium, and globulin levels and decreased albumin/globulin ratio in high dose females, and decreased plasma glucose and chloride levels, increased levels of uric acid, total bilirubin, and phosphorus, and increased activities of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and gamma glutamyl transferase in high dose males and females. Following the recovery period, no treatment-related effects were detected on

clinical chemistry parameters. Treatment-related effects on urinalysis parameters included increased urine production in high dose females and decreased urine pH in high dose males, both of which completely resolved after the recovery period. Gross pathological findings detected in the high dose group at the end of the treatment period included stomach foci in 1/5 males and 5/5 females, thickening of the thyroid gland in 1/5 male, decreased thymus size in 5/5 males and 2/5 females, and decreased spleen size in 2/5 females. At the end of the recovery period, stomach foci were detected in 1/5 males and 1/1 female and decreased thymus size was detected in 3/5 males and 1/1 female. Treatment-related organ weight changes included increased absolute liver weights in low dose males, increased absolute and relative liver weights in mid and high dose males and females, increased absolute and relative adrenal weights in high dose males and females (statistically significant only in males), decreased absolute and relative thymus weights in high dose males and females (statistically significant only in males), and increased absolute and relative kidney weights in mid and high dose females.

After the recovery period, high dose males exhibited decreased absolute and relative thymus weights, increased relative adrenal weights, and increased absolute liver weights. Histopathological changes detected at the end of the treatment period included increased incidences of centrilobular hepatocytic hypertrophy in mid and high dose males and females, an increased severity of extramedullary hemopoiesis in the spleen of mid dose females and high dose males and females, increased incidences hypertrophy of the zona fasciculata in the adrenal glands, increased severity of periportal fat vacuolation of the liver in high dose males and females, and increased incidence and severity of lymphocyte depletion of the splenic marginal zones, lymphocyte depletion in the thymus, and focal erosion of the gastric glandular mucosa in high dose males and females. Additionally, bilateral degeneration of the germinal testicular epithelium was detected in high dose males and single cell death in the renal proximal convoluted tubules and foci of alveolar macrophages in the lungs were detected in high dose females. After the recovery period, high dose males still exhibited degeneration of the germinal epithelium in the testes while the other histopathological changes were partially reversible. The sole surviving female in the dosed recovery group did not exhibit any treatment-related histopathological changes. The REACH registration dossier authors identified a NOAEL and LOAEL of 30 and 150 mg/kg/day, respectively, based on salivation, changes to hematology and clinical chemistry parameters, organ weights, and histopathological changes in the liver and spleen at 150 mg/kg/day (Klimisch 1, reliable without restriction).

  - Note: The U.S. EPA (2015b) authors also identified the NOAEL as 30 mg/kg/day and LOAEL as 150 mg/kg/day for this study.

- In summary, the repeated dose toxicity studies consistently identified treatment-related effects on the liver, kidneys, spleen, and adrenal glands in multiple studies. Based on the NOAEL and LOAEL of 25 and 50 mg/kg/day in the subchronic repeated dose toxicity study identified based on treatment-related effects on the liver, ToxServices classified benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a GHS Category 2 specific target organ toxicant following repeated oral doses under GHS criteria (UN 2019). GHS criteria define Category 2 specific target organ toxicants following repeated oral doses as chemicals that produce LOAEL values greater than 10 and up to 100 mg/kg/day in subchronic oral repeated dose toxicity studies.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for neurotoxicity (single dose) based on the lack of clinical signs of toxicity and gross pathology effects suggestive of neurotoxicity in acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available, and they are not classified under GHS for single dose systemic toxicity based on neurotoxicity (CPA 2019b). Confidence in the score is low as there are no specific neurobehavioral assessments in the acute toxicity tests.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2020a
  - *Oral*: In the acute oral toxicity test that identified an oral LD_{50} >2,000 mg/kg in Wistar rats, no neurological clinical signs of toxicity identified during the observation period. There were no gross pathological findings. However, a neurobehavioral assessment was not included in the study design (Klimisch 1, reliable without restriction).
  - *Dermal*: In the acute dermal toxicity test that identified a dermal LD_{50} > 2,000 mg/kg in Wistar rats, no neurological clinical signs of toxicity identified during the observation period. There were no gross pathological findings. However, a neurobehavioral assessment was not included in the study design (Klimisch 1, reliable without restriction).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for neurotoxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated exposures based on neurotoxicity under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2020a
  - *Oral*: A GLP-compliant subchronic repeated dose toxicity study conducted according to OECD Guideline 408 was performed with Wistar rats (10/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in polyethylene glycol at 0, 12.5, 25, 50, or 150 mg/kg/day for 91-92 days. Additional groups of 5 animals/sex/group were administered 0 or 150 mg/kg/day for 91-92 days and then maintained for four weeks without treatment (recovery group). The animals were evaluated for in a functional observational battery that included assessments of forelimb and hind limb grip strength, motor activity, and total activity. Additionally, relative and absolute brain weights and the gross pathology and histopathology of the brain, spinal cord, and optic and sciatic nerves were investigated. No treatment-related effects were identified on these parameters; therefore, ToxServices identified a neurotoxicity NOAEL of 150 mg/kg/day for this study (Klimisch 1, reliable without restriction).

  - *Oral*: A GLP-compliant repeated dose toxicity study conducted according to OECD Guideline 407 was performed with Wistar rats (5/sex/group) administered gavage doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in polyethylene glycol at 0, 30, 150, or 750 mg/kg/day for 28 days. Additional animals were administered 0 or 750 mg/kg/day for 28 days and then maintained for an additional 14 days without treatment (recovery groups). The animals were evaluated in a functional observational battery, which included assessments of hind limb and forelimb grip strength, locomotor activity, and total activity, and brain weight. Decreased forelimb grip strength was detected in high dose females and decreased hindlimb grip strength was detected in low dose males and females. The REACH registration dossier authors concluded that these effects were incidental as the effects did not correlate between the different limbs. Total mean locomotor activity decreased 19% for high dose males and 48% for high dose females compared to the concurrent controls, with the difference being statistically significant in females. No effects on locomotor activity was detected at 30 or 150 mg/kg/day. High dose females also exhibited increased incidences of sedation and hypothermia. At necropsy, high dose males exhibited statistically significantly increased relative brain weights at the end of the exposure and recovery periods. ToxServices identified a neurotoxicity NOAEL of 150 mg/kg/day based on decreased forelimb grip strength, decreased locomotor activity, and increased brain weights detected at 750 mg/kg/day (Klimisch 1, reliable without restriction).

- In summary, a neurotoxicity NOAEL of 150 mg/kg/day was identified in a 28-day repeated oral dose toxicity study based on effects on neurobehavior and brain weights at 750 mg/kg/day, and a neurotoxicity NOAEL of 150 mg/kg/day was identified in a 90-day repeated oral dose toxicity study based on the lack of neurotoxicity detected at the highest dose tested. As the NOAEL of 150 mg/kg/day in the 90-day study exceeds the GHS guidance value of 100 mg/kg/day for chronic oral toxicity studies (UN 2019), ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a specific target organ toxicant following repeated exposures based on neurotoxicity under GHS criteria.

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for skin sensitization based on ToxServices not classifying it as a skin sensitizer under GHS criteria. 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 measured data from a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - A GLP-compliant guinea pig maximization test conducted according to OECD Guideline 406 was performed with Himalayan guinea pigs (10 in test group, 5 in control groups) administered dermal doses of benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (>99% purity). The induction doses were applied as intradermal injections of 1:1 (v/v) mixture of Freund's complete adjuvant (FCA) and physiological saline, 5% benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) in corn oil, and 5% benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) in a 1:1 (v/v) mixture of FCA and physiological saline. On study day

eight, a topical application of 50% benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) in corn oil under occlusive dressing for 48 hours. The challenge dose was applied on day 22 as a topical application of 0.5% benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) in corn oil under occlusive dressing for 24 hours. 2-Mercaptobenzothiazole was used as the positive control. At 24 and 48 hours, 1/10 and 0/10 animals, respectively, exhibited positive dermal reactions following challenge with benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-). Therefore, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not sensitizing to the skin under the conditions of this test (Klimisch 1, reliable without restriction).

- Based on the lack of dermal sensitization potential identified in a guinea pig maximization test, ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a dermal sensitizer under GHS criteria (UN 2019).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for respiratory sensitization based on a lack of dermal sensitization potential, according to ECHA's guideline (ECHA 2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative, and it is not GHS classified (CPA 2018b). Confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020
  - Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) does not contain any structural alerts for respiratory sensitization (Appendix F)
- 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 benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) 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 benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-), and as benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) does not contain any structural alerts for respiratory sensitization (OECD 2019), benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not expected to be a respiratory sensitizer.

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for skin irritation/corrosivity based on ToxServices not classifying it as a skin irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - A GLP-compliant dermal irritation test conducted according to OECD Guideline 404 was performed with New Zealand White rabbits (1 male, 2 females) administered topical applications of 0.5 mg benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified) in water to shaved skin under semi-occlusive dressing for 4 hours. The dermal irritation responses were evaluated at 1, 24, 48, and 72 hours. At 24, 48, and 72 hours, the mean erythema and edema scores were both 0/4. Based on the lack of irritation effects detected on the exposed skin, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not irritating to the skin under the tested conditions (Klimisch 1, reliable without restriction).
- Based on the lack of dermal irritation tested in the above study, ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a skin irritant under GHS criteria (UN 2019).

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for eye irritation/corrosivity based on ToxServices not classifying it as an ocular irritant under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - A GLP-compliant ocular irritation test conducted according to OECD Guideline 405/EU Method B.5 was performed with New Zealand White rabbits (1 male, 2 females) administered ocular instillations of 0.1 g benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (purity not specified). The eyes were not rinsed, and an observation period of 72 hours followed the instillation. At 24, 48, and 72 hours, the mean corneal opacity score was 0/4, the mean iris score was 0/2, the mean conjunctival score was 0.44/3, and the mean chemosis score was 0.22/4. The conjunctival redness and chemosis were fully reversible within 72 hours. Based on these results, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not irritating to the eyes under the conditions of this test (Klimisch 1, reliable without restriction).
- Based on the above results, ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as an ocular irritant under GHS criteria (UN 2019). Under GHS criteria, a chemical is classified as irritating to the eyes if it produces mean

scores ≥ 1 for corneal opacity, ≥ 1 for iritis, ≥ 2 for conjunctival redness, and/or ≥ 2 for chemosis in at least 2 of 3 animals following readings at 24, 48, and 72 hours, with reversibility of the irritation effects occurring within 21 days (Category 2A) or 7 days (Category 2B). As the only signs of ocular irritation (mean conjunctival score of 0.44 and mean chemosis score of 0.22) are less than these thresholds, benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) did not produce ocular irritation sufficient for GHS classification.

Ecotoxicity (Ecotox)

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of High for acute aquatic toxicity based on measured acute aquatic toxicity values as low as 3 mg/L in algae based on growth rate effects. While a lower 72-hour EC_{50} of 0.77 mg/L was identified in algae based on biomass, GHS criteria prefer data based on growth rate over biomass. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when acute aquatic toxicity values are no greater than 1 mg/L (CPA 2018b). The confidence in the score is high as measured data are available 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 2020a
  - 96-hour LC_{50} (*Danio rerio*, zebrafish) > 64 mg/L (measured) (GLP-compliant, OECD Guideline 203) (Klimisch 1, reliable without restriction).
  - 48-hour mobility EC_{50} (*Daphnia magna*) = 56 mg/L (measured) (GLP-compliant, OECD Guideline 202) (Klimisch 1, reliable without restriction).
  - 72-hour EC_{50} (*Desmodesmus subspicatus*, algae) = 0.77 mg/L (biomass, nominal), 3 mg/L (growth rate, nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
  - 96-hour EC_{50} (*D. subspicatus*, algae) = 6.3 mg/L (biomass, nominal), > 10 mg/L (growth rate, nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions, test design significantly altered).
  - 72-hour EC_{50} (*D. subspicatus*, algae) = 1.3 mg/L (biomass, nominal), 3.2 mg/L (growth rate, nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction, test design was amplified ("recovery period in untreated test medium")).

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of High for chronic aquatic toxicity based on the lowest measured chronic aquatic toxicity value of 0.22 mg/L for green algae based on growth rate effects. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 0.1 to 1.0 mg/L (CPA 2018b). The confidence in the score is high as measured data are available 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.
  - *Other:*
    - EU - GHS (H-Statements) - H411 - Toxic to aquatic life with long lasting effects.
    - GHS – Australia - H411 - Toxic to aquatic life with long lasting effects.

- ECHA 2020a
    - 32-day development, growth, length, survival NOEC (*Pimephales promelas*, fathead minnow) = 0.89 mg/L (measured) (GLP-compliant, EPA OPPTS 850.1400) (Klimisch 1, reliable without restriction).
    - 21-day reproduction NOEC (*D. magna*) = 10.2 mg/L (GLP-compliant, OECD Guideline 211) (Klimisch 1, reliable without restriction).
    - 72-hour growth rate NOEC (*D. subspicatus*, algae) = 0.22 mg/L (nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction).
    - 96-hour biomass, growth rate NOEC (*D. subspicatus*, algae) = 2.2 mg/L (nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 2, reliable with restrictions, test design significantly altered).
    - 72-hour biomass, growth rate NOEC (*D. subspicatus*, algae) < 0.46 mg/L (nominal) (GLP-compliant, OECD Guideline 201) (Klimisch 1, reliable without restriction, test design was amplified ("recovery period in untreated test medium")).

Environmental Fate (Fate)

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of High for persistence based on an estimated half-life of 120 days in soil, its dominant environmental compartment. Experimental data indicate that the compound is not readily biodegradable, but is inherently biodegradable. GreenScreen® criteria classify chemicals as a High hazard for persistence when the half-life in soil is greater than 60 to 180 days (CPA 2018b). The confidence in the score is low as it is based on a modeled half-life in the predicted dominant environmental compartment.

- 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 2020a
    - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 B (CO_2 evolution test) was performed with non-adapted, activated domestic sludge exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as Pergafast 201, 96.68% purity) at 20 mg/L (TOC) for 28 days. At the end of the exposure period, the level of degradation was 3%. The positive control (aniline) performed adequately. Therefore, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not readily biodegradable under the tested conditions (Klimisch 1, reliable without restriction).
    - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301 F/EU Method C.4-D (manometric respirometry test) was performed with non-adapted, activated domestic sludge exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methyl phenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as FAT 55'556/A, >99% purity) at 100 mg/L for 28 days. At the end of the exposure period, the level of degradation was 1.2%. The positive control (sodium benzoate) performed adequately. Therefore, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not readily biodegradable under the tested conditions (Klimisch 1, reliable without restriction).

  - A GLP-compliant ready biodegradability test conducted according to a Japanese Testing Method for New Chemical Substances was performed with non-adapted, activated sludge exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as FAT 55'556/A, 99% purity) at 100 mg/L for 28 days. At the end of the exposure period, the level of degradation was 0%. The positive control (aniline) performed adequately. Therefore, the REACH registration dossier authors concluded that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not readily biodegradable under the tested conditions (Klimisch 1, reliable without restriction).
  - A non-GLP-compliant inherent biodegradability tests conducted according to OECD Guideline 302 B (Zahn-Wellens/EMPA test) was performed with non-adapted, activated domestic sludge exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl) sulfonyl]oxy]phenyl] amino]carbonyl]-) (as FAT 55'556/A, 99% purity) at 50 µg/L for 28 days. No positive control was included in the experimental design. After 3 hours and 28 days, the level of degradation was 73.5 and > 99%, respectively. ToxServices concludes that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was inherently biodegradable under the tested conditions (Klimisch 2, reliable with restrictions, non-GLP study).
  - An OECD Guideline 307 (Aerobic and Anaerobic Transformation in Soil) study is presented in the REACH dossier for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-). However, the study was assigned a Klimisch score of 3 (not reliable) due to "major methodological deficiencies" and the REACH dossier authors indicate it is "insufficient for the assessement of the mineralisation of the test substance." Therefore, ToxServices did not factor the results of this study into our hazard classification of the persistence endpoint.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not expected to be readily biodegradable (Appendix G). Fugacity modeling (MCI method) predicts 84.6% will partition to soil with a half-life of 120 days, 8.18% will partition to water with a half-life of 60 days, and 7.17% will partition to sediment with a half-life of 542 days.

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Very Low for bioaccumulation based on measured BCF values < 8 in fish. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are no greater than 100 (CPA 2018b). The confidence in the score is high as it is based on measured data from a high quality study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - A GLP-compliant bioaccumulation test conducted according to OECD Guideline 305 was performed with carp (*Cyprinus carpio*) exposed to benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) (as FAT 55'556/A, 99% purity) at nominal concentrations of 0.02 or 0.2 mg/L for 28 days. No details on a depuration period were provided. At the end of the exposure period, the BCF values were < 8 and < 1 for the 0.02 and 0.2 mg/L solutions, respectively (Klimisch 1, reliable without restriction).

Physical Hazards (Physical)

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is available (CPA 2018b). The confidence in the score was high based on measured data for explosiveness.

- 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 2020a
  - In a GLP-compliant EU Method A.14 (explosive properties) test, benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was not thermally sensitive when heated under defined confinement, was not sensitive to impact (40 J), and was not sensitive to friction (friction load of 360 N). Therefore, the REACH registration dossier authors concluded that it did not exhibit explosive properties under the tested conditions (Klimisch 1, reliable without restriction).
  - According to the REACH registration dossier authors, benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) does not contain functional groups associated with oxidizing properties.
- BASF 2017
  - A safety data sheet for benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl] oxy]phenyl] amino]carbonyl]-) indicates that it has a physical/reactivity hazard of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives (e.g., helium)") and NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water (e.g. helium, N_2)").
- Based on the above information indicating that benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not explosive, not likely to be oxidizing, and has low overall reactivity, ToxServices did not classifying it as a reactive chemical under GHS criteria.

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

Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was assigned a score of Low for flammability based on ToxServices not classifying it as a flammable solid under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is available (CPA 2018b). The confidence in the score was high as it is based on measured data from high quality studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2020a
  - Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not auto-flammable as it did not ignite under the conditions of a GLP-compliant EU Method A.16 (relative self-ignition temperature for solids) test (Klimisch 1, reliable without restriction).

  - Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) is not considered highly flammable as it immediately melted and formed a clear, brown-black colored material in a GLP-compliant EU Method A.10 (flammability (solids)) test (Klimisch 1, reliable without restriction).
  - Benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) was thermally stable in a non-GLP-compliant DIN 51007 at temperatures < 150°C (Klimisch 1, reliable without restriction).
- Based on the above data indicating that it is not self-igniting, is not highly flammable, and is thermally stable under environmental conditions, ToxServices did not classify benzenesulfonamide, 4-methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] amino]carbonyl]-) as a flammable solid under GHS criteria (UN 2019).

References

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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 Benzenesulfonamide, 4-Methyl-N-[[3-[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

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	**Benzenesulfonamide, 4-Methyl-N-[[3-[(4-**	**232938-43-1**	*M*	**L**	*M*	*M*	DG	**L**	**L**	**M**	*L*	**L**	**L**	*L*	**L**	**L**	**H**	**H**	*H*	**vL**	**L**	**L**

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Benzenesulfonamide, 4-Methyl-N-[[3-[(4-	2

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

Table 6

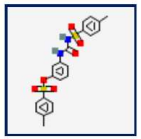
Chemical Name	Final GreenScreen® Benchmark Score
Benzenesulfonamide, 4-Methyl-N-[[3-[(4-	2

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 Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)



232938-43-1

N-(p-toluenesulfonyl)-N'-(3-(p-toluenesulfonyloxy)phenyl)urea

ALSO CALLED 3-((((4-Methylphenyl)sulfonyl)carbamoyl)amino)phenyl 4-methylbenzenesulfonate, 3-(3-Tosylureido)phen...

View all synonyms (3)

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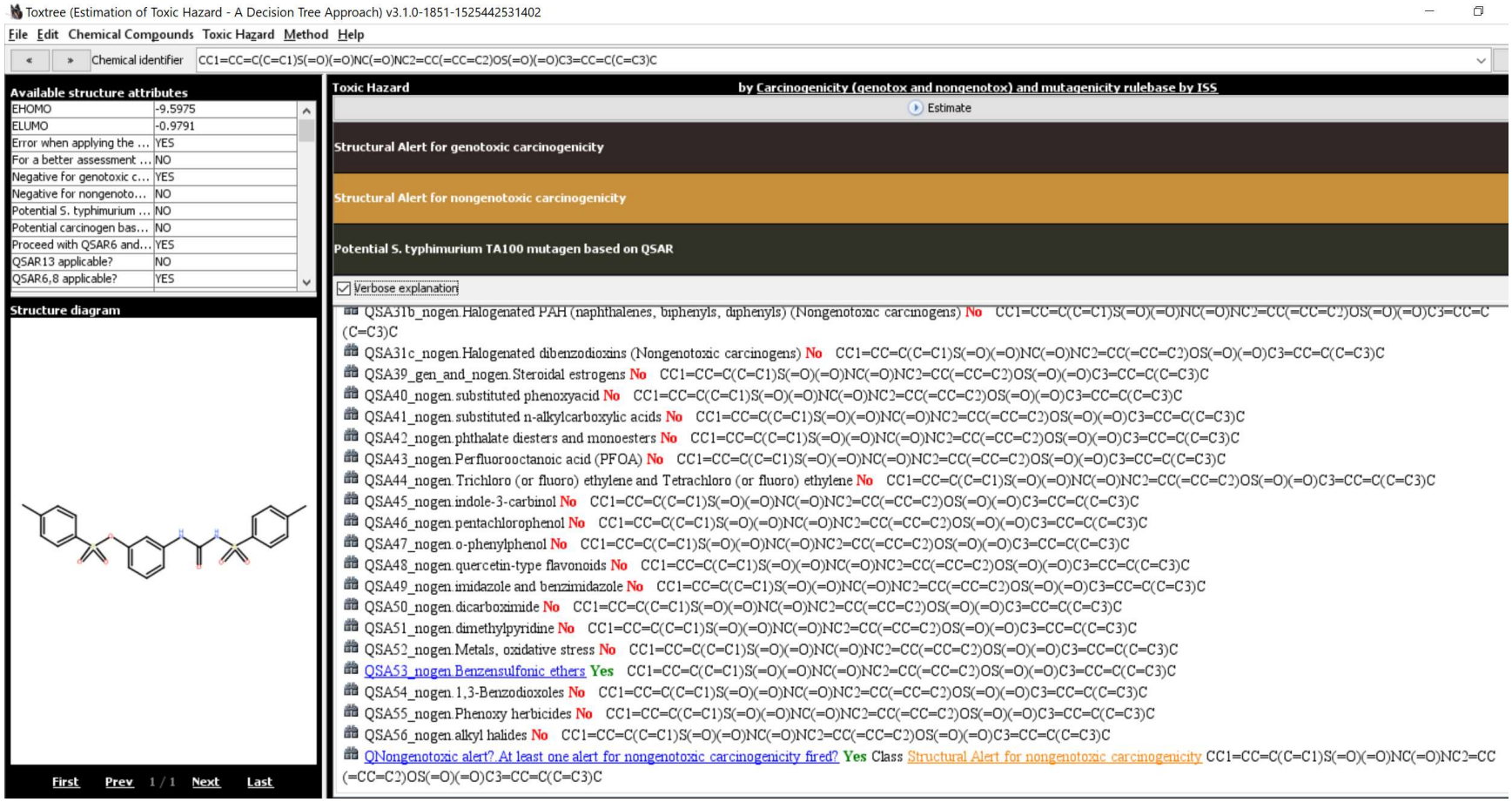
ENDPOINT	HAZARD LEVEL	HAZARD LIST	HAZARD DESCRIPTION	OTHER LISTS
Chron aquatic	High	EU - GHS (H-Statements)	H411 - Toxic to aquatic life with long lasting effects	+1
	High	GHS - Australia	H411 - Toxic to aquatic life with long lasting effects	
Restricted list	Potential Concern	EU - PACT-RMOA Substances	Substances selected for RMOA or hazard assessment	+1
	Potential Concern	Living Building Challenge 4.0 - Red List of Materials & Chemicals	Watch List Substances Considered for Inclusion in the Living Building Challenge Red List	

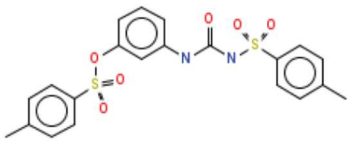
APPENDIX D: Toxtree Carcinogenicity Results for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl]Amino]carbonyl]-) (CAS #232938-43-1)



APPENDIX E: VEGA Carcinogenicity Results for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

1. Prediction Summary

Prediction for compound Molecule 0

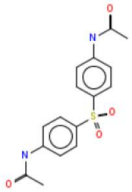


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
P(Carcinogen): 0.151
P(NON-Carcinogen): 0.849
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

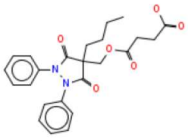
CAS: 77-46-3
Dataset id: 714 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.766

Experimental value: Carcinogen
Predicted value: Carcinogen

Compound #2

CAS: 968-81-0
Dataset id: 4 (Training set)
SMILES: O=C(NC1CCCCC1)NS(=O)(=O)c2ccc(cc2)C(=O)C
Similarity: 0.749

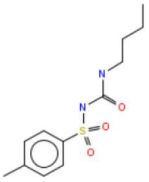
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 27470-51-5
Dataset id: 715 (Training set)
SMILES: O=C(O)CCC(=O)OCC2(C(=O)N(c1ccccc1)N(C2(=O))c3ccccc3)CCCC
Similarity: 0.744

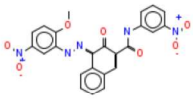
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 64-77-7
Dataset id: 752 (Training set)
SMILES: O=C(NCCCC)NS(=O)(=O)c1ccc(cc1)C
Similarity: 0.743

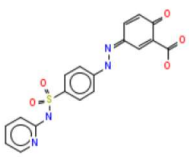
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 6471-49-4
Dataset id: 687 (Training set)
SMILES: O=C(Nc1cccc(c1)[N+](=O)[O-])C3=Cc4ccccc4(C(=NNc2cc(ccc2(OC))[N+](=O)[O-])C3(=O))
Similarity: 0.74

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



Compound #6

CAS: 599-79-1
Dataset id: 701 (Training set)
SMILES: O=C(O)C3=CC(=NNc1ccc(cc1)S(=O)(=O)Nc2ncccc2)C=CC3(=O)
Similarity: 0.731

Experimental value: Carcinogen
Predicted value: NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.372 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.757 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✖	**Concordance for similar molecules** Concordance index = 0.492 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✖	**Atom Centered Fragments similarity check** ACF index = 0.51 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments and 1 infrequent fragments found).
✔	**Model class assignment reliability** Pos/Non-Pos difference = 0.697 Explanation: model class assignment is well defined.
✔	**Neural map neurons concordance** Neurons concordance = 1 Explanation: predicted value agrees with experimental values of training set compounds laying in the same neuron.

Symbols explanation:

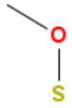
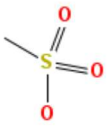
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

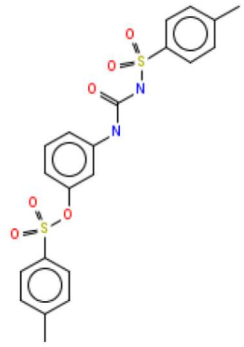
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

	Fragment defined by the SMILES: O(c)S The fragment has less than 3 occurrences in the model's training set
	Fragment defined by the SMILES: O=S(=O)(O)c The fragment has never been found in the model's training set

1. Prediction Summary

Prediction for compound Molecule 0

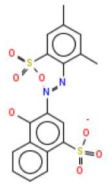


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not adequate
- some similar molecules found in the training set have experimental values that disagree with the predicted value
The following alerts have been found: SA53 Benzensulfonic ethers

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Carcinogen activity: Carcinogen
Structural alerts: SA53 Benzensulfonic ethers
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

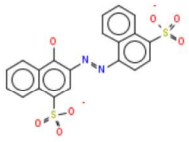
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 4548-53-2
Dataset id: 414 (Training set)
SMILES: O=S(=O)([O-])c3cc(cc(c3(N=Nc1cc(c2ccccc2(c1(O)))S(=O)(=O)[O-]))C)C
Similarity: 0.787

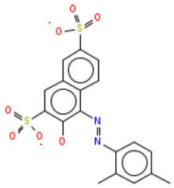
Experimental value: Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 3567-69-9
Dataset id: 82 (Training set)
SMILES: O=S(=O)([O-])c4ccc(N=Nc1cc(c2ccccc2(c1(O)))S(=O)(=O)[O-])c3ccccc34
Similarity: 0.785

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

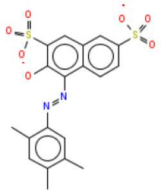


Compound #3

CAS: 3761-53-3
Dataset id: 420 (Training set)
SMILES: O=S(=O)([O-])c2ccc3c(N=Nc1ccc(cc1C)C)c(O)c(cc3(c2))S(=O)(=O)[O-]
Similarity: 0.781

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA29 Aromatic diazo

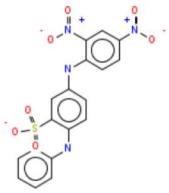


Compound #4

CAS: 3564-09-8
Dataset id: 418 (Training set)
SMILES: O=S(=O)([O-])c2ccc3c(N=Nc1cc(c(cc1C)C)C)c(O)c(cc3(c2))S(=O)(=O)[O-]
Similarity: 0.78

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA29 Aromatic diazo



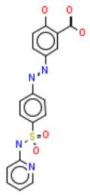
Compound #5

CAS: 6373-74-6
Dataset id: 623 (Training set)
SMILES: O=[N+]([O-])c3ccc(Nc2ccc(Nc1ccccc1)c(c2)S(=O)(=O)[O-])c(c3)[N+](=O)[O-]
Similarity: 0.778

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): SA27 Nitro aromatic

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



Compound #6

CAS: 599-79-1
Dataset id: 688 (Training set)
SMILES: O=C(O)c3cc(N=Nc1ccc(cc1)S(=O)(=O)Nc2ncccc2)ccc3(O)
Similarity: 0.775

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): SA53 Benzensulfonic ethers

Alerts (not found in the target): SA29 Aromatic diazo

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.627 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.786 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✖	**Accuracy of prediction for similar molecules** Accuracy index = 0.499 Explanation: accuracy of prediction for similar molecules found in the training set is not adequate.
⚠	**Concordance for similar molecules** Concordance index = 0.501 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.
✔	**Atom Centered Fragments similarity check** ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set.

Symbols explanation:

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

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

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

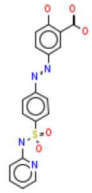
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: SA53 Benzensulfonic ethers

Benzensulfonic ethers

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

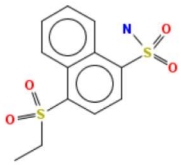


CAS: 599-79-1
Dataset id: 688 (Training set)
SMILES: O=C(O)c3cc(N=Nc1ccc(cc1)S(=O)(=O)Nc2ncccc2)ccc3(O)
Similarity: 0.775

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): SA53 Benzensulfonic ethers

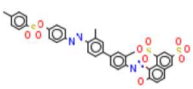
Alerts (not found in the target): SA29 Aromatic diazo



CAS: 842-00-2
Dataset id: 439 (Training set)
SMILES: O=S(=O)(N)c2ccc(c1ccccc12)S(=O)(=O)CC
Similarity: 0.725

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): SA53 Benzensulfonic ethers



CAS: 6459-94-5
Dataset id: 654 (Training set)
SMILES: O=S(=O)([O-])c6cc5ccc(O)c(N=Nc1ccc(cc1C)c4ccc(N=Nc3ccc(OS(=O)(=O)c2ccc(cc2)C)cc3)c(c4)C)c5c(c6)S(=O)(=O)[O-]
Similarity: 0.716

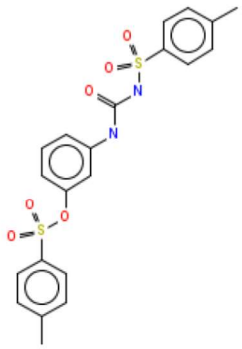
Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): SA53 Benzensulfonic ethers

Alerts (not found in the target): SA29 Aromatic diazo

1. Prediction Summary

Prediction for compound Molecule 0

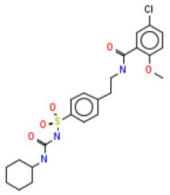


Prediction: Reliability:

Prediction is Carcinogen, but the result may be not reliable. A check of the information given in the following section should be done, paying particular attention to the following issues:
- only moderately similar compounds with known experimental value in the training set have been found
- accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found)
The following relevant fragments have been found: Carcinogenity alert no. 93

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Mutagen activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural alerts: Carcinogenity alert no. 93
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

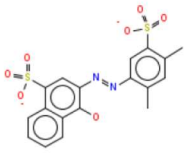
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: N.A.
Dataset id: 962 (Training set)
SMILES: O=C(NC1CCCCC1)NS(=O)(=O)c2ccc(cc2)CCNC(=O)c3cc(ccc3(OC))Cl
Similarity: 0.791

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



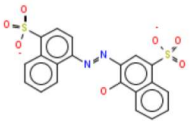
Compound #2

CAS: N.A.
Dataset id: 1055 (Training set)
SMILES: O=S(=O)([O-])c3cc(N=Nc1cc(c(cc1C)C)S(=O)(=O)[O-])c(O)c2ccccc23
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 93

Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 31; Carcinogenity alert no. 35; Carcinogenity alert no. 37; Carcinogenity alert no. 39; Carcinogenity alert no. 42; Carcinogenity alert no. 71

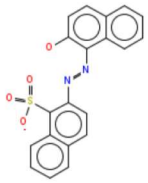


Compound #3

CAS: N.A.
Dataset id: 1054 (Training set)
SMILES: O=S(=O)([O-])c4ccc(N=Nc1cc(c2ccccc2(c1(O)))S(=O)(=O)[O-])c3ccccc34
Similarity: 0.785

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 35; Carcinogenity alert no. 37; Carcinogenity alert no. 39; Carcinogenity alert no. 42; Carcinogenity alert no. 71

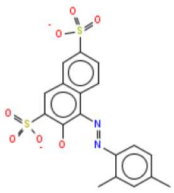


Compound #4

CAS: N.A.
Dataset id: 1113 (Training set)
SMILES: O=S(=O)([O-])c4c(N=Nc1c(O)ccc2ccccc12)ccc3ccccc34
Similarity: 0.782

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 35; Carcinogenity alert no. 37; Carcinogenity alert no. 71



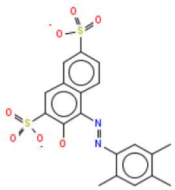
Compound #5

CAS: N.A.
Dataset id: 1056 (Training set)
SMILES: O=S(=O)([O-])c2ccc3c(N=Nc1ccc(cc1C)C)c(O)c(cc3(c2))S(=O)(=O)[O-]
Similarity: 0.781

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 31; Carcinogenity alert no. 37; Carcinogenity alert no. 42; Carcinogenity alert no. 71

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



Compound #6

CAS: N.A.
Dataset id: 1053 (Training set)
SMILES: O=S(=O)([O-])c2ccc3c(N=Nc1cc(c(cc1C)C)C)c(O)c(cc3(c2))S(=O)(=O)[O-]
Similarity: 0.78

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 31; Carcinogenity alert no. 33; Carcinogenity alert no. 37; Carcinogenity alert no. 42; Carcinogenity alert no. 71

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.518
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.788
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.668
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.333
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 0.85
Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found).

Symbols explanation:

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

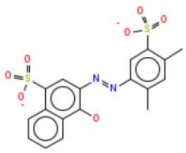
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

Fragment found: Carcinogenity alert no. 93

Structural alert for carcinogenity defined by the SMARTS: Cc1ccc(cc1)S(O)(=O)=O

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

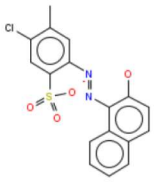


CAS: N.A.
Dataset id: 1055 (Training set)
SMILES: O=S(=O)([O-])c3cc(N=Nc1cc(c(cc1C)C)S(=O)(=O)[O-])c(O)c2ccccc23
Similarity: 0.787

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 93

Alerts (not found in the target): Carcinogenity alert no. 27; Carcinogenity alert no. 28; Carcinogenity alert no. 31; Carcinogenity alert no. 35; Carcinogenity alert no. 37; Carcinogenity alert no. 39; Carcinogenity alert no. 42; Carcinogenity alert no. 71

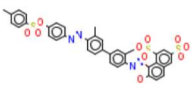


CAS: N.A.
Dataset id: 1094 (Training set)
SMILES: O=S(=O)([O-])c3cc(c(cc3(N=Nc1c(O)ccc2ccccc12))C)Cl
Similarity: 0.772

Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 93

Alerts (not found in the target): Carcinogenity alert no. 33; Carcinogenity alert no. 37; Carcinogenity alert no. 71



CAS: N.A.
Dataset id: 1138 (Training set)
SMILES: O=S(=O)([O-])c6cc5ccc(O)c(N=Nc1ccc(cc1C)c4ccc(N=Nc3ccc(OS(=O)(=O)c2ccc(cc2)C)cc3)c(c4)C)c5c(c6)S(=O)(=O)[O-]
Similarity: 0.716

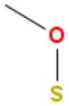
Experimental value: Carcinogen
Predicted value: Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 93

Alerts (not found in the target): Carcinogenity alert no. 23; Carcinogenity alert no. 24; Carcinogenity alert no. 28; Carcinogenity alert no. 37; Carcinogenity alert no. 71

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

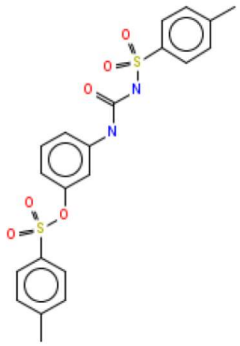
(Molecule 0) Reasoning on rare and missing Atom Centered Fragments.
The following Atom Centered Fragments have been found in the molecule, but they are not found or rarely found in the model's training set:



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

1. Prediction Summary

Prediction for compound Molecule 0

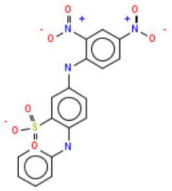


Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- only moderately similar compounds with known experimental value in the training set have been found
- 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
- some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found)
The following relevant fragments have been found: Carcinogenity alert no. 42

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Mutagen activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural alerts: Carcinogenity alert no. 42
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



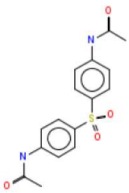
Compound #1

CAS: 6373-74-6
Dataset id: 686 (Training set)
SMILES: O=[N+]([O-])c3ccc(Nc2ccc(Nc1ccccc1)c(c2)S(=O)(=O)[O-])c(c3)[N+](=O)[O-]
Similarity: 0.778

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. 35

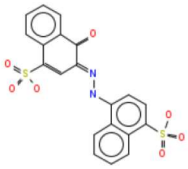


Compound #2

CAS: 77-46-3
Dataset id: 426 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.766

Experimental value: Carcinogen
Predicted value: Carcinogen

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



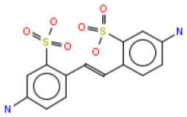
Compound #3

CAS: 3567-69-9
Dataset id: 65 (Training set)
SMILES: O=C3C(=NNc1ccc(c2ccccc12)S(=O)(=O)O)C=C(c4ccccc34)S(=O)(=O)O
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

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

Alerts (not found in the target): Carcinogenity alert no. 30; Carcinogenity alert no. 32



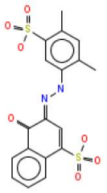
Compound #4

CAS: 7336-20-1
Dataset id: 547 (Training set)
SMILES: O=S(=O)(O)c2cc(N)ccc2(C=Cc1ccc(N)cc1S(=O)(=O)O)
Similarity: 0.756

Experimental value: NON-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

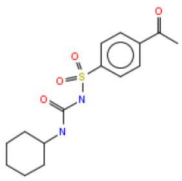
CAS: 4548-53-2
Dataset id: 341 (Training set)
SMILES: O=C2C(=NNc1cc(c(cc1C)C)S(=O)(=O)O)C=C(c3ccccc23)S(=O)(=O)O
Similarity: 0.751

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. 6; Carcinogenity alert no. 32; Carcinogenity alert no. 41

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



Compound #6

CAS: 968-81-0
Dataset id: 73 (Training set)
SMILES: O=C(NC1CCCCC1)NS(=O)(=O)c2ccc(cc2)C(=O)C
Similarity: 0.749

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.61
Explanation: the predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.769
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

Accuracy of prediction for similar molecules
Accuracy index = 0.67
Explanation: accuracy of prediction for similar molecules found in the training set is not optimal.

Concordance for similar molecules
Concordance index = 0.67
Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value.

Atom Centered Fragments similarity check
ACF index = 0.85
Explanation: some atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 infrequent fragments found).

Symbols explanation:

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

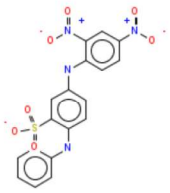
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

(Molecule 0) Reasoning on fragments/structural alerts:

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.

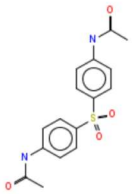


CAS: 6373-74-6
Dataset id: 686 (Training set)
SMILES: O=[N+]([O-])c3ccc(Nc2ccc(Nc1ccccc1)c(c2)S(=O)(=O)[O-])c(c3)[N+](=O)[O-]
Similarity: 0.778

Experimental value: Carcinogen
Predicted value: Carcinogen

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

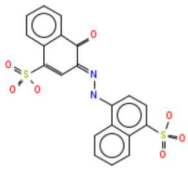
Alerts (not found in the target): Carcinogenity alert no. 35



CAS: 77-46-3
Dataset id: 426 (Training set)
SMILES: O=C(Nc1ccc(cc1)S(=O)(=O)c2ccc(cc2)NC(=O)C)C
Similarity: 0.766

Experimental value: Carcinogen
Predicted value: Carcinogen

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



CAS: 3567-69-9
Dataset id: 65 (Training set)
SMILES: O=C3C(=NNc1ccc(c2ccccc12)S(=O)(=O)O)C=C(c4ccccc34)S(=O)(=O)O
Similarity: 0.764

Experimental value: NON-Carcinogen
Predicted value: Carcinogen

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

Alerts (not found in the target): Carcinogenity alert no. 30; Carcinogenity alert no. 32

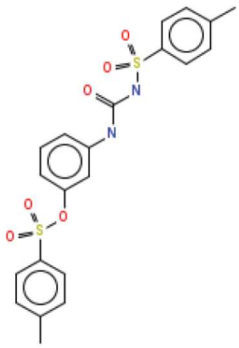
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

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

1. Prediction Summary

Prediction for compound Molecule 0

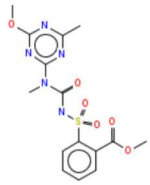


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

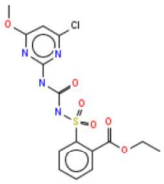
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 101200-48-0
Dataset id: 710 (Test set)
SMILES: O=C(OC)c1ccccc1S(=O)(=O)NC(=O)N(c2nc(nc(n2)C)OC)C
Similarity: 0.761

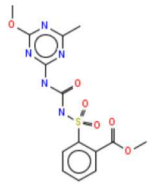
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 90982-32-4
Dataset id: 381 (Training set)
SMILES: O=C(OCC)c1ccccc1S(=O)(=O)NC(=O)Nc2nc(OC)cc(n2)Cl
Similarity: 0.76

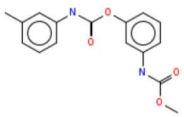
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 74223-64-6
Dataset id: 594 (Test set)
SMILES: O=C(OC)c1ccccc1S(=O)(=O)NC(=O)Nc2nc(nc(n2)C)OC
Similarity: 0.757

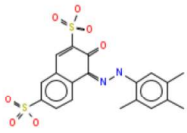
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 13684-63-4
Dataset id: 631 (Training set)
SMILES: O=C(Oc1cccc(c1)NC(=O)OC)Nc2cccc(c2)C
Similarity: 0.748

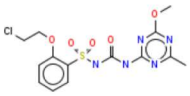
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 3564-09-8
Dataset id: 262 (Training set)
SMILES: O=C2C(=NNc1cc(c(cc1C)C)C)c3ccc(cc3(C=C2S(=O)(=O)O))S(=O)(=O)O
Similarity: 0.747

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 82097-50-5
Dataset id: 709 (Training set)
SMILES: O=C(Nc1nc(nc(n1)C)OC)NS(=O)(=O)c2ccccc2(OCCCl)
Similarity: 0.747

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.523
Explanation: the predicted compound is outside the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.76
Explanation: only moderately similar compounds with known experimental value in the training set have been found.

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

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

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

Atom Centered Fragments similarity check
ACF index = 0.6
Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

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

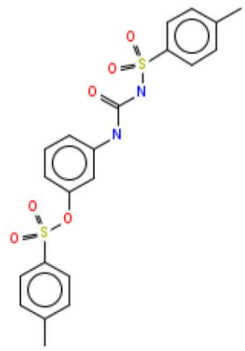
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

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

1. Prediction Summary

Prediction for compound Molecule 0

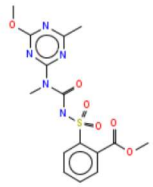


Prediction: Reliability:

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

Compound: Molecule 0
Compound SMILES: O=C(Nc2cccc(OS(=O)(=O)c1ccc(cc1)C)c2)NS(=O)(=O)c3ccc(cc3)C
Experimental value: -
Predicted Inhalation Carcinogenic class: NON-Carcinogen
Reliability: the predicted compound is outside the Applicability Domain of the model
Remarks:
none

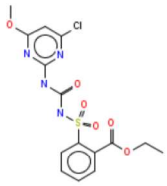
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 101200-48-0
Dataset id: 705 (Test set)
SMILES: O=C(OC)c1ccccc1S(=O)(=O)NC(=O)N(c2nc(nc(n2)C)OC)C
Similarity: 0.761

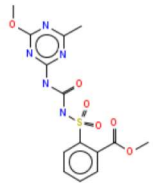
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #2

CAS: 90982-32-4
Dataset id: 338 (Training set)
SMILES: O=C(OCC)c1ccccc1S(=O)(=O)NC(=O)Nc2nc(OC)cc(n2)Cl
Similarity: 0.76

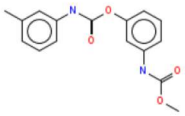
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #3

CAS: 74223-64-6
Dataset id: 575 (Test set)
SMILES: O=C(OC)c1ccccc1S(=O)(=O)NC(=O)Nc2nc(nc(n2)C)OC
Similarity: 0.757

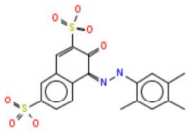
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #4

CAS: 13684-63-4
Dataset id: 617 (Training set)
SMILES: O=C(Oc1cccc(c1)NC(=O)OC)Nc2cccc(c2)C
Similarity: 0.748

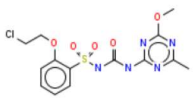
Experimental value: NON-Carcinogen
Predicted value: NON-Carcinogen



Compound #5

CAS: 3564-09-8
Dataset id: 223 (Test set)
SMILES: O=C2C(=NNc1cc(c(cc1C)C)C)c3ccc(cc3(C=C2S(=O)(=O)O))S(=O)(=O)O
Similarity: 0.747

Experimental value: Carcinogen
Predicted value: Carcinogen



Compound #6

CAS: 82097-50-5
Dataset id: 704 (Training set)
SMILES: O=C(Nc1nc(nc(n1)C)OC)NS(=O)(=O)c2ccccc2(OCCCl)
Similarity: 0.747

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

3.2 Applicability Domain:
Measured Applicability Domain Scores

✖	**Global AD Index** AD index = 0.523 Explanation: the predicted compound is outside the Applicability Domain of the model.
⚠	**Similar molecules with known experimental value** Similarity index = 0.76 Explanation: only moderately similar compounds with known experimental value in the training set have been found.
✔	**Accuracy of prediction for similar molecules** Accuracy index = 1 Explanation: accuracy of prediction for similar molecules found in the training set is good.
✔	**Concordance for similar molecules** Concordance index = 1 Explanation: similar molecules found in the training set have experimental values that agree with the predicted value.
✔	**Model's descriptors range check** Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set.
✖	**Atom Centered Fragments similarity check** ACF index = 0.6 Explanation: a prominent number of atom centered fragments of the compound have not been found in the compounds of the training set or are rare fragments (1 unknown fragments found).

Symbols explanation:

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

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

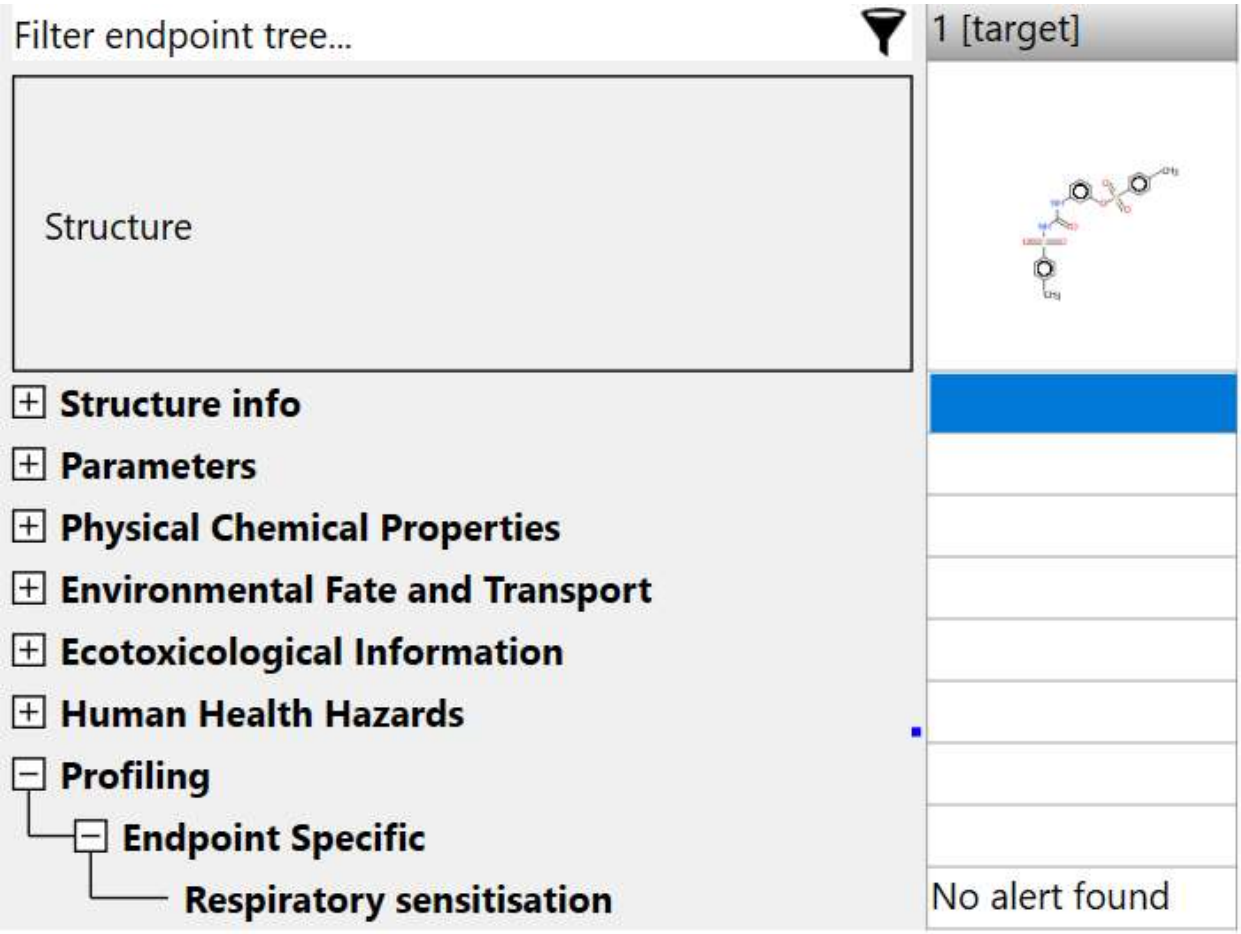
✖ The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

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

APPENDIX F: OECD Toolbox Respiratory Sensitization Results for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)



APPENDIX G: EPI Suite Modeling Results for Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) (CAS #232938-43-1)

CAS Number: 232938-43-1
SMILES : Cc1ccc(cc1)S(=O)(=O)NC(=O)Nc2cc(ccc2)OS(=O)(=O)c3ccc(cc3)C
CHEM :
MOL FOR: C21 H20 N2 O6 S2
MOL WT : 460.52
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.60
Boiling Point (deg C) : ------
Melting Point (deg C) : 157.70
Vapor Pressure (mm Hg) : 1.01E-014
Water Solubility (mg/L): 34.7
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 4.21

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 662.30 (Adapted Stein & Brown method)
Melting Pt (deg C): 288.41 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 7.4E-014 (Modified Grain method)
VP (Pa, 25 deg C) : 9.87E-012 (Modified Grain method)
Subcooled liquid VP: 2.07E-013 mm Hg (-999 deg C, user-entered VP)
: 2.76E-011 Pa (-999 deg C, user-entered VP)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 15.61
log Kow used: 2.60 (user entered)
melt pt used: 157.70 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 0.0012255 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters
Sulfonyl Ureas

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 1.66E-015 atm-m3/mole (1.68E-010 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: 1.764E-016 atm-m3/mole (1.787E-011 Pa-m3/mole)
VP: 1.01E-014 mm Hg (source: User-Entered)

WS: 34.7 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.60 (user entered)
Log Kaw used: -13.168 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 15.768
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.6376
Biowin2 (Non-Linear Model) : 0.0850
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.0318 (months)
Biowin4 (Primary Survey Model) : 3.0463 (weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : -0.1513
Biowin6 (MITI Non-Linear Model): 0.0031
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -1.0526
Ready Biodegradability Prediction: NO

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 2.76E-011 Pa (2.07E-013 mm Hg)
Log Koa (Koawin est): 15.768
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 1.09E+005
Octanol/air (Koa) model: 1.44E+003
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 201.2720 E-12 cm3/molecule-sec
Half-Life = 0.053 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 0.638 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
1 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.152E+004 L/kg (MCI method)

Log Koc: 4.062 (MCI method)
Koc : 451.1 L/kg (Kow method)
Log Koc: 2.654 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.382 (BCF = 24.13 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.0786 days (HL = 0.08344 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.255 (BCF = 17.97)
Log BAF Arnot-Gobas method (upper trophic) = 1.255 (BAF = 17.97)
log Kow used: 2.60 (user entered)

Volatilization from Water:
Henry LC: 1.76E-016 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 7.124E+012 hours (2.968E+011 days)
Half-Life from Model Lake : 7.771E+013 hours (3.238E+012 days)

Removal In Wastewater Treatment:
Total removal: 3.41 percent
Total biodegradation: 0.11 percent
Total sludge adsorption: 3.31 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	0.00306	1.28	1000
Water	8.18	1.44e+003	1000
Soil	84.6	2.88e+003	1000
Sediment	7.17	1.3e+004	0

Persistence Time: 2.88e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.00306	1.28	1000
Water	8.18	1.44e+003	1000
water	(8.04)		
biota	(0.00016)		
suspended sediment	(0.139)		
Soil	84.6	2.88e+003	1000
Sediment	7.17	1.3e+004	0

Persistence Time: 2.88e+003 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount	Half-Life	Emissions

	(percent)	(hr)	(kg/hr)
Air	0.00385	1.28	1000
Water	14.1	1.44e+003	1000
water	(14.1)		
biota	(0.00028)		
suspended sediment	(0.00345)		
Soil	85.8	2.88e+003	1000
Sediment	0.147	1.3e+004	0
Persistence Time:	2.29e+003 hr		

Licensed GreenScreen® Profilers

Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

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

Benzenesulfonamide, 4-Methyl-N-[[[3-[[(4-methylphenyl)sulfonyl]oxy]phenyl] Amino]carbonyl]-) GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

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