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POTASSIUM CITRATE

(CAS #866-84-2)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: March 18, 2024

Expiration Date: March 18, 2029

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TABLE OF CONTENTS

GreenScreen® Executive Summary for Potassium Citrate (CAS #866-84-2) i
Chemical Name 1
GreenScreen® Summary Rating for Potassium Citrate 2
Environmental Transformation Products 3
Introduction 3
U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL) 3
GreenScreen® List Translator Screening Results 4
Hazard Statement and Occupational Control 4
Physicochemical Properties of Potassium Citrate 4
Toxicokinetics 5
Hazard Classification Summary 6
- Group I Human Health Effects (Group I Human) 6
  - Carcinogenicity (C) Score 6
  - Mutagenicity/Genotoxicity (M) Score 7
  - Reproductive Toxicity (R) Score 9
  - Developmental Toxicity incl. Developmental Neurotoxicity (D) Score 10
  - Endocrine Activity (E) Score 11
- Group II and II* Human Health Effects (Group II and II* Human) 11
  - Acute Mammalian Toxicity (AT) (Group II) Score 11
  - Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score 12
  - Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score 13
  - Neurotoxicity (single dose, N-single) (Group II) Score 14
  - Neurotoxicity (repeated dose, N-repeated) (Group II*) Score 15
  - Skin Sensitization (SnS) (Group II*) Score 15
  - Respiratory Sensitization (SnR) (Group II*) Score 16
  - Skin Irritation/Corrosivity (IrS) (Group II) Score 17
  - Eye Irritation/Corrosivity (IrE) (Group II) Score 17
- Ecotoxicity (Ecotox) 18
  - Acute Aquatic Toxicity (AA) Score 18
  - Chronic Aquatic Toxicity (CA) Score 20
- Environmental Fate (Fate) 20
  - Persistence (P) Score 20
  - Bioaccumulation (B) Score 21
- Physical Hazards (Physical) 22
  - Reactivity (Rx) Score 22
  - Flammability (F) Score 22

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Use of New Approach Methodologies (NAMs) in the Assessment, Including Uncertainty Analyses of Input and Output 23
References 26
APPENDIX A: Hazard Classification Acronyms 29
APPENDIX B: Results of Automated GreenScreen® Score Calculation for Potassium Citrate (CAS #866-84-2) 30
APPENDIX C: Pharos Output for Potassium Citrate (CAS #866-84-2) 31
APPENDIX D: Toxtree Carcinogenicity Results for Potassium Citrate (CAS #866-84-2) 32
APPENDIX E: VEGA Carcinogenicity Results for the Surrogate Citric Acid (CAS #77-92-9) 33
APPENDIX F: OncoLogic™ Carcinogenicity Results for Potassium Citrate (CAS #866-84-2) 53
APPENDIX G: Danish QSAR Carcinogenicity Results for Potassium Citrate (CAS #866-84-2) 54
APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Potassium Citrate (CAS #866-84-2) 55
APPENDIX I: ECOSAR Modeling Results for Potassium Citrate (CAS #866-84-2) 56
APPENDIX J: EPI Suite™ Modeling Results for Potassium Citrate (CAS #866-84-2) 58
APPENDIX K: Known Structural Alerts for Reactivity 62
APPENDIX L: Change in Benchmark Score 66
Licensed GreenScreen® Profilers 67

TABLE OF FIGURES

Figure 1: GreenScreen® Hazard Summary Table for Potassium Citrate 3

TABLE OF TABLES

Table 1: GHS H Statements for Potassium Citrate (CAS #866-84-2) (ECHA, CAS #866-84-2, 2024) 4
Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Potassium Citrate (CAS #866-84-2) 4
Table 3: Physical and Chemical Properties of Potassium Citrate (CAS #866-84-2) 5
Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses 23
Table 5: Change in GreenScreen® Benchmark™ for Potassium Citrate 66

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GreenScreen® Executive Summary for Potassium Citrate (CAS #866-84-2)

Potassium citrate is a white crystalline solid under standard temperature and pressure that is not reactive or flammable. Since it decomposes prior to boiling, it is not a volatile organic chemical (VOC). Potassium citrate functions as a buffering and chelating agent. The United States Food and Drug Administration (U.S. FDA) recognizes potassium citrate, as tripotassium citrate monohydrate (CAS #6100-05-6), as an indirect food additive and as generally recognized as safe (GRAS).

Potassium citrate was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement" Due to Data Gaps). Prior to data gap analysis, sodium citrate was assigned a preliminary Benchmark™ Score of 4 based on the following hazard score combinations:

- Benchmark 4 (lowered to Benchmark 3_{DG} because of data gaps)
    - Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D),
    - Low Group II Human Toxicity (acute toxicity-AT, single dose systemic toxicity-STs, single dose neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE),
    - Low Group II* Human Toxicity (repeated dose systemic toxicity-STr*, repeated dose neurotoxicity-Nr*, skin sensitization-SnS*, and respiratory sensitization-SnR*),
    - Low Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA),
    - Very Low Persistence-P,
    - Low Bioaccumulation-B, and
    - Low Physical Hazards (reactivity-Rx and flammability-F).

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), potassium citrate does not meet the requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. In a worst-case scenario, if potassium citrate were assigned a High score for the data gap E, it would be categorized as a Benchmark 1 Chemical.

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

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

Type I (input data) uncertainties in potassium citrate's NAMs dataset include insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Potassium citrate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of Oncologic models to evaluate sodium citrate's carcinogenic potential, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of potassium citrate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

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GreenScreen® Hazard Summary Table for Potassium Citrate

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

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GreenScreen® Chemical Assessment for Potassium Citrate (CAS #866-84-2)

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

GreenScreen® Assessment (v.1.4) Prepared By:
Name: Zach Guerrette, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: January 23, 2024

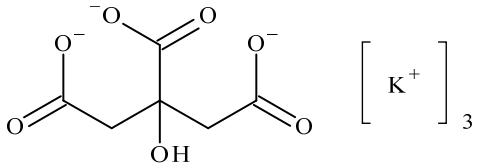
Quality Control Performed By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: March 18, 2023

Expiration Date: March 18, 2029[2]

Chemical Name: Potassium Citrate

CAS Number: 866-84-2

Chemical Structure(s):



Also called:
TRIPOTASSIUM CITRATE; Potassium citrate anhydrous; Kaliksir; Litocit; 7778-49-6; Potassiumcitrate; Urocit K; K citrate; Potassium tribasic citrate; ACALKA; CCRIS 6566; Kalii citras; EINECS 212-755-5; Potassium Citrate (anhydrous); 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tripotassium salt; CHEBI:64733; potassium citrate (anh.); anhydrous potassium citrate; tripotassium 2-hydroxypropane-1,2,3-tricarboxylate; tripotassium;2-hydroxypropane-1,2,3-tricarboxylate; tripotassium citrate (anh.); 86R1NVR0HW; anhydrous tripotassium citrate; INS NO.332(II); tripotassium citrate (anhydrous); INS-332(II); EC 212-755-5;E-332(II); Porekal; Kajos; NSC-760107; Seltz-K; Citric acid, tripotassium salt; potassium citrate (II); CHEBI:64746; Citrate, Potassium; tripotassium citrate anhydrous; potassium citrate (USP-RS); potassium citrate anhydrous (mart.); potassium citrate anhydrous [mart.]; potassium citrate (EP MONOGRAPH); potassium citrate (USP monograph); Anhydrous, Potassium Citrate; Potassium-cit; Kali Citricum; tripotassium cirtate; EINECS 231-905-0; tri potassium citrate; citric acid tripotassium salt (anh.); potassium citrate extended release; citric acid tripotassium salt (anhydrous); E332; potassium citrate anhydrous [HSDB]; potassium 2-hydroxypropane-1,2,3-tricarboxylate; tripotassium 2-oxidanylpropane-1,2,3-tricarboxylate; 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, potassium salt (1:?); 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, potassium salt (1:3) (PubChem 2024)

[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).

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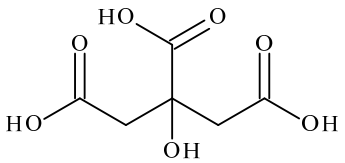
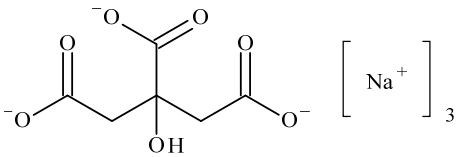
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Limited potassium citrate data were identified for some endpoints. ToxServices used data for citric acid (CAS #77-92-9) and trisodium citrate (CAS #68-04-2) to address these data gaps as these chemicals share the citrate moiety with potassium citrate. The potassium ions are not expected to contribute significantly towards the toxicity of potassium citrate since they are natural constituents of surface waters and biological fluids.



Surrogate: Citric acid (CAS #77-92-9)



Surrogate: Trisodium citrate (CAS #68-04-2)

Identify Applications/Functional Uses (EC 2024)**:**
1. Buffering agent
2. Chelating agent

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

<u>GreenScreen® Summary Rating for Potassium Citrate</u>[4,5 6,7]: Potassium citrate was assigned a **GreenScreen Benchmark™ Score of 3_{DG}** ("Use but Still Opportunity for Improvement" Due to Data Gaps) (CPA 2018b). Prior to data gap analysis, sodium citrate was assigned a preliminary Benchmark™ Score of 4 based on the following hazard score combinations:

- Benchmark 4 (lowered to Benchmark 3_{DG} because of data gaps)
    - Low Group I Human Toxicity (carcinogenicity-C, mutagenicity-M, reproductive toxicity-R, and developmental toxicity-D),
    - Low Group II Human Toxicity (acute toxicity-AT, single dose systemic toxicity-STs, single dose neurotoxicity-Ns, skin irritation-IrS, and eye irritation-IrE),
    - Low Group II* Human Toxicity (repeated dose systemic toxicity-STr*, repeated dose neurotoxicity-Nr*, skin sensitization-SnS*, and respiratory sensitization-SnR*),
    - Low Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA),

[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.

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- Very Low Persistence-P,
- Low Bioaccumulation-B, and
- Low Physical Hazards (reactivity-Rx and flammability-F).

Data gaps (DG) exist for endocrine activity-E and repeated dose neurotoxicity-Nr*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), potassium citrate does not meet the requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. In a worst-case scenario, if potassium citrate 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 Potassium Citrate

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

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

Environmental Transformation Products

Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for a Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As potassium citrate is readily biodegradable, it is not expected to have relevant transformation products.

Introduction

Potassium citrate functions as a buffering and chelating agent (EC 2024). It is produced via neutralization of citric acid with potassium bicarbonate or potassium carbonate (HSDB 2003). The United States Food and Drug Administration (U.S. FDA) recognizes potassium citrate, as tripotassium citrate monohydrate (CAS #6100-05-6), as an indirect food additive under 21 CFR §175.300 and as generally recognized as safe (GRAS) under 21 CFR §184.1625 (U.S. FDA 2024). The Cosmetic Ingredient Review (CIR) Expert Panel concluded potassium citrate is safe for use in cosmetics in the present practices of use and concentration, up to 0.5% in leave-on products and up to 0.6% in rinse-off products (CIR 2014).

ToxServices assessed potassium citrate against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2024b). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

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Potassium citrate is listed on the U.S. EPA SCIL as a chelating agent and processing aid and additive with a full green circle (FGC).

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 2024) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for potassium citrate can be found in Appendix C.

- Potassium citrate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Potassium citrate is not listed on the U.S. DOT list.
- Potassium citrate is not listed 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

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for potassium citrate, as indicated in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for Potassium Citrate (CAS #866-84-2) (ECHA, CAS #866-84-2, 2024)

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

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Potassium Citrate (CAS #866-84-2)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Gloves, eye protection, protective clothing, dust mask	Expert judgement	None identified	N/A

Physicochemical Properties of Potassium Citrate

Potassium citrate is a white crystalline solid under standard temperature and pressure. Based on data for citric acid, potassium citrate has a low vapor pressure (1.65E-8 mm Hg), indicating it exists mostly in the solid phase, and is more soluble in water than in octanol (log K_{ow} = -1.8 to -0.2).

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

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Table 3: Physical and Chemical Properties of Potassium Citrate (CAS #866-84-2)		
Property	**Value**	**Reference**
Molecular formula	$K_3C_6H_5O_7$ $C_6H_5K_3O_7$	PubChem 2024
SMILES Notation	C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+].[K+].[K+].[K+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O	PubChem 2024 U.S. EPA 2024
Molecular weight	306.39 g/mol	PubChem 2024
Physical state	Solid	ECHA, CAS #866-84-2, 2024
Appearance	White, crystalline	ECHA, CAS #866-84-2, 2024
Melting point	Decomposes at 230°C	ECHA, CAS #866-84-2, 2024
Boiling point	Decomposes prior to boiling	ECHA, CAS #866-84-2, 2024
Vapor pressure	< 2.21E-6 Pa (1.65E-8 mm Hg) at 25°C for citric acid 2.09E-12 mm Hg at 25°C	ECHA, CAS #866-84-2, 2024 CIR 2014
Water solubility	606 g/L (606,000 mg/L) at 25°C 1,540 g/L (1,540,000 mg/L) at 25°C	ECHA, CAS #866-84-2, 2024
Dissociation constant	Not relevant for a salt pKa 1 = 3.13, pKa 2 = 4.76, and pKa 3 = 6.4 for citric acid	ECHA, CAS #866-84-2, 2024
Density/specific gravity	Relative density = 1.98 at 20°C	ECHA, CAS #866-84-2, 2024
Partition coefficient	Log K_{ow} = -1.8 to -0.2 for citric acid	ECHA, CAS #866-84-2, 2024

Toxicokinetics

Absorption
Surrogate: Citric acid (CAS #77-92-9): Citric acid is readily absorbed following oral administration (CIR 2014).

Distribution
Surrogate: Citric acid (CAS #77-92-9): Citric acid is found in all body tissues, with the greatest percentage in the hard tissue of bones (ECHA 2018).

Metabolism
Surrogate: Citric acid (CAS #77-92-9): Citric acid originating endogenously or exogenously is metabolized in the cellular energy processes and serves as an intermediate in the Krebs or citric acid cycle (CIR 2014).

Excretion/Elimination
Surrogate: Citric acid (CAS #77-92-9): Approximately 65-90% of circulating citric acid is reabsorbed in the glomerulus of the kidneys, and the remaining 10-35% is excreted in the urine (CIR 2014). Metabolized citric acid is eliminated as exhaled carbon dioxide (ECHA 2018).

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Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Potassium citrate was assigned a score of Low for carcinogenicity based on negative carcinogenicity results in limited studies of the surrogate citric acid supported by negative modeling predictions. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on limited experimental evidence and 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.
- UNEP 2004
  - *Surrogate: Citric acid (CAS #77-92-9):* In a two-year dietary study in 20 male rats that received 3% or 5% citric acid in feed (contributing doses of 1,200 or 2,000 mg/kg/day, respectively, according to the SIDS dossier authors), no evidence of carcinogenicity was reported. The SIDS dossier reports this study with a reliability score of 4 (not assignable) (Horn et al. 1957).
  - *Surrogate: Citric acid (CAS #77-92-9):* Insufficient or negative evidence of a tumor-promoting effect was noted in several non-standard studies in which rats were co-treated with citric acid or citrate salt and a known carcinogen.
  - *Surrogate: Citric acid (CAS #77-92-9):* Based on the limited evidence available, UNEP concluded that citric acid is not a potential carcinogen.
- Toxtree 2018
  - Potassium citrate does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (Appendix D).
- VEGA 2023
  - VEGA does not accept potassium salts as input. Therefore, ToxServices used the structure for citric acid as input into VEGA.
  - *Surrogate: Citric acid (CAS #77-92-9)*: ToxServices predicted the carcinogenicity potential of citric acid using the following five VEGA v1.2.3 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/ISSCAN-CGX v1.0.2, IRFMN/Antares v1.0.2, IRFMN oral classification v1.0.1, and IRFMN inhalation classification v1.0.1 models. If an external compound is beyond the defined scope of a given model, it is considered outside that model' s applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index range from 0 (worst case) to 1 (best case). Generally, AD index values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016). The CAESAR, ISS, IRFMN-ISSCAN-CGX, and IRFMN-Antares models indicate citric acid is not a carcinogen based on experimental data. The results for these models are not discussed further herein (Appendix E).
  - *Surrogate: Citric acid (CAS #77-92-9)*: Citric acid is within the AD of the IRFMN oral classification model (global AD index = 0.893) and the model predicts that it is a non-carcinogen. The similarity index of 0.797 and the accuracy and concordance indices of 1 support the use of this model. Therefore, ToxServices concluded the IRFMN oral classification model's prediction of citric acid as a non-carcinogen is reliable (Appendix E).
  - *Surrogate: Citric acid (CAS #77-92-9)*: Citric acid is within the AD of the IRFMN inhalation classification model (global AD index = 0.758) and the model predicts that it is a

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non-carcinogen. The similarity index of 0.808 and the accuracy index of 1 support the use of this model, while the concordance index of 0.506 does not support the use of this model due to disagreement between the measured and predicted values for similar chemicals. Therefore, ToxServices concluded the IRFMN inhalation classification model's prediction of citric acid as a non-carcinogen is not reliable (Appendix E).

- U.S. EPA 2019, 2021
  - ToxServices attempted to evaluate the carcinogenic potential of potassium citrate using OncoLogic™ v9.0 (U.S. EPA 2021). However, this chemical belongs to a class of compounds not supported by the software at the time of writing (Appendix F). Additionally, potassium citrate does not belong to the organic chemical classes included in the OncoLogic™ v8.0 (U.S. EPA 2019). Therefore, ToxServices could not use OncoLogic™ to determine the carcinogenic potential of potassium citrate.
- DTU 2024
  - Potassium citrate is inside of the applicability domains of all seven E Ultra FDA RCA carcinogenicity models included in the Danish (Q)SAR Models, and is predicted to be negative in all seven (male rats, female rats, rats, male mice, female mice, mice, and rodents). Additionally, it is inside the applicability domains for four of the seven Leadscope FDA RCA carcinogenicity models included in the Danish (Q)SAR Models, and is predicted to be negative in all four (female rats, rats, mice, and rodents). Finally, potassium citrate is outside the applicability domain for the battery of liver-specific cancer models in mice or rats, with a negative, in domain prediction from the SciQSAR model (Appendix G).
- In summary, the surrogate citric acid was not carcinogenic in a limited two-year carcinogenicity study in male rats (the current OECD Guideline 451 recommends testing be performed with 50 animals per sex, link) and did not exhibit tumor-promoting activity in non-standard tests performed with known carcinogens. Potassium citrate does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity as identified with Toxtree (2018), and in domain modeling predictions from VEGA (2023) and Danish (Q)SAR Models (DTU 2024) indicate potassium citrate is not likely to be carcinogenic. Therefore, ToxServices concludes potassium citrate is not likely to possess carcinogenic potential.

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

Potassium citrate was assigned a score of Low for mutagenicity/genotoxicity based on negative *in vitro* mutagenicity results and negative *in vivo* clastogenicity results for the surrogate citric acid, and ToxServices not classifying it as genotoxic under GHS criteria. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *In vitro*: *Surrogate: Citric acid (CAS #77-92-9)*: Positive results for clastogenicity were obtained in a mammalian cell micronucleus test (GLP status not specified) conducted in a manner similar to OECD Guideline 487. Human peripheral lymphocytes were exposed to citric acid (purity not specified) in water at 50-3,000 µg/mL without metabolic activation. Treatment induced cytotoxicity at 3,000 µg/mL and statistically significantly increased the percentage of binucleated cells with micronuclei at 50 (1.65%), 100 (2.35%), and 200 µg/mL (2.60%) relative to the negative control (0.30%) in a concentration-dependent

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manner. The vehicle and positive (cyclophosphamide) controls were reported as valid. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yilmaz et al. 2008).

- *In vitro*: Surrogate: Citric acid (CAS #77-92-9): Negative results for mutagenicity were obtained in a bacterial reverse mutation assay (GLP status not specified) performed in a manner similar to OECD Guideline 471 (no specific positive controls included). *S. typhimurium* tester strains TA92, TA94, TA98, TA100, TA1535, and TA1537 were exposed to citric acid (99.9% purity) in phosphate buffer at up to 5,000 µg/plate with and without exogenous metabolic activation (S9 mix from livers of polychlorinated biphenyl-induced rats). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. Results for the vehicle and untreated negative controls were not specified; positive results were obtained with other test substances evaluated at the same time as citric acid. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Ishidate et al. 1984).
- *In vitro*: Surrogate: Citric acid (CAS #77-92-9): Negative results for clastogenicity were obtained in a mammalian cell chromosome aberration test (GLP status not specified) conducted in a manner similar to OECD Guideline 473 (no activation). Chinese hamster lung cells were exposed to citric acid (99.9% purity) in phosphate buffer at up to 5.0 mg/mL without exogenous metabolic activation. Treatment did not increase the frequency of chromosome aberrations in the absence of metabolic activation. The vehicle and untreated negative controls were not specified, but other substances tested at the same time provided positive results. The REACH dossier reports this study with a reliability score of 4 (not assignable) (Ishidate et al. 1984).
- *In vivo*: Surrogate: Citric acid (CAS #77-92-9): Negative results for clastogenicity were obtained in a non-GLP-compliant mammalian bone marrow chromosome aberration test conducted in a manner similar to OECD Guideline 475 (only 50 cells evaluated per animal). Male Sprague-Dawley rats (5/dose group) were administered gavage doses of citric acid (purity not specified) in physiological saline as a single dose (acute study) or daily for 5 days (subacute study). For the acute study, the animals were dosed with 300, 500, 3,000, or 3,500 mg/kg and were sacrificed 6, 24, or 48 hours after dosing. For the subacute study, the animals were dosed with 1.2, 12, or 120 mg/kg/day on 5 sequential days and were sacrificed 6 hours after administration of the final dose. Treatment did not increase the frequency of chromosome aberrations in the acute or subacute studies. The vehicle and positive (triethylenemelamine) controls were reported as valid. The REACH dossier reports this study with a reliability score of 2 (reliable with restriction) (Unnamed study 1975).
- *In vivo*: Surrogate: Citric acid (CAS #77-92-9): Negative results for genotoxicity were obtained in a non-GLP-compliant dominant lethal assay performed in a manner similar to EU Method B.22 (no information regarding mating). Male Sprague-Dawley rats (10/group) were administered gavage doses of citric acid (purity not specified) in physiological saline either as a single dose or daily for 5 consecutive days. The single doses were 0, 300, 500, or 3,500 mg/kg and the subacute doses were 1.2, 12.0 or 120 mg/kg/day. Treated males were then mated with two virgin females each week for 7 or 8 weeks. The females were sacrificed two weeks after mating and the fertility indices, pre-implantation loss, and lethal effects were evaluated. Treatment did not adversely affect these parameters in the acute study. Treatment with 1.2 and 12.0 mg/kg/day in the subacute study increased the preimplantation losses per female during week 4 but not during week 1 or week 7 and no adverse effects were noted on this endpoint at the high dose during week 4. The vehicle and positive (triethylenemelamine) controls were reported as valid. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1975).

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- UNEP 2004
  - *Surrogate: Citric acid (CAS #77-92-9)*: Citric acid was not mutagenic in *in vitro* tests with *Salmonella typhimurium*, *Escherichia coli*, or *Saccharomyces cerevisiae*, in both the presence and absence of metabolic activation. It was negative for chromosomal damage in human and hamster cell cultures and in a dominant lethal assay in rats.
- ECHA, CAS #77-92-9, 2024
  - *In vitro*: *Surrogate: Citric acid (CAS #77-92-9)*: Positive results for genotoxicity were obtained in a comet assay (GLP status not specified). Human lymphocytes were exposed to citric acid (≥ 99% purity) in distilled water at 50-3,000 µg/mL without exogenous metabolic activation. Treatment induced cytotoxicity at 3,000 µg/mL and statistically significantly increased the mean tail intensity and mean tail length at 200 µg/mL. The vehicle control was reported as valid, but the positive control (hydrogen peroxide) was not considered valid due to the lack of historical data for this chemical and other genotoxicity tests not using it as a positive control. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yilmaz et al. 2014).
  - *In vitro*: *Surrogate: Citric acid (CAS #77-92-9)*: Negative results for mutagenicity were obtained in a bacterial reverse mutation assay (GLP status not specified) conducted in a manner similar to OECD Guideline 471 (only 4 strains and 3 concentrations used). *S. typhimurium* tester strains TA97, TA98, TA100, and TA104 were exposed to citric acid (purity and vehicle not specified) at 0, 500, or 1,000 µg/plate with and without exogenous metabolic activation (S9 mix from livers of phenobarbital-induced rats). Treatment did not increase the mutation frequency in the presence or absence of metabolic activation. The vehicle and one positive (2-aminoanthracene) controls were reported as valid. The REACH dossier reports this study with a reliability score of 4 (not assignable) (Al-ani and Al-Lami 1988).
  - *In vitro*: *Surrogate: Citric acid (CAS #77-92-9)*: Positive results for clastogenicity were obtained in a mammalian cell chromosome aberration test (GLP-compliance not specified) conducted in a manner similar to OECD Guideline 473 (no activation, sister chromatid unions scored as aberrations). Human peripheral lymphocytes were exposed to citric acid (purity not specified) in water at 50-3,000 µg/mL without exogenous metabolic activation. After the 24- or 48-hour exposures, treatment at 3,000 µg/mL induced cytotoxicity and treatment with 50, 100, or 200 µg/mL statistically significantly increased the percentage of abnormal cells and the number of chromosome aberrations per cell. Concentration-dependent increases were identified for both endpoints at the 24-hour exposure and for the number of chromosome aberrations/cell at the 48-hour exposure. The vehicle and positive controls were reported as valid. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yilmaz et al. 2008).
- In summary, the surrogate citric acid was not mutagenic *in vitro* but produced positive results in some *in vitro* clastogenicity assays. However, it was not clastogenic in an *in vivo* bone marrow chromosome aberration test and was not genotoxic in a dominant lethal assay, indicating citric acid is not likely to be genotoxic in intact organisms. Therefore, ToxServices did not classify potassium citrate as genotoxic under GHS criteria (UN 2023).

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

Potassium citrate was assigned a score of Low for reproductive toxicity based on the lack of adverse effects on reproductive parameters in one- and two-generation studies in rats exposed to the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in

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the score is high as it is based on measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2024c
  - *Surrogate: Citric acid (CAS #77-92-9)*: In a two-generation study, rats were provided feed containing 0 or 1.2% citric acid (contributing doses of 0 or 600 mg/kg/day). Exposure began 29 weeks prior to mating and continued for a few months after mating. Treatment did not adversely affect reproduction; therefore, the authors assigned the reproductive toxicity NOAEL as 600 mg/kg/day, the only dose tested.
  - *Surrogate: Citric acid (CAS #77-92-9)*: In a one-generation study, female rats (strain and number not specified) and female mice (strain and number not specified) were provided feed containing 5% citric acid (contributing a dose of 2,500 mg/kg/day) prior to, during, and after mating. Treatment reduced the mouse body weight gain and survival time (statistical significance not provided). Treatment did not adversely affect pregnancy rate, litter size, or pup survival during the postnatal period. No effects identified in rats were specifically stated. The authors identified a LOAEL of 2,500 mg/kg/day for mice based on the reduced body weight gain and survival. ToxServices identified a reproductive toxicity NOAEL of 2,500 mg/kg/day based on the lack of adverse effects on reproductive parameters at the only dose tested.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Potassium citrate was assigned a score of Low for developmental toxicity based on the lack of developmental toxicity produced by the surrogate citric acid in experimental animals up to the highest dose tested in prenatal developmental toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low because although the REACH dossier assigned Klimisch 2 scores to the developmental toxicity studies on the surrogate citric acid, OECD assigned lower reliability scores, the studies were not GLP-compliant or according to guidelines, and the secondary sources provided limited and conflicting details.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- CIR 2014
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: An embryotoxicity test was performed with 9.5-day-old embryos isolated from pregnant female Han Wistar rats exposed to ≤ 115 µmol/L trisodium citrate without exogenous metabolic activation. Treatment did not induce developmental toxicity including abnormalities or alter crown-rump length (Bechter and Brouillard 1988).
- UNEP 2004; ECHA, CAS #68-04-2, 2024
  - *Surrogate: Citric acid (CAS #77-92-9)*: No developmental toxicity was detected in a non-GLP-compliant study in which pregnant female albino CD-1 mice (30/dose group) were administered gavage doses of citric acid (purity not specified) at ≤ 241 mg/kg/day on GD 6-15. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) while the SIDS dossier reports this study with a reliability score of 4 (not assignable) (Food & Drug Research Laboratories, Inc. 1973 or Unnamed summary report 1973). *ToxServices notes that the 'Applicant's summary and conclusion' section of the REACH dossier study entry identifies the animals as pregnant rats.*

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- *Surrogate: Citric acid (CAS #77-92-9)*: No developmental toxicity was detected in a non-GLP-compliant study in which pregnant female Dutch belted rabbits (25/dose group) were administered gavage doses of citric acid (purity not specified) at ≤ 425 mg/kg/day on GD 6-15. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) while the SIDS dossier reports this study with a reliability score of 4 (not assignable) (Food & Drug Research Laboratories, Inc. 1973 or Unnamed summary report 1973).
- *Surrogate: Citric acid (CAS #77-92-9)*: No developmental toxicity was detected in a non-GLP-compliant study in which pregnant hamsters (30/dose group) were administered gavage doses of citric acid (purity not specified) at ≤ 272 mg/kg/day on GD 6-10. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) while the SIDS dossier reports this study with a reliability score of 4 (not assignable) (Food & Drug Research Laboratories, Inc. 1973 or Unnamed summary report 1973). *ToxServices notes that, in the REACH dossier, the experimental animals are identified as albino CD-1 mice in the test animals section and as pregnant hamsters in the 'Applicant's summary and conclusion' section.*
- *Surrogate: Citric acid (CAS #77-92-9)*: No developmental toxicity was detected in a non-GLP-compliant study in which pregnant female Wistar rats (25/dose group) were administered gavage doses of citric acid (purity not specified) at ≤ 295 mg/kg/day on GD 6-15. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) while the SIDS dossier reports this study with a reliability score of 4 (not assignable) (Food & Drug Research Laboratories, Inc. 1973 or Unnamed summary report 1973).

Endocrine Activity (E) Score (H, M, or L): DG
Potassium citrate was assigned a score of Data Gap for endocrine activity based on the lack of data for endocrine receptor binding or circulating endocrine hormone 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.
- UNEP 2004
  - *Surrogate: Citric acid (CAS #77-92-9)*: Citric acid is a natural component of eukaryotic cellular energy metabolism as part of the citric acid or Krebs cycle. It is unlikely to exhibit endocrine activity.

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
Potassium citrate was assigned a score of Low for acute toxicity based on based on oral LD_{50} values ≥ 5,400 mg/kg in rats and mice and a dermal LD_{50} > 2,000 mg/kg in rats for the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are > 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate.

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

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  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: LD_{50} (mouse, Füllinsdorf Albino (SPF), male/female) = 5,400 mg/kg. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1981).
  - *Dermal*: *Surrogate: Citric acid (CAS #77-92-9)*: LD_{50} (rats, Sprague-Dawley, male/female) > 2 000 mg/kg (GLP-compliant, OECD Guideline 402). The REACH dossier reports this study with a reliability score of 1 (reliable without restriction (Unnamed study 2006).
- ECHA, CAS #77-92-9, 2024
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: LD_{50} (rat, ICR-JCL, male) = 11,700 mg/kg. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yokotani et al. 1971).
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: LD_{50} (mice, SD-JCL, male) = 5,790 mg/kg. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yokotani et al. 1971).

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

Potassium citrate was assigned a score of Low for systemic toxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant following single exposures for respiratory irritation under GHS criteria based on oral and dermal data for the surrogate citric acid. 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 reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2004:
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: A young woman ingested a single dose of 25 g (417 mg/kg) of citric acid, causing her to vomit and nearly die (Nazario 1952).
  - *Inhalation*: *Surrogate: Citric acid (CAS #77-92-9)*: Exposure to an unspecified concentration of citric acid caused bronchoconstriction in dogs, "which have non-specific airway hyperactivity." No additional details were provided (Lindemann et al. 1989).
  - *Inhalation*: *Surrogate: Citric acid (CAS #77-92-9)*: In human asthmatics, unspecific concentrations of citric acid produced bronchoconstriction. No additional details were provided (Lindemann et al. 1989).
- ECHA, CAS #866-84-2, 2024
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity study that identified an oral LD_{50} value of 5,400 mg/kg in Füllinsdorf Albino (SPF) mice (5/sex/group), the animals were dosed via gavage with 3,000, 4,200, 6,000, 8,500, or 12,000 mg/kg. Treatment with 6,000 mg/kg produced "slight relaxation" two hours after dosing. No clinical signs of toxicity were identified at ≤ 4,200 mg/kg and all animals dosed with ≥ 8,500 mg/kg died. No data for body weights were presented and gross pathological observations were not conducted. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1981).
  - *Dermal*: *Surrogate: Citric acid (CAS #77-92-9)*: In the GLP-compliant, OECD Guideline 402 acute dermal toxicity test that identified a dermal LD_{50} value greater than 2,000 mg/kg in Sprague-Dawley rats (5/sex/group), the only dose tested was 2,000 mg/kg. Treatment did

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not induce clinical signs of toxicity, changes to body weights, or gross pathological abnormalities. The REACH dossier reports this study with a reliability score of 1 (reliable without restriction (Unnamed study 2006).

- ECHA, CAS #77-92-9, 2024
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity studies that identified oral $_{LD50}$ values of 11,700 mg/kg and 5,790 mg/kg in male ICR-JCL rats (6/group) and SD-JCL mice (6/group), respectively. The rats were dosed (presumably via gavage) with 1,800 or 12,500 mg/kg and the mice were dosed with 5,790 or 7,000 mg/kg. The spontaneous movement of the animals in the cages increased several minutes following dosing. Motor ataxia, mydriasis (dilation of the pupil), and decreased rate of respiration were observed approximately 50 minutes after dosing. Deaths observed were caused by respiratory failure. Animals that survived to the scheduled sacrificed showed full recovery within several hours of dosing and exhibited no adverse clinical signs of toxicity 24 hours after dosing. Hemorrhage of the gastric mucosa was the only gross pathological change observed at necropsy. The lowest doses tested were 5,790 mg/kg for mice and 1,800 mg/kg for rats. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yokotani et al. 1971).
- UNEP 2004; ECHA, CAS #77-92-9, 2024
  - *Inhalation*: *Surrogate: Citric acid (CAS #77-92-9)*: In a study in guinea pigs, citric acid aerosol at the concentration of 0.93 M or 75 mg/mL induced 90 +/-1.9 coughs during a three-minute exposure. Bronchoconstriction occurred after 3-4 minutes. No additional details were provided. The REACH dossier reports this study with a reliability score of 4 (not assignable) (Forsberg and Karlsson 1986).
- ECHA 2019
  - *Inhalation*: *Surrogate: Citric acid (CAS #77-92-9)*: In several human volunteer studies where subjects were exposed to citric acid aerosol, the main treatment-related effect was cough response.
- In summary, the only gross pathological effect noted with oral exposure to the surrogate citric acid was hemorrhaging of the gastric mucosa which is likely a local effect following ingestion of an irritating substance. Single oral and dermal dosing did not produce evidence of systemic toxicity based on limited evaluations. Citric acid produces a cough response in exposed humans and is classified as a GHS Category 3 specific target organ toxicant following single exposure for respiratory irritation in the EU harmonized classification (ECHA, CAS #77-92-9, 2024). However, the citric acid's respiratory irritation effects are likely to it is acidity. Since 5% solutions of potassium citrate and citric acid have pH values of 8.7 and 1.8, respectively (ECHA 2024), potassium citrate is not likely to be irritating to the respiratory tract. Therefore, ToxServices did not classify potassium citrate as a specific target organ toxicant following single exposure for respiratory irritation under GHS criteria (UN 2023).

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

Potassium citrate was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it as a specific target organ toxicant following repeated doses under GHS criteria based on oral data for the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data and no GHS classification are available (CPA 2018b). Although all of the studies were reported with limited details, consistently negative results across multiple studies and species, in conjunction with the strong surrogate citric acid's endogenous functions, support high confidence.

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- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- UNEP 2004
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: No treatment-related effects were reported in a repeated dose toxicity study in which rabbits (15/dose group, strain and sex not specified) were provided feed containing 7.7% sodium citrate (approximately 1,500 mg citric acid/kg/day) for 150 days. No further details were provided. *ToxServices identified a NOAEL of 1,500 mg/kg/day based on the available information for this study*.
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: No treatment-related effects were reported in a repeated dose toxicity study in which dogs (3/dose group, strain and sex not specified) were provided feed containing citric acid at 1,380 mg/kg/day for 120 days. No further details were provided. *ToxServices identified a NOAEL of 1,380 mg/kg/day based on the available information for this study*.
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In a two-year repeated dose toxicity study, male rats (20/dose group, strain not specified) were provided feed containing 3% or 5% citric acid (equivalent to 1,200 and 2,000 mg/kg/day, respectively). Slightly decreased growth was measured in both dose groups and food consumption decreased in the high dose group. No gross pathological abnormalities were observed at necropsy. The study authors identified a NOAEL of 1,200 mg/kg/day.
- U.S EPA 2024c
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: Rats given 600 mg/kg/day orally for 90 days had no weight, blood, histopathological or reproductive effects.
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In a 1-year three-generation rat oncogenic/chronic toxicity feeding study, no adverse effects were noted on growth, reproduction, mortality, hematology, or metabolism at the highest dose level (800 mg/kg/day citric acid).
- GHS criteria (UN 2023) identifies oral guidance values of 10 and 100 mg/kg/day for subchronic repeated oral dose toxicity studies. Since the available subchronic and chronic repeated oral dose toxicity data for the surrogate citric acid identified NOAELs > 100 mg/kg/day, ToxServices did not classify potassium citrate as a specific target organ toxicant following repeated doses under GHS criteria (UN 2023).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Potassium citrate was assigned a score of Low for neurotoxicity (single dose) based on ToxServices not classifying it as a specific target organ toxicant following single exposures for neurotoxicity under GHS criteria based on oral and dermal data on the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is low as the acute toxicity studies did not include detailed functional analyses.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity study that identified an oral LD_{50} value of 5,400 mg/kg in Füllinsdorf Albino (SPF) mice (5/sex/group), the animals were dosed with 3,000, 4,200, 6,000, 8,500, or 12,000 mg/kg. Treatment with 6,000 mg/kg produced "slight relaxation" two hours after dosing. No clinical signs of toxicity were

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identified at ≤ 4,200 mg/kg and all animals dosed with ≥ 8,500 mg/kg died. No gross pathological observations were conducted. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 1981).
    - *Dermal*: *Surrogate: Citric acid (CAS #77-92-9)*: In the GLP-compliant, OECD Guideline 402 acute dermal toxicity test that identified a dermal LD_{50} value greater than 2,000 mg/kg in Sprague-Dawley rats (5/sex/group), the only dose tested was 2,000 mg/kg. Treatment did not induce clinical signs of toxicity or gross pathological abnormalities. The REACH dossier reports this study with a reliability score of 1 (reliable without restriction (Unnamed study 2006).
- ECHA, CAS #77-92-9, 2024
    - *Oral*: *Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity studies that identified oral LD_{50} values of 11,700 mg/kg and 5,790 mg/kg in male ICR-JCL rats (6/group) and SD-JCL mice (6/group), respectively. The rats were dosed with 1,800 or 12,500 mg/kg and the mice were dosed with 5,790 or 7,000 mg/kg. The spontaneous movement of the animals in the cages increased several minutes following dosing. Motor ataxia, mydriasis (dilation of the pupil), and decreased rate of respiration were observed approximately 50 minutes after dosing. Deaths observed were caused by respiratory failure. Animals that survived to the scheduled sacrificed showed full recovery within several hours of dosing and exhibited no adverse clinical signs of toxicity 24 hours after dosing. Hemorrhage of the gastric mucosa was the only gross pathological change observed at necropsy. The lowest doses tested were 5,790 mg/kg for mice and 1,800 mg/kg for rats. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Yokotani et al. 1971).
- GHS criteria (UN 2023) define chemicals as specific target organ toxicant following single doses when they produce non-lethal neurotoxicity following single oral or dermal doses ≤ 2,000 mg/kg or inhalation exposures to aerosols ≤ 5.0 mg/L (Categories 1 or 2) or reversible narcotic effects (defined as ataxia, narcosis, lethargy, and lack of coordination righting reflex) at any dose/concentration (Category 3). Based on the lack of clear neurobehavioral or neuropathological changes following single exposures to the surrogate citric acid, ToxServices did not classify potassium citrate as a specific target organ toxicant following single exposures for neurotoxicity under GHS criteria (UN 2023). Although one study reported potential neurological signs (e.g., ataxia, pupil dilation, and altered respiratory rate), these effects occurred at very high and lethal doses that also resulted in hemorrhage of the gastric mucosa; therefore, these effects are likely due to severe discomfort following exposure to an irritating chemical.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
Potassium citrate was assigned a score of Data Gap for neurotoxicity (repeated dose) based on the lack of data identified for this endpoint.
- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- No data were identified.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): L
Potassium citrate was assigned a score of Low for skin sensitization based on the lack of skin sensitization reactions identified in a guinea pig maximization test performed with the surrogate trisodium citrate and the lack of skin sensitization identified in clinical tests with the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate

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and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured experimental and clinical data for strong surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: A GLP-compliant, OECD Guideline 406 guinea pig maximization test was performed with male Himalayan Spotted (Ibm:GOHI) guinea pigs (10 vehicles, 20 test animals) administered dermal doses of sodium citrate (purity not specified). The induction doses were administered as intradermal injections of 5% sodium citrate and topical applications of 75% sodium citrate in water under occlusive dressing for 48 hours. The challenge dose was applied on day 22 as topical applications of 25%, 50%, or 75% citric acid in water under occlusive dressing for 24 hours. At readings 24 and 48 hours after the challenge dose, challenge treatment did not include any positive dermal reactions. Therefore, the authors concluded sodium citrate was not sensitizing to the skin under the tested conditions. The REACH dossier reports this study with a reliability score of 1 (reliable with restrictions) (Unnamed study 1995).
- UNEP 2004:
  - *Surrogate: Citric acid (CAS #77-92-9)*: Patch testing of 60 eczema patients with 2.5% citric acid in petrolatum did not produce any irritant or allergic reactions (Niinimäki 1987).
- CIR 2014
  - *Surrogate: Citric acid (CAS #77-92-9)*: A human repeat insult patch test (HRIPT) was performed with 56 patients administered topical application of a cuticle cream containing 4% citric acid under semi-occlusive dressing three times per week for three weeks. A challenge dose was applied two weeks after the last induction dose. Citric acid was not sensitizing to the skin under the tested conditions (Clinical Research Laboratories Inc. 2007).
  - *Surrogate: Citric acid (CAS #77-92-9)*: A skin prick test was performed with 91 patients with chronic angioedema or urticaria exposed to a 2.5% aqueous solution of citric acid. Three patients (3%) exhibited positive dermal reactions, with one of these patients also reacting to propionic and benzoic acids (Malanin and Kalimo 1989).

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

Potassium citrate was assigned a score of Low for respiratory sensitization based on the lack of dermal sensitization potential according to the ECHA guidance (2017). GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when they are not GHS classified (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - Potassium citrate does not contain any structural alerts for respiratory sensitization (Appendix H).
- 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

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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 potassium citrate is not sensitizing to the skin based on surrogate data (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by potassium citrate, and as potassium citrate does not contain any structural alerts for respiratory sensitization (OECD 2022), potassium citrate is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): L
Potassium citrate was assigned a score of Low for skin irritation/corrosivity based on ToxServices' conclusion that it does not warrant classification as a skin irritant under GHS criteria (UN 2023) based on results of two irritation studies in rabbits exposed to the surrogate trisodium citrate. 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 reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: A GLP-compliant, OECD Guideline 404 dermal irritation test was performed with New Zealand White rabbits (3 total) administered topical applications of 0.5 g trisodium citrate (purity not specified) moistened with distilled water to shaved skin under semi-occlusive dressing for 4 hours. At 24, 48, and 72 hours, the mean overall irritation score was 0.11/8. Treatment did not produce erythema and one animal had an edema score of 1 at 24 hours. The edema was fully reversible within 48 hours. Therefore, the authors concluded sodium citrate was not irritating under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 1995).
- ECHA, CAS #68-04-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: A GLP-compliant, OECD Guideline 404 dermal irritation test was performed with New Zealand White rabbits (6 total) administered topical applications of unspecified amount of trisodium citrate (purity not specified) moistened with water to shaved skin under semi-occlusive dressing for 4 hours. At 1, 24, 48, and 72 hours, the mean primary dermal irritation index (PDII) was 0/8. Therefore, the authors concluded sodium citrate was not irritating under the tested conditions. The REACH dossier reported this study with a reliability score of 1 (reliable without restriction) (Unnamed study 1990).
- GHS criteria define skin irritants as chemicals that produce mean scores ≥ 1.5 for erythema and/or edema in at least 2 of 3 animals following readings at 24, 48, and 72 hours (UN 2023). The surrogate trisodium citrate did not produce sufficient dermal irritation to warrant classification of potassium citrate as a skin irritant under GHS criteria based on the results of available skin irritation studies.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): L
Potassium citrate was assigned a score of Low for eye irritation/corrosivity based on ToxServices' conclusion that it does not warrant classification as an eye irritant under GHS criteria (UN 2023) based on results of two irritation studies in rabbits with the surrogate trisodium citrate. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate and negative data and no

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GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: A GLP-compliant, OECD Guideline 405 ocular irritation test was performed with New Zealand White rabbits (3 total) administered ocular instillations of 0.1 g sodium citrate (purity not specified). The eyes were not rinsed. At 24, 48, and 72 hours, the mean primary irritation score was 0.11/13. The irritation effects were fully reversible within 48 hours. At 24 hours, one animal had grade 1 chemosis. No other signs of irritation were identified from 24-72 hours. Therefore, the authors concluded sodium citrate was not irritating to the eyes under the tested conditions. The REACH dossier reports this study with a reliability score of 1 (reliable without restriction) (Unnamed study 1995).
- ECHA, CAS #68-04-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: A GLP-compliant, OECD Guideline 405 ocular irritation test was performed with New Zealand White rabbits (6 total) administered ocular instillations of 100 mg sodium citrate (purity not specified). At 24, 48, and 72 hours, the mean conjunctival redness score was 0.5/3 and the mean chemosis score was 0.7/4. The ocular irritation was fully reversible within 72 hours. The authors concluded that sodium citrate was not irritating to the eyes under the tested conditions. The REACH dossier reports this study with a reliability score of 1 (reliable without restriction) (Unnamed study 1991).
- GHS criteria (UN 2023) define chemicals as irritating to the eyes if they produce 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). The surrogate trisodium citrate did not produce sufficient ocular irritation to warrant classification of potassium citrate as an eye irritant under GHS criteria based on the results of available eye irritation studies.

Ecotoxicity (Ecotox)

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

Potassium citrate was assigned a score of Low for acute aquatic toxicity based on equivalent acute aquatic toxicity values > 159 mg/L derived from acute aquatic toxicity values for the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values > 100 mg/L CPA 2018b). The confidence in the score is high as it is based on measured data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #68-04-2, 2024
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: 24-hour LC_{50} (*Ptychocheilus oregonensis*, northern pikeminnow) > 10 mg/L. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (MacPhee and Ruelle 1969).
  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: 24-hour LC_{50} (*Oncorhynchus tshawytscha*, Chinook salmon) > 10 mg/L. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (MacPhee and Ruelle 1969).

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  - *Surrogate: Trisodium citrate (CAS #68-04-2)*: 24-hour LC_{50} (*Oncorhynchus kisutch*, coho salmon) > 10 mg/L. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (MacPhee and Ruelle 1969).
- UNEP 2004; ECHA, CAS #77-92-9, 2024
  - *Surrogate: Citric acid (CAS #77-92-9):* 96-hour LC_{50} (*Lepomis macrochirus,* bluegill) = 1,516 mg/L (US EPA (1973) EPA -600/2-74-003) (nominal or measured not specified). The REACH dossier reported this study with a reliability score of 4 (not assignable) while the SIDS dossier reported it with a reliability score of 2 (reliable with restrictions) (Schwarz 1973).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 48-hour or 96-hour LC_{50} (*Leuciscus idus melanotus*, ide) = 440-760 mg/L (non-GLP-compliant, OECD 203). The REACH and SIDS dossiers reported this study with a reliability score of 2 (reliable with restrictions) (Deutsche Einheitsverfahren zur Wasser- 1976 and Juhnke and Ludemann 1978). *ToxServices notes that the SIDS dossier reports the exposure duration as 96 hours while the REACH dossier reports the exposure duration as 48 hours.*
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 24-hour EC_{50} (*Daphnia magna*) = 1,535 mg/L (non-GLP-compliant, neutralized conditions). The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) while the SIDS dossier reports this study with a reliability score of 4 (not assignable) (Bringmann and Kühn 1982).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 48-hour LC_{50} (*Carcinus maenas*, European green crab) = 160 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 4 (not assignable) while the SIDS dossier reports this study with a reliability score of 2 (reliable with restrictions) (Portmann and Wilson 1971).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 7-day or 8-day cell density toxicity threshold (EC_0) (*Scenedesmus quadricauda*, algae) = 640 mg/L (non-GLP-compliant). The REACH and SIDS dossiers report this study with a reliability score of 2 (reliable with restrictions) (Bringmann and Kühn 1978 and 1980). *ToxServices notes the SIDS dossier reports the exposure duration as 7 days while the REACH dossier reports the exposure duration as 8 days*.
- UNEP 2004
  - *Surrogate: Citric acid (CAS #77-92-9):* 24-hour EC_{50} (*D. magna*) = 85 mg/L (not neutralized). The SIDS dossier reports this study with a reliability score of 4 (not assignable) (Bringmann and Kühn 1982).
- ECHA, CAS #77-92-9, 2024
  - *Surrogate: Citric acid (CAS #77-92-9):* 48-hour LC_{50} (*L. idus*, ide) = 2,600 mg/L (nominal or measured not specified). The REACH dossier reports this study with a reliability score of 4 (not assignable) (Schöberl et al. 1988).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) > 100 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Terhaar et al. 1972).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 48-hour attachment to substrate EC_{50} (*Dreissena polymorpha*, zebra mussel) > 50 mg/L (non-GLP-compliant, ASTM (1993) PCN 03-547093-16). The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Cope et al. 1997).
  - *Surrogate: Citric acid (CAS #77-92-9):* Estimated 72-hour mobility EC_{50} (*D. magna*) = 120 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 4 (not assignable) (Ellis 1937).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 24-hour LC_{50} (*Artemia franciscana*, brine

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shrimp) = 190-270 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 4 (not assignable) (Nelson and Kursar 1999).

- With one exception, the acute aquatic toxicity values for the surrogate citric acid are > 100 mg/L. One 24-hour EC_{50} of 85 mg/L was identified for daphnia under non-neutralized conditions, suggesting that the acute toxic effects were due to decreased pH rather than a direct chemical effect. As natural surface waters have buffering capacity,[9] citric acid is not likely to cause acute toxicity towards aquatic organisms. Based on molecular weight adjustments, the next lowest citric acid concentration of > 100 mg/L is equivalent to a potassium citrate concentration > 159 mg/L.[10]

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *L*
Potassium citrate was assigned a score of Low for chronic aquatic toxicity based on measured (surrogate) or estimated chronic aquatic toxicity values > 10 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are > 10 mg/L (CPA 2018b). The confidence in the score is low as measured data are available for only one trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #77-92-9, 2024
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal estimated 8-day cell density NOAEC (*S. quadricauda*, green algae) = 425 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Bringmann and Kühn 1978 and 1980).
  - *Surrogate: Citric acid (CAS #77-92-9):* Nominal 8-day growth rate toxicity threshold (*Microcystis aeruginosa*, cyanobacteria) = 80 mg/L (non-GLP-compliant). The REACH dossier reports this study with a reliability score of 4 (not assignable) (Bringmann and Kühn 1978).
- U.S. EPA 2022
  - Potassium citrate belongs to the Neutral Organics ECOSAR chemical class. The most conservative predicted chronic values (ChVs) are 4.46E04 mg/L in fish, 4.82E04 mg/L in daphnia, and 2.87E04 mg/L in green algae (Appendix I).

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vL*
Potassium citrate was assigned a score of Very Low for persistence based on modeling that predicts that it is readily biodegradable, with support from numerous studies demonstrating that the surrogate citric acid meets the pass level in ready biodegradability tests. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they meet the 10-day window (CPA 2018b). The confidence in the score is low as it is based in part on modeling, as experimental studies did not report on the 10-day window.

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

[9] https://www.usgs.gov/special-topics/water-science-school/science/alkalinity-and-water; https://www.epa.gov/caddis-vol2/ph
[10] Citric acid has a molecular weight of 192.12 g/mol and potassium citrate has a molecular weight of 306.39 g/mol (PubChem 2024); therefore, 100 mg citric acid/L * 1 mmol citric acid/192.12 mg citric acid * 1 mmol potassium citrate/1 mmol citric acid * 306.39 mg potassium citrate/1 mmol potassium citrate = 159 mg potassium citrate/L.

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  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - *Surrogate: Citric acid (CAS #77-92-9):* An OECD Guideline 301 E ready biodegradability (modified OECD screening) test was performed with 0.05% effluent (no further details provided) exposed to citric acid (purity not specified) at 3-20 mg/L for 19 days. At the end of the exposure period, the level of degradation was 100% based on DOC removal. The study authors concluded citric acid was readily biodegradable under the tested conditions. No information regarding the 10-day window was provided for this test. The REACH dossier reports this study with a reliability score of 2 reliable with restrictions) (Gerike and Fischer 1979).
  - *Surrogate: Citric acid (CAS #77-92-9):* An OECD Guideline 302 B inherent biodegradability (Zahn-Wellens/EMPA) test was performed with sludge (1g/L) exposed to citric acid (purity not specified) at 400 mg/L for 14 days. At the end of the exposure period, the level of degradation was 85% based on DOC removal. The study authors concluded that citric acid was inherently biodegradable under the tested conditions. The REACH dossier reports this study with a reliability score of 2 reliable with restrictions) (Gerike and Fischer 1979).
  - *Surrogate: Citric acid (CAS #77-92-9):* An OECD Guideline 301 B ready biodegradability (CO_2 Evolution Test) test was performed with effluents after acclimation (no further details provided) exposed to citric acid (purity not specified) at 10 mg/L for 28 days. The level of degradation after the exposure period was 97%. The study authors concluded that citric acid was readily biodegradable in this test. No information regarding the 10-day window was provided for this test. The REACH dossier reports this study with a reliability score of 2 reliable with restrictions) (Gerike and Fischer 1979).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that potassium citrate is expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 71.8% will partition to soil with a half-life of 416 hours (17.3 days), 28.1% will partition to water with a half-life of 208 hours (8.7 days), and 0.0592% will partition to sediment with a half-life of 1,870 hours (77.9 days) (Appendix J).

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

Potassium citrate was assigned a score of Very Low for bioaccumulation based on measured log K_{ow} values ≤ -0.2 for the surrogate citric acid and estimated BCF values ≤ 3.162. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are ≤ 4 and BCF values are ≤ 100 (CPA 2018b). The confidence in the score is high as it is based in part on measured log K_{ow} data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #68-04-2, 2024
  - *Surrogate: Citric acid (CAS #77-92-9):* Measured log K_{ow} values for citric acid ranged from -1.8 to -0.2 from multiple sources.
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 3.162 using the regression based model based on a measured log K_{ow} of -1.64, and a BCF of 0.8934 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix J).

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Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Potassium citrate was assigned a score of Low for reactivity based on ToxServices not classifying it as a reactive chemical under GHS criteria due to its lack of explosive and oxidizing properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification is warranted (CPA 2018b). The confidence in the score is low based on the absence of measured data or authoritative listings.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #688-84-2, 2024
  - Potassium citrate does not contain functional groups associated with explosive or oxidizing properties.
- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of potassium citrate. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, potassium citrate is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix K).
  - Based on the structure of its components or moieties, potassium citrate is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of potassium citrate has seven oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.

Flammability (F) Score (vH, H, M, or L): L
Potassium citrate was assigned a score of Low for flammability based on its lack of sustained ignition in a burning test. GreenScreen® criteria classify chemicals as a Low hazard for flammability when no GHS classification is warranted (CPA 2018b). The confidence in the score is high as it is based on measured data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #866-84-2, 2024
  - In a VDI 2263, Part 1 flammability test, potassium citrate (purity not specified) did not ignite in contact with air and, when exposed to a flame, briefly ignited followed by a quick extinction. Therefore, the REACH dossier authors concluded potassium citrate was not flammable under the tested conditions (Unnamed study 2004).
- Based on the lack of sustained ignition by target chemical during a burning test, ToxServices did not classify potassium citrate as a flammable solid under GHS criteria (UN 2023).

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

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

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

As shown in Table 5, Type I (input data) uncertainties in potassium citrate's NAMs dataset include insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Potassium citrate's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of Oncologic models to evaluate sodium citrate's carcinogenic potential, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of potassium citrate's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity**: Only limited experimental data are available. **Endocrine activity**: No experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). OncoLogic™ could not evaluate the carcinogenic potential of this chemical. **Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12].

[11] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).
[12] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427

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	The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[13] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[14]. The *in vitro* mammalian cell micronucleus test (as defined in OECD Guideline 487) detects chromosomal damage only in cells that have undergone cell division during or after exposure to the test chemical, and may overestimate chromosomal damage potential because aberrations measured in metaphase cells may not necessarily be transmitted to daughter cells. Additionally, the exogenous metabolic activation system does not entirely mirror *in vivo* conditions[15]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OncoLogic™/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay/*in vitro* micronucleus assay/comet assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	

[13] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[14] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352
[15] https://www.oecd.org/chemicalsafety/test-no-487-in-vitro-mammalian-cell-micronucleus-test-9789264264861-en.htm

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Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™ Non-animal testing: OECD 301 B, D, E Biodegradation tests
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

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APPENDIX B: Results of Automated GreenScreen® Score Calculation for Potassium Citrate (CAS #866-84-2)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	Chemical Name	CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No	Potassium Citrate	866-84-2	*L*	L	L	*L*	DG	L	L	L	*L*	DG	L	*L*	L	L	L	*L*	*vL*	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	No	No	No	No	No
3	No	No	No	No			
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Potassium Citrate	4

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Potassium Citrate	3DG

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												
3												
4	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	3DG

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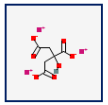
APPENDIX C: Pharos Output for Potassium Citrate (CAS #866-84-2)



866-84-2

Potassium citrate anhydrous

ALSO CALLED 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, potassium salt, 1,2,3-Propanetricarboxylic acid, 2-hydr...

View all synonyms (40)

Share Profile

Hazards | Properties | Functional Uses | Resources

All Hazards View

Show PubMed Results | Request Assessment | Add to Comparison

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

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause respiratory irritation (unverified) [Specific target organ toxicity - single exposure; Respiratory tract irritation - Category 3]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	

Restricted Substance Lists (3)

- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active

Positive Lists (4)

- Cosmetic Ingredient Review (CIR): Safe as Used
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2021): Cosmetic Ingredients
- US EPA - DfE Safer Chemicals Ingredients list (SCIL): Chelating Agents - Green Circle (Verified Low Concern)
- US EPA - DfE Safer Chemicals Ingredients list (SCIL): Processing Aids-Additives - Green Circle (Verified Low Concern)

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APPENDIX D: Toxtree Carcinogenicity Results for Potassium Citrate (CAS #866-84-2)

Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) v3.1.0-1851-1525442531402

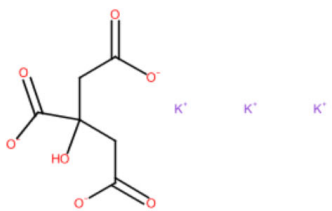
File Edit Chemical Compounds Toxic Hazard Method Help

Chemical identifier C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]

Available structure attributes

Error when applying the ...	NO
For a better assessment ...	NO
Negative for genotoxic c...	YES
Negative for nongenoto...	YES
Potential S. typhimurium ...	NO
Potential carcinogen bas...	NO
QSAR13 applicable?	NO
QSAR6,8 applicable?	NO
SA10_gen	NO
SA11_gen	NO
SA12_gen	NO

Structure diagram



First Prev 1 / 1 Next Last

Toxic Hazard by Carcinogenicity (genotox and nongenotox) and mutagenicity rulebase by ISS

Estimate

For a better assessment a QSAR calculation could be applied.

Negative for genotoxic carcinogenicity

Negative for nongenotoxic carcinogenicity

Error when applying the decision tree

Verbose explanation

QSA31b_nogen.Halogenated PAH (naphthalenes, biphenyls, diphenyls) (Nongenotoxic carcinogens) No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA31c_nogen.Halogenated dibenzodioxins (Nongenotoxic carcinogens) No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA39_gen_and_nogen.Steroidal estrogens No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA40_nogen.substituted phenoxyacid No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA41_nogen.substituted n-alkylcarboxylic acids No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA42_nogen.phthalate diesters and monoesters No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA43_nogen.Perfluorooctanoic acid (PFOA) No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA44_nogen.Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA45_nogen.indole-3-carbinol No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA46_nogen.pentachlorophenol No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA47_nogen.o-phenylphenol No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA48_nogen.quercetin-type flavonoids No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA49_nogen.imidazole and benzimidazole No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA50_nogen.dicarboximide No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA51_nogen.dimethylpyridine No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA52_nogen.Metals, oxidative stress No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA53_nogen.Benzensulfonic ethers No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA54_nogen.1,3-Benzodioxoles No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA55_nogen.Phenoxy herbicides No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QSA56_nogen.alkyl halides No C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]
QNongenotoxic alert?.At least one alert for nongenotoxic carcinogenicity fired? No Class Negative for nongenotoxic carcinogenicity C(C(=O)[O-])C(CC(=O)[O-])(C(=O)[O-])O.[K+].[K+].[K+]

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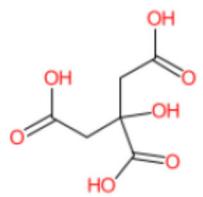
APPENDIX E: VEGA Carcinogenicity Results for the Surrogate Citric Acid (CAS #77-92-9)

VEGA Carcinogenicity model (CAESAR) 2.1.10 page 1

1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).

Compound: Molecule 0
Compound SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Experimental value: NON-Carcinogen
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.549
P(NON-Carcinogen): 0.451
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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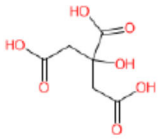
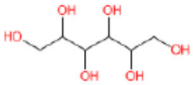
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



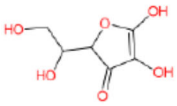
Compound #1

CAS: 77-92-9
Dataset id:173 (Training Set)
SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Similarity: 1
Experimental value : NON-Carcinogen
Predicted value : Carcinogen



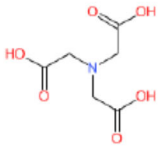
Compound #2

CAS: 69-65-8
Dataset id:421 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.817
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



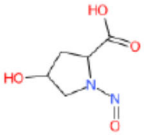
Compound #3

CAS: 50-81-7
Dataset id:58 (Training Set)
SMILES: O=C1C(O)=C(O)OC1C(O)CO
Similarity: 0.802
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



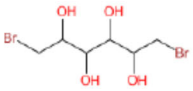
Compound #4

CAS: 139-13-9
Dataset id:498 (Training Set)
SMILES: O=C(O)CN(CC(=O)O)CC(=O)O
Similarity: 0.8
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 30310-80-6
Dataset id:593 (Training Set)
SMILES: O=NN1CC(O)CC1(C(=O)O)
Similarity: 0.758
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 10318-26-0
Dataset id:213 (Training Set)
SMILES: OC(CBr)C(O)C(O)C(O)CBr
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Similar molecules with known experimental value
Similarity index = 1
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 0
Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..

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

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

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

Model class assignment reliability
Pos/Non-Pos difference = 0.098
Explanation: model class assignment is uncertain..

Neural map neurons concordance
Neurons concordance = 0.75
Explanation: predicted value disagrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

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

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

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

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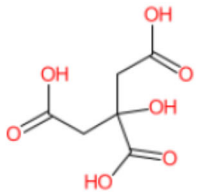
1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).
The following alerts have been found: SA41 Substituted n-alkylcarboxylic acids

Compound: Molecule 0
Compound SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Experimental value: NON-Carcinogen
Predicted Carcinogen activity: Carcinogen
Structural Alerts: SA41 Substituted n-alkylcarboxylic acids
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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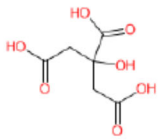
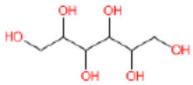
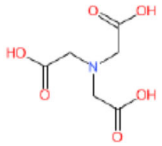
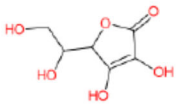
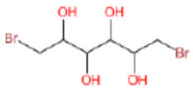
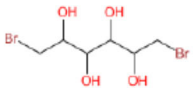
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

	Compound #1 CAS: 77-92-9 Dataset id:829 (Training Set) SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O Similarity: 1 Experimental value : NON-Carcinogen Predicted value : Carcinogen Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids
	Compound #2 CAS: 69-65-8 Dataset id:86 (Training Set) SMILES: OCC(O)C(O)C(O)C(O)CO Similarity: 0.817 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #3 CAS: 139-13-9 Dataset id:206 (Training Set) SMILES: O=C(O)CN(CC(=O)O)CC(=O)O Similarity: 0.8 Experimental value : Carcinogen Predicted value : NON-Carcinogen
	Compound #4 CAS: 50-81-7 Dataset id:31 (Training Set) SMILES: O=C1OC(C(O)=C1(O))C(O)CO Similarity: 0.777 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #5 CAS: 10318-26-0 Dataset id:445 (Training Set) SMILES: OC(CBr)C(O)C(O)C(O)CBr Similarity: 0.755 Experimental value : Carcinogen Predicted value : Carcinogen Alerts (not found also in the target): SA8 Aliphatic halogens
	Compound #6 CAS: 488-41-5 Dataset id:484 (Training Set) SMILES: OC(CBr)C(O)C(O)C(O)CBr Similarity: 0.755 Experimental value : Carcinogen Predicted value : Carcinogen Alerts (not found also in the target): SA8 Aliphatic halogens

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3.2 Applicability Domain:
Measured Applicability Domain Scores

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

Similar molecules with known experimental value
Similarity index = 1
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 0
Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..

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

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

Symbols explanation:

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

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

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

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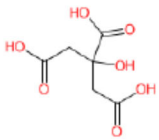
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: SA41 Substituted n-alkylcarboxylic acids

Substituted n-alkylcarboxylic acids

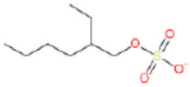
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 77-92-9
Dataset id:829 (Training Set)
SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Similarity: 1

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

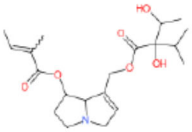
Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids



CAS: 126-92-1
Dataset id:77 (Training Set)
SMILES: O=S(=O)([O-])OCC(CC)CCCC
Similarity: 0.675

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids



CAS: 22571-95-5
Dataset id:486 (Training Set)
SMILES: O=C(OC2CCN1CC=C(COC(=O)C(O)(C(O)C)C(C)C)C12)C(=CC)C
Similarity: 0.616

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids

Alerts (not found also in the target): SA37 Pyrrolizidine Alkaloids

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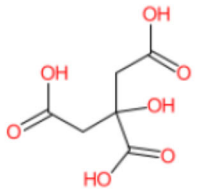
1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is Possible NON-Carcinogen (GOOD reliability).

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

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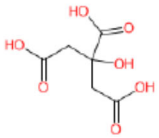
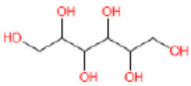
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



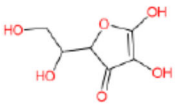
Compound #1

CAS: 77-92-9
Dataset id:745 (Training Set)
SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Similarity: 1
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



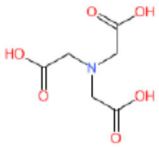
Compound #2

CAS: 69-65-8
Dataset id:69 (Training Set)
SMILES: OCC(O)C(O)C(O)C(O)CO
Similarity: 0.817
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

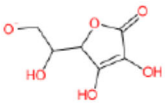
CAS: 50-81-7
Dataset id:25 (Training Set)
SMILES: O=C1C(O)=C(O)OC1C(O)CO
Similarity: 0.802
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

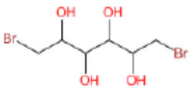
CAS: 139-13-9
Dataset id:167 (Training Set)
SMILES: O=C(O)CN(CC(=O)O)CC(=O)O
Similarity: 0.8
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 34



Compound #5

CAS: 6381-77-7
Dataset id:943 (Training Set)
SMILES: O=C1OC(C(O)=C1(O))C(O)C[O-]
Similarity: 0.767
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #6

CAS: 10318-26-0
Dataset id:369 (Training Set)
SMILES: OC(CBr)C(O)C(O)C(O)CBr
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 1
Explanation: The predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 1
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

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

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

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

Symbols explanation:

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

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

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

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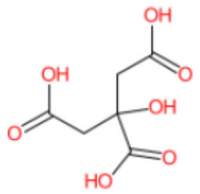
1. Prediction Summary

Prediction for compound Molecule 0 -



EXPERIMENTAL DATA

E xperimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).
The following relevant fragments have been found: Carcinogenity alert no. 21

Compound: Molecule 0
Compound SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Experimental value: NON-Carcinogen
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 21
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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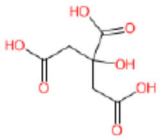
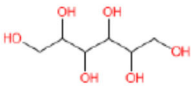
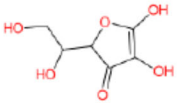
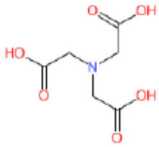
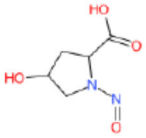
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values

	Compound #1 CAS: 77-92-9 Dataset id:173 (Training Set) SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O Similarity: 1 Experimental value : NON-Carcinogen Predicted value : Carcinogen Alerts (found also in the target): Carcinogenity alert no. 21
	Compound #2 CAS: 69-65-8 Dataset id:421 (Training Set) SMILES: OCC(O)C(O)C(O)C(O)CO Similarity: 0.817 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen
	Compound #3 CAS: 50-81-7 Dataset id:58 (Training Set) SMILES: O=C1C(O)=C(O)OC1C(O)CO Similarity: 0.802 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen
	Compound #4 CAS: 139-13-9 Dataset id:498 (Training Set) SMILES: O=C(O)CN(CC(=O)O)CC(=O)O Similarity: 0.8 Experimental value : Carcinogen Predicted value : Possible NON-Carcinogen
	Compound #5 CAS: 30310-80-6 Dataset id:593 (Training Set) SMILES: O=NN1CC(O)CC1(C(=O)O) Similarity: 0.758 Experimental value : NON-Carcinogen Predicted value : Carcinogen Alerts (not found also in the target): Carcinogenity alert no. 8; Carcinogenity alert no. 11; Carcinogenity alert no. 15; Carcinogenity alert no. 46; Carcinogenity alert no. 47; Carcinogenity alert no. 50; Carcinogenity alert no. 51; Carcinogenity alert no. 54; Carcinogenity alert no. 55; Carcinogenity alert no. 63

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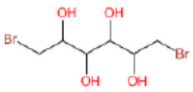
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #6

CAS: 10318-26-0
Dataset id:213 (Training Set)
SMILES: OC(CBr)C(O)C(O)C(O)CBr
Similarity: 0.755
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 58; Carcinogenity alert no. 59

3.2 Applicability Domain:
Measured Applicability Domain Scores

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

✓ Similar molecules with known experimental value
Similarity index = 1
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

✗ Accuracy of prediction for similar molecules
Accuracy index = 0
Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..

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

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

Symbols explanation:

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

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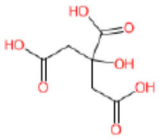
4.1 Reasoning:
Relevant Chemical Fragments and Moieties

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

Fragment found: Carcinogenity alert no. 21

Structural alert for carcinogenity defined by the SMARTS: CC(C)(O)C(O)=O

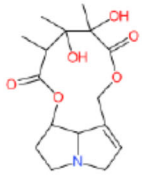
Following, the most similar compounds from the model's dataset having the same fragment.



CAS: 77-92-9
Dataset id:173 (Training Set)
SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Similarity: 1

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 21

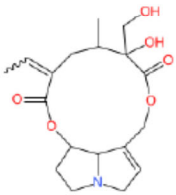


CAS: 315-22-0
Dataset id:488 (Test Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
Similarity: 0.653

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 21

Alerts (not found also in the target): Carcinogenity alert no. 20; Carcinogenity alert no. 41; Carcinogenity alert no. 77; Carcinogenity alert no. 115



CAS: 480-54-6
Dataset id:694 (Training Set)
SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(CO)C(C)CC1(=CC))C23
Similarity: 0.629

Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 21

Alerts (not found also in the target): Carcinogenity alert no. 20; Carcinogenity alert no. 41; Carcinogenity alert no. 76; Carcinogenity alert no. 77; Carcinogenity alert no. 106; Carcinogenity alert no. 115

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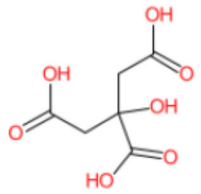
1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

Prediction is NON-Carcinogen, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.Anyway some issues could be not optimal:
- Only moderately similar compounds with known experimental value in the training set have been found

Compound: Molecule 0
Compound SMILES: O=C(O)CC(O)(C(=O)O)CC(=O)O
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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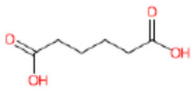
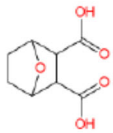
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



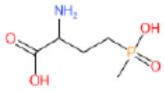
Compound #1

CAS: 124-04-9
Dataset id:541 (Training Set)
SMILES: O=C(O)CCCCC(=O)O
Similarity: 0.816
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



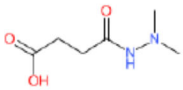
Compound #2

CAS: 145-73-3
Dataset id:494 (Training Set)
SMILES: O=C(O)C2C1OC(CC1)C2(C(=O)O)
Similarity: 0.78
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



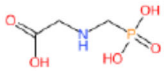
Compound #3

CAS: 77182-82-2
Dataset id:528 (Training Set)
SMILES: O=C(O)C(N)CCP(=O)(O)C
Similarity: 0.765
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



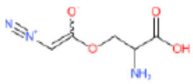
Compound #4

CAS: 1596-84-5
Dataset id:88 (Training Set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.753
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 1071-83-6
Dataset id:531 (Training Set)
SMILES: O=C(O)CNCP(=O)(O)O
Similarity: 0.744
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 115-02-6
Dataset id:27 (Training Set)
SMILES: N#[N+]C=C([O-])OCC(N)C(=O)O
Similarity: 0.74
Experimental value : Carcinogen
Predicted value : NON-Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.893
Explanation: The predicted compound is into the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.797
Explanation: Only moderately similar compounds with known experimental value in the training set have been found..

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

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

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

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

Symbols explanation:

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

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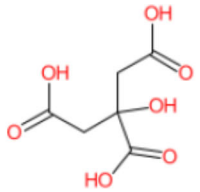
1. Prediction Summary

Prediction for compound Molecule 0 -



Prediction: Reliability:

Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:
- similar molecules found in the training set have experimental values that disagree with the predicted value

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

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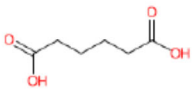
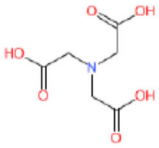
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



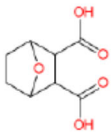
Compound #1

CAS: 124-04-9
Dataset id:517 (Training Set)
SMILES: O=C(O)CCCCC(=O)O
Similarity: 0.816
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



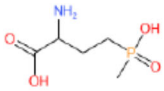
Compound #2

CAS: 139-13-9
Dataset id:178 (Training Set)
SMILES: O=C(O)CN(CC(=O)O)CC(=O)O
Similarity: 0.8
Experimental value : Carcinogen
Predicted value : Carcinogen



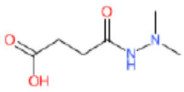
Compound #3

CAS: 145-73-3
Dataset id:466 (Training Set)
SMILES: O=C(O)C2C1OC(CC1)C2(C(=O)O)
Similarity: 0.78
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



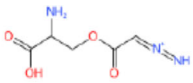
Compound #4

CAS: 77182-82-2
Dataset id:503 (Training Set)
SMILES: O=C(O)C(N)CCP(=O)(O)C
Similarity: 0.765
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #5

CAS: 1596-84-5
Dataset id:74 (Training Set)
SMILES: O=C(O)CCC(=O)NN(C)C
Similarity: 0.753
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #6

CAS: 115-02-6
Dataset id:24 (Training Set)
SMILES: O=C(O)C(N)COC(=O)C=[N+]=N
Similarity: 0.749
Experimental value : Carcinogen
Predicted value : Carcinogen

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3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.758 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.808 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	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 = 0.506 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

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

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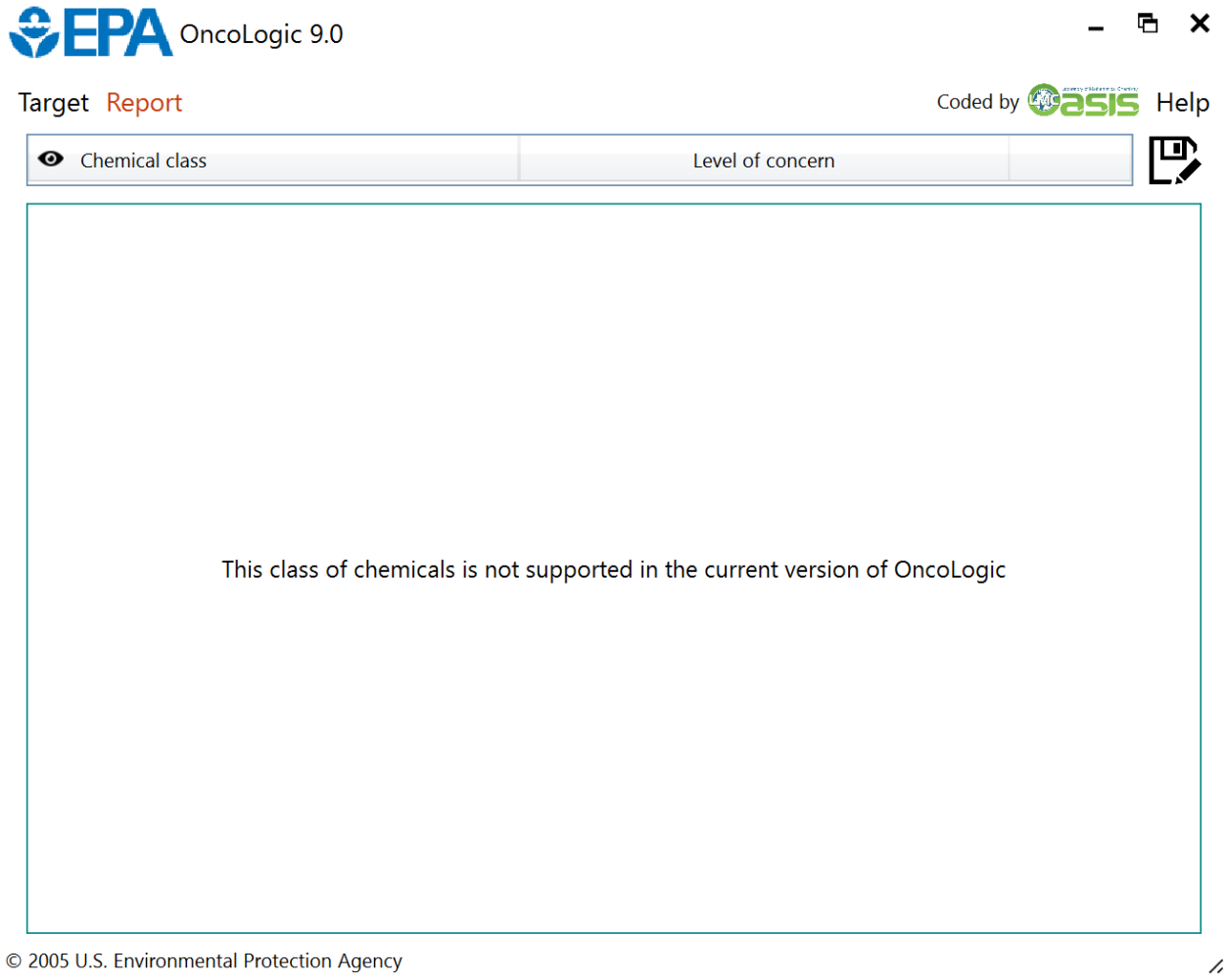
APPENDIX F: OncoLogic™ Carcinogenicity Results for Potassium Citrate (CAS #866-84-2)



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APPENDIX G: Danish QSAR Carcinogenicity Results for Potassium Citrate (CAS #866-84-2)

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

Commercial models from CASE Ultra and Leadscope

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

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

OECD QSAR Toolbox v.4.2 profilers

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

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

DTU-developed models

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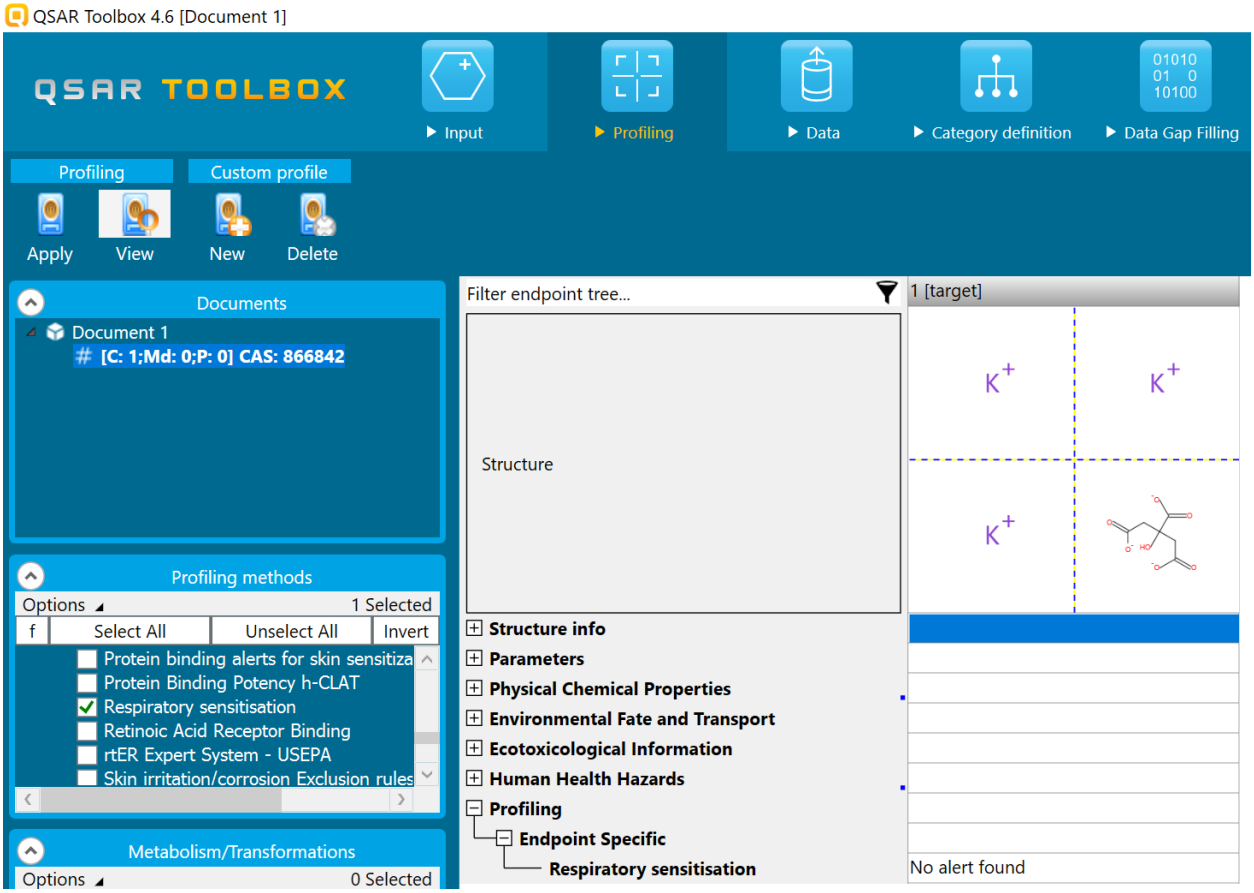
APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Potassium Citrate (CAS #866-84-2)



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APPENDIX I: ECOSAR Modeling Results for Potassium Citrate (CAS #866-84-2)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
866842	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tripotassium salt	[O-]C(=O)CC(O)(C(=O)[O-])CC(=O)[O-].[K+].[K+].[K+]

Structure

Details	
Mol Wt	192.13
Selected LogKow	◆
Selected Water Solubility (mg/L)	◆
Selected Melting Point (°C)	◆
Estimated LogKow	-1.67
Estimated Water Solubility (mg/L)	999999.94
Measured LogKow	-1.64
Measured Water Solubility (mg/L)	1000000
Measured Melting Point (°C)	153

Class Results:	

Neutral Organics

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

1 / 2

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Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	3.14E06	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	1.27E06	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	2.33E05	6.4	
Fish		ChV	2.06E05	8	
Daphnid		ChV	4.82E04	8	
Green Algae		ChV	2.87E04	8	
Fish (SW)	96h	LC50	3.87E06	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Mysid	96h	LC50	3.46E07	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Fish (SW)		ChV	4.46E04	8	
Mysid (SW)		ChV	8.89E06	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Earthworm	14d	LC50	8.03E03	6	

2 / 2

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APPENDIX J: EPI Suite™ Modeling Results for Potassium Citrate (CAS #866-84-2)

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

CAS Number: 866-84-2
SMILES : O(K)C(=O)CC(O)(C(=O)O(K))CC(=O)O(K)
CHEM : 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, tripotassium salt
MOL FOR: C6 H5 O7 K3
MOL WT : 306.40
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log Kow (octanol-water): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = -0.28

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 499.18 (Adapted Stein & Brown method)
Melting Pt (deg C): 210.96 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 2.09E-012 (Modified Grain method)
VP (Pa, 25 deg C) : 2.79E-010 (Modified Grain method)
Subcooled liquid VP: 1.98E-010 mm Hg (25 deg C, Mod-Grain method)
: 2.64E-008 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 6.338e+004
log Kow used: -0.28 (estimated)
no-melting pt equation used
Water Sol (Exper. database match) = 6.06e+005 mg/L (deg C)
Exper. Ref: MERCK INDEX (1996)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1e+006 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : Incomplete
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]:

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HLC: 1.329E-017 atm-m3/mole (1.347E-012 Pa-m3/mole)
VP: 2.09E-012 mm Hg (source: MPBPVP)
WS: 6.34E+004 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Can Not Estimate (can not calculate HenryLC)

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.6902
Biowin2 (Non-Linear Model) : 0.6193
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.6563 (days-weeks)
Biowin4 (Primary Survey Model) : 4.5738 (hours-days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 1.1307
Biowin6 (MITI Non-Linear Model): 0.9754
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 1.1142
Ready Biodegradability Prediction: YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 2.64E-008 Pa (1.98E-010 mm Hg)
Log Koa (): not available
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 114
Octanol/air (Koa) model: not available
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1
Mackay model : 1
Octanol/air (Koa) model: not available

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 2.3405 E-12 cm3/molecule-sec
Half-Life = 4.570 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 54.839 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1 (Junge-Pankow, Mackay avg)
not available (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 10 L/kg (MCI method)
Log Koc: 1.000 (MCI method)

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Koc : 0.3885 L/kg (Kow method)
Log Koc: -0.411 (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 = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -3.0769 days (HL = 0.0008378 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.049 (BCF = 0.8934)
Log BAF Arnot-Gobas method (upper trophic) = -0.049 (BAF = 0.8934)
log Kow used: -1.64 (expkow database)

Volatilization from Water:
Henry LC: 1.33E-017 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 7.709E+013 hours (3.212E+012 days)
Half-Life from Model Lake : 8.41E+014 hours (3.504E+013 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 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	**2.73e-006**	**110**	**1000**
Water	**28.1**	**208**	**1000**
Soil	**71.8**	**416**	**1000**
Sediment	**0.0592**	**1.87e+003**	**0**

Persistence Time: 414 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	2.73e-006	110	1000
Water	28.1	208	1000
water	(28.1)		
biota	(7.38e-007)		
suspended sediment	(0.000422)		
Soil	71.8	416	1000
Sediment	0.0592	1.87e+003	0

Persistence Time: 414 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)

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Air 2.92e-006 110 1000
Water 34.2 208 1000
water (34.2)
biota (8.99e-007)
suspended sediment (1.11e-005)
Soil 65.7 416 1000
Sediment 0.0595 1.87e+003 0
Persistence Time: 388 hr

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APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List

Explosivity – reactive groups

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

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

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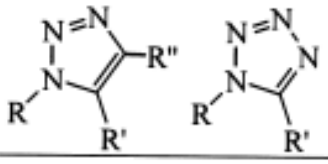
Explosivity – Full List

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

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
>CN_2	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
>C–C< (O)	1,2-Epoxides
>C=N–O—Metal	Metal Fulminates or *aci*-Nitro Salts
>N–Metal	N-Metal Derivatives (especially heavy metals)
>N–N=O >N–NO_2	N-Nitroso and N-Nitro Compounds
>N^+–N–NO_2	N-Azolium Nitroimidates
>C–N=N–C<	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

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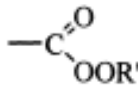
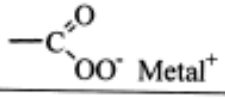
Chemical group	Chemical Class
[1] ROOR',  [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal,  [2]	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O—C–N_2^{+}$	Arenediazonium oxides i.e.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

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

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Self-Reactive Substances

Screening procedures

- Not in CLP, but UN Manual of Tests and Criteria Appendix 6
- No explosive groups (see 2.1) plus

Structural feature	Chemical classes
Mutually reactive groups	Aminonitriles, haloanilines, organic salts of oxidising agents
S=O	Sulphonyl halides, sulphonyl cyanides, sulphonyl hydrazides
P–O	Phosphites
Strained rings	Epoxides, aziridines
Unsaturation	Olefins, cyanates

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APPENDIX L: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for potassium citrate. The original GreenScreen® assessment was performed in 2024 under version 1.4 criteria and ToxServices assigned a Benchmark 3_{DG} (BM-3_{DG}) score.

Table 5: Change in GreenScreen® Benchmark™ for Potassium Citrate

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
March 18, 2024	BM-3_{DG}	v. 1.4	New GreenScreen® assessment.

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