

SODIUM CITRATE (ANHYDROUS, DIHYDRATE)
(CAS #68-04-2, 994-36-5, 6132-04-3)
GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: March 18, 2024

Expiration Date: March 18, 2029



TABLE OF CONTENTS

GreenScreen® Executive Summary for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	i
Chemical Name.....	1
GreenScreen® Summary Rating for Sodium Citrate.....	3
Environmental Transformation Products.....	3
Introduction.....	4
U.S. EPA Safer Choice Program's Safer Chemical Ingredients List (SCIL)	4
GreenScreen® List Translator Screening Results	4
Hazard Statement and Occupational Control.....	4
Physicochemical Properties of Sodium Citrate.....	5
Toxicokinetics.....	6
Hazard Classification Summary	6
Group I Human Health Effects (Group I Human).....	6
Carcinogenicity (C) Score.....	6
Mutagenicity/Genotoxicity (M) Score	8
Reproductive Toxicity (R) Score	10
Developmental Toxicity incl. Developmental Neurotoxicity (D) Score.....	11
Endocrine Activity (E) Score	12
Group II and II* Human Health Effects (Group II and II* Human)	12
Acute Mammalian Toxicity (AT) (Group II) Score.....	12
Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score.....	14
Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score	15
Neurotoxicity (single dose, N-single) (Group II) Score.....	16
Neurotoxicity (repeated dose, N-repeated) (Group II*) Score.....	17
Skin Sensitization (SnS) (Group II*) Score	17
Respiratory Sensitization (SnR) (Group II*) Score	18
Skin Irritation/Corrosivity (IrS) (Group II) Score.....	18
Eye Irritation/Corrosivity (IrE) (Group II) Score.....	19
Ecotoxicity (Ecotox).....	20
Acute Aquatic Toxicity (AA) Score	20
Chronic Aquatic Toxicity (CA) Score	22
Environmental Fate (Fate).....	22
Persistence (P) Score.....	22
Bioaccumulation (B) Score	23
Physical Hazards (Physical)	23
Reactivity (Rx) Score	23
Flammability (F) Score	24

Use of New Approach Methodologies (NAMs) in the Assessment, Including Uncertainty Analyses of Input and Output.....	25
References.....	28
APPENDIX A: Hazard Classification Acronyms.....	31
APPENDIX B: Results of Automated GreenScreen® Score Calculation for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)	32
APPENDIX C: Pharos Output for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	33
APPENDIX D: Toxtree Carcinogenicity Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)	36
APPENDIX E: VEGA Carcinogenicity Results for the Surrogate Citric Acid (CAS #77-92-9).....	37
APPENDIX F: OncoLogic™ Carcinogenicity Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	57
APPENDIX G: Danish QSAR Carcinogenicity Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	58
APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	59
APPENDIX I: ECOSAR Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)	60
APPENDIX J: EPI Suite™ Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	62
APPENDIX K: Known Structural Alerts for Reactivity	66
APPENDIX L: Change in Benchmark Score	70
Licensed GreenScreen® Profilers.....	71

TABLE OF FIGURES

Figure 1: GreenScreen® Hazard Summary Table for Sodium Citrate	3
--	---

TABLE OF TABLES

Table 1: GHS H Statements for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3) (ECHA, CAS #68-04-2, 2024).....	5
Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3).....	5
Table 3: Physical and Chemical Properties of Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)	5
Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	25
Table 5: Change in GreenScreen® Benchmark™ for Sodium Citrate	70

GreenScreen® Executive Summary for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

Sodium citrate is a crystalline solid under standard temperature and pressure that is not reactive or flammable. It is not a volatile organic chemical (VOC) since it decomposes prior to boiling. Sodium citrate functions as a buffering agent, emulsifier/emulsifier salt, color or coloring adjunct, flavoring agent or adjuvant, malting or fermenting aid, nutrient supplement, pH control agent, sequestrant/chelant, stabilizer, thickener, or surface-active agent. The United States Food and Drug Administration (U.S. FDA) recognizes sodium citrate as an indirect food additive, prior-sanctioned ingredient, and as generally recognized as safe (GRAS).

Sodium 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),
 - 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), sodium citrate does not meet requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. In a worst-case scenario, if sodium 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 sodium citrate’s NAMs dataset include insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Sodium 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 sodium citrate’s type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Sodium 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.

GreenScreen® Chemical Assessment for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

Method Version: GreenScreen® Version 1.4

Assessment Type¹: 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 22, 2024

Quality Control Performed By:

Name: Jennifer Rutkiewicz, Ph.D.

Title: Senior Toxicologist

Organization: ToxServices LLC

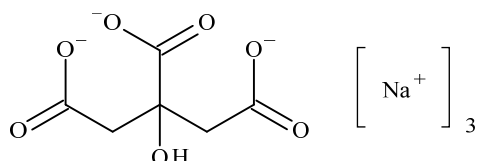
Date: March 18, 2024

Expiration Date: March 18, 2029²

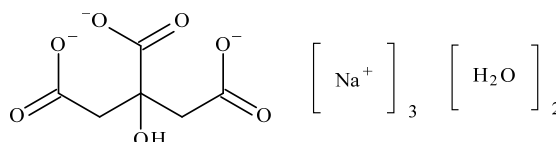
Chemical Name: Sodium Citrate (anhydrous, dihydrate)

CAS Number: 68-04-2, 994-36-5, 6132-04-3

Chemical Structure(s):



Sodium citrate anhydrous (CAS #68-04-2, 994-36-5)



Sodium citrate dihydrate (CAS #6132-04-3)

Also called:

CAS #68-04-2: Trisodium citrate; 2-Hydroxy-1,2,3-propanetricarboxylic acid, trisodium salt, anhydrous; 2-Hydroxy-1,2,3-propanetricarboxylic acid, trisodium salt; 2-Hydroxy-1,2,3-propanetricarboxylic acid trisodium salt; 1,2,3-propanetricarboxylic acid, 2-hydroxy -, trisodium salt; 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, sodium salt (1:3); Trisodium 2-hydroxypropane-1,2,3-tricarboxylate; 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt; Citric acid, trisodium salt; CITRATE, TRISODIUM; Cystemme; Citrosodine; Citrosodina; Citreme; citrato de trisodio; Citrate de trisodium; Citnatin; Urisal; Unifine P 3; Ional; Citra-lock (U.S. EPA 2024a). EC 200-675-3 (ECHA 2024).

CAS #994-36-5: 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, sodium salt; 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, sodium salt (1:1); citric acid, sodium salt; Sodium citrate (x:1); 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, sodium salt (1:x); Citric acid sodium salt; 2-Hydroxy-1,2,3-propanetricarboxylic acid sodium salt (1:1); Sodium 2-hydroxy-1,2,3-propanetricarboxylate; Cellmic ; MB 9082; E 331; Acide citrique, sel de sodium; acido citrico, sal de sodio; Bicitra; Pneucid; Zitronensaure, Natriumsalz; EINECS 213-618-2 (U.S. EPA 2024a). EC 213-618-2 (ECHA 2024).

¹ GreenScreen® reports are either “UNACCREDITED” (by unaccredited person), “AUTHORIZED” (by Authorized GreenScreen® Practitioner), or “CERTIFIED” (by Licensed GreenScreen® Profiler or equivalent).

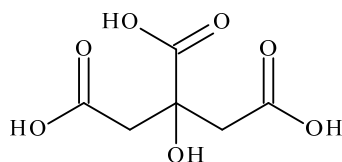
² Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

CAS #6132-04-3:

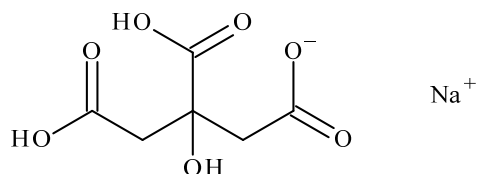
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, sodium salt, hydrate (1:3:2); Sodium 2-hydroxypropane-1,2,3-tricarboxylate--water (3/1/2); Trisodium citrate dihydrate; 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt, dihydrate; 2-Hydroxy-1,2,3-propanetricarboxylic acid, trisodium salt, dihydrate; citrate, sodium, dihydrate; citrate, trisodium, 2-hydrate; citric acid, trisodium salt, dihydrate; natriumcitrat-dihydrat; sodium citrate dihydrate; trisodium-2-hydroxypropane-1,2,3-tricarboxylate dihydrate; 2-hydroxy-1,2,3-propanetricarboxylic acid trisodium salt dihydrate; Citronensäure, Trinatrium-Salz-Dihydrat; Natrum citricum; Sodium citrate hydrate; UNII-B22547B95K (U.S. EPA 2024a). EC 612-118-5 (ECHA 2024).

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):

Limited sodium citrate data were identified for some endpoints. ToxServices used data for citric acid (CAS #77-92-9) and monosodium citrate (CAS #18996-35-5), also known as sodium dihydrogen citrate, to address these data gaps as these chemicals share the citrate moiety with sodium citrate. The sodium ions are not expected to contribute significantly towards the toxicity of sodium citrate since they are natural constituents of surface waters and biological fluids.



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



Surrogate: Monosodium citrate (CAS #18996-35-5)

Identify Applications/Functional Uses (EC 2024, U.S. FDA 2024):

1. Buffering agent
2. Emulsifier/emulsifier salt
3. Color or coloring adjunct
4. Flavoring agent or adjuvant
5. Malting or fermenting aid
6. Nutrient supplement,
7. pH control agent
8. Sequestrant/chelant
9. Stabilizer
10. Thickener
11. Surface-active agent.

Known Impurities³:

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

³ Impurities of the chemical will be assessed at the product level instead of in this GreenScreen®.

GreenScreen® Summary Rating for Sodium Citrate^{4,5,6,7}: Sodium 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),
 - 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), sodium citrate does not meet requirements for a GreenScreen Benchmark™ Score of 4 due to the hazard data gaps. In a worst-case scenario, if sodium 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 Sodium 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*	*	*							
<i>L</i>	<i>L</i>	<i>L</i>	<i>L</i>	DG	L	L	L	L	DG	L	<i>L</i>	L	L	<i>L</i>	vL	vL	<i>L</i>	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 sodium citrate is readily biodegradable, it is not expected to have relevant transformation products.

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.

Introduction

Sodium citrate functions as a buffering agent, emulsifier/emulsifier salt, color or coloring adjunct, flavoring agent or adjuvant, malting or fermenting aid, nutrient supplement, pH control agent, sequestrant/chelant, stabilizer, thickener, or surface-active agent (EC 2024, U.S. FDA 2024). It is produced via addition of sodium carbonate or sodium sulfate to citric acid (HSDB 2002). The United States Food and Drug Administration (U.S. FDA) recognizes sodium citrate as an indirect food additive under 21 CFR §175.300, as a prior-sanctioned ingredient under 21 CFR §181.29, and as generally recognized as safe (GRAS) under 21 CFR §184.1751 (U.S. FDA 2024). The Cosmetic Ingredient Review (CIR) Expert Panel concluded sodium citrate is safe for use in cosmetics in the present practices of use and concentration (up to 10% in rinse-off and leave-on products) (CIR 2014).

ToxServices assessed sodium 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).

Sodium citrate (CASRN 68-04-2, 994-36-5, and 6132-04-3) is listed on the U.S. EPA SCIL as a chelating agent, preservative and antioxidant, and processing aid and additive.

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 sodium citrate can be found in Appendix C.

- Sodium citrate is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Sodium citrate is not listed on the U.S. DOT list.
- Sodium citrate is on the following list for multiple endpoints
 - German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters.
- 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 sodium 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.

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

Table 1: GHS H Statements for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3) (ECHA, CAS #68-04-2, 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 Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)			
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 Sodium Citrate

Sodium citrate is a crystalline solid under standard temperature and pressure. It is highly water soluble (425,000-667,000 mg/L). Based on data for citric acid, sodium 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).

Table 3: Physical and Chemical Properties of Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)		
Property	Value	Reference
Molecular formula	C ₆ H ₅ Na ₃ O ₇ (anhydrous) C ₆ H ₉ Na ₃ O ₉ (dihydrate)	U.S. EPA 2024a
SMILES Notation	[Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O (anhydrous) O.O.[Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O (dihydrate)	U.S. EPA 2024a
Molecular weight	258.068 g/mol (anhydrous) 294.098 g/mol (dihydrate)	U.S. EPA 2024a
Physical state	Solid	ECHA, CAS #68-04-2, 2024
Appearance	Crystalline	ECHA, CAS #68-04-2, 2024
Melting point	Decomposes prior to melting at ≥ 150°C > 300°C	ECHA, CAS #68-04-2, 2024 CIR 2014
Boiling point	Decomposes without boiling	ECHA, CAS #68-04-2, 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 #68-04-2, 2024 CIR 2014
Water solubility	425-667 g/L (425,000-667,000 mg/L) at 25°C 425 g/L (425,000 mg/L) at 25°C	ECHA, CAS #68-04-2, 2024 CIR 2014
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 #68-04-2, 2024
Density/specific gravity	Relative density = 1.857 at 20°C	ECHA, CAS #68-04-2, 2024
Partition coefficient	Log K _{ow} = -1.8 to -0.2 for citric acid	ECHA, CAS #68-04-2, 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).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Sodium 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
 - Sodium citrate does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (Appendix D).

- VEGA 2023
 - VEGA does not accept sodium 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 v1.0.3, 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 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 sodium 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, sodium 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 sodium citrate.
- DTU 2024
 - Sodium citrate acid 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, sodium 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. Sodium 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 the surrogate citric acid and

sodium citrate, respectively, are not likely to be carcinogenic. Therefore, ToxServices concludes sodium citrate is not likely to possess carcinogenic potential.

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

Sodium 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 surrogates citric acid and monosodium citrate, 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 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 #68-04-2, 2024
 - *In vitro: Surrogate: Monosodium citrate (CAS #18996-35-5)*: A bacterial reverse mutation assay conducted in a manner similar to OECD Guideline 471 was performed with *Salmonella typhimurium* tester strains TA1535, TA100, TA98, TA1537, TA92, and TA94 exposed to monosodium citrate (as sodium dihydrogen citrate, 99.6% purity) in phosphate buffer at $\leq 5,000$ $\mu\text{g}/\text{plate}$ 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. The results for the vehicle and untreated negative controls were not specified, and positive results were identified with other substances tested at the same time. 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)*: 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 $\mu\text{g}/\text{mL}$ without metabolic activation. Treatment induced cytotoxicity at 3,000 $\mu\text{g}/\text{mL}$ and statistically significantly increased the percentage of binucleated cells with micronuclei at 50 (1.65%), 100 (2.35%), and 200 $\mu\text{g}/\text{mL}$ (2.60%) relative to the negative control (0.30%) in a concentration-dependent 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 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 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).
- *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).
 - 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)*: 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)*: 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 surrogates citric acid and monosodium citrate were not mutagenic *in vitro* but the surrogate citric acid 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 sodium citrate as genotoxic under GHS criteria (UN 2023).

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

Sodium 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 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

Sodium 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
 - An embryotoxicity test was performed with 9.5-day-old embryos isolated from pregnant female Han Wistar rats exposed to ≤ 115 $\mu\text{mol/L}$ sodium 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 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).
 - 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 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.*

Endocrine Activity (E) Score (H, M, or L): DG

Sodium 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

Sodium citrate was assigned a score of Low for acute toxicity based on based on oral LD₅₀ values $\geq 5,400$ mg/kg in rats and mice and a dermal LD₅₀ $> 2,000$ mg/kg in rats for the surrogate citric acid. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD₅₀ 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.
 - *Screening*: Not present on any screening lists for this endpoint.
- ECHA, CAS #68-04-2, 2024
 - *Oral: Surrogate: Citric acid (CAS #77-92-9)*: LD₅₀ (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)*: LD₅₀ (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)*: LD₅₀ (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)*: LD₅₀ (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

Sodium 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 #68-04-2, 2024
 - *Oral: Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity study that identified an oral LD₅₀ 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 LD₅₀ 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, 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 sacrifice 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 sodium citrate and citric acid have pH values of 8.4 and 1.8, respectively (ECHA 2024), sodium citrate is not likely to be irritating to the respiratory tract. Therefore, ToxServices did not classify sodium 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

Sodium 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.

- 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
 - The REACH dossier for sodium citrate presents several repeated oral dose toxicity tests with exposure durations of 7-10 days. As the results of studies with such short exposure durations are of little value in predicting effects following subchronic or chronic exposures, ToxServices did not summarize the results of these studies in the present assessment.
- 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 sodium 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

Sodium 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 #68-04-2, 2024
 - *Oral: Surrogate: Citric acid (CAS #77-92-9)*: In the acute oral toxicity study that identified an oral LD₅₀ 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 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 LD₅₀ 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 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 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 sacrifice 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 $\leq 2,000$ 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 sodium 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

Sodium 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

Sodium 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 target chemical 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 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 the target chemical supported by clinical 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
 - 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

Sodium 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
 - Sodium 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 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 sodium citrate was not sensitizing to the skin (see skin sensitization section above), and a literature search did not find any human evidence of respiratory sensitization by sodium citrate, and as sodium citrate does not contain any structural alerts for respiratory sensitization (OECD 2023), sodium citrate is not expected to be a respiratory sensitizer.

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

Sodium 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. 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 on 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 #68-04-2, 2024
 - 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 sodium 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).
 - 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 sodium 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). Sodium citrate did not produce sufficient dermal irritation to warrant classification 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

Sodium 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. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate and negative data and no GHS classification are available (CPA 2018b). The confidence in the score is high as it is based on reliable measured data on 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 #68-04-2, 2024
 - 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).

- 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). Sodium citrate did not produce sufficient ocular irritation to warrant classification 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

Sodium citrate was assigned a score of Low for acute aquatic toxicity based on equivalent acute aquatic toxicity values > 134 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
 - 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).
 - 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).
 - 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 EC₅₀ (*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 LC₅₀ (*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 (EC₀) (*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 EC₅₀ (*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 LC₅₀ (*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 LC₅₀ (*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 EC₅₀ (*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 EC₅₀ (*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 LC₅₀ (*Artemia franciscana*, brine 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 EC₅₀ 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 sodium citrate concentration > 134 mg/L.¹⁰

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 sodium citrate has a molecular weight of 258.07 g/mol (PubChem 2024); therefore, 100 mg citric acid/L * 1 mmol citric acid/192.12 mg citric acid * 1 mmol sodium citrate/1 mmol citric acid * 258.07 mg sodium citrate/1 mmol sodium citrate = 134 mg sodium citrate/L.

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

Sodium 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
 - Sodium 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

Sodium 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.
 - *Screening*: Not present on any screening lists for this endpoint.
- ECHA, CAS #68-04-2, 2024
 - *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 (CO₂ 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).

- 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).
- U.S. EPA 2017
 - The BIOWIN modeling Ready Biodegradable Predictor indicates that sodium 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

Sodium 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).

Physical Hazards (Physical)

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

Sodium 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 #68-04-2, 2024
 - Sodium citrate does not contain functional groups associated with oxidizing or explosive properties.

- No measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of sodium citrate. These procedures are listed in the GHS (UN 2021).
 - Based on the structure of its components or moieties, sodium 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, sodium 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 sodium citrate has seven oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.
- Based on the information presented above, ToxServices did not classify sodium citrate as a reactive chemical under GHS criteria (UN 2023).

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

Sodium citrate was assigned a score of Low for flammability based on the lack of ignition of the surrogate monosodium citrate 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 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: Monosodium citrate (CAS #18996-35-5): Monosodium citrate (as dihydrogen sodium citrate, purity not specified) did not ignite in contact with air and, when exposed to a flame, ignited briefly with a rapid extinction in a VDI method 2263 test. Therefore, the authors concluded monosodium citrate was not flammable under the tested conditions. The REACH dossier reports this study with a reliability score of 2 (reliable with restrictions) (Unnamed study 2005).
- Based on the lack of ignition by the surrogate monosodium citrate during a burning test, ToxServices did not classify sodium citrate as a flammable solid under GHS criteria (UN 2023).

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 4, Type I (input data) uncertainties in sodium citrate’s NAMs dataset include insufficient experimental data for carcinogenicity, endocrine activity, and respiratory sensitization, and lack of established test methods for respiratory sensitization. Sodium 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 sodium 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 <i>in vivo</i> 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/docs/server/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427>

	<p>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 <i>in vivo</i> metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).¹³</p> <p>The <i>in vitro</i> 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 <i>in vivo</i> metabolism¹⁴.</p> <p>The <i>in vitro</i> 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 <i>in vivo</i> conditions¹⁵.</p> <p>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.</p>	
Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (<i>in silico</i> modeling/ <i>in vitro</i> biological profiling/frameworks)
Carcinogenicity	Y	<i>In silico</i> modeling: VEGA/Toxtree/OncoLogic™/Danish QSAR
Mutagenicity	Y	<i>In vitro</i> data: Bacterial reverse mutation assay/ <i>in vitro</i> gene mutation assay/ <i>in vitro</i> chromosome aberration assay/ <i>in vitro</i> 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>

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

References

Clean Production Action (CPA). 2018a. GreenScreen® Assessment Expiration Policy. October 2, 2018.

Clean Production Action (CPA). 2018b. The GreenScreen® for Safer Chemicals Guidance. Version 1.4 Guidance. Dated January, 2018. Available:

https://www.greenscreenchemicals.org/static/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf

Cosmetic Ingredient Review (CIR). 2014. Safety assessment of citric acid, inorganic citrate salts, and alkyl citrate esters as used in cosmetics. *Int. J. Toxicol.* 33(2 suppl): 16S-46S. Available:

<https://journals.sagepub.com/doi/10.1177/1091581814526891>

Danish Technical University (DTU). 2024. National Food Institute. Danish QSAR Database. Available: <http://qsar.food.dtu.dk/>.

European Chemicals Agency (ECHA). 2017. Guidance on information requirements and Chemical Safety Assessment. Chapter R.7a: Endpoint specific guidance. Version 6.0. Dated: July 2017. Available:

https://echa.europa.eu/documents/10162/17224/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f?t=1500286622893

European Chemicals Agency (ECHA). 2018. CLH report for citric acid (CAS #77-92-9). Proposal for Harmonised Classification and Labelling based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2. Version 3, dated October 30, 2018. Available:

<https://echa.europa.eu/documents/10162/7b5164b3-6025-874c-7b14-bbb62ee465fc>

European Chemicals Agency (ECHA). 2019. Opinion proposing harmonised classification and labelling at EU level of citric acid (CAS #77-92-9). Committee for Risk Assessment (RAC). CLH-O-0000001412-86-299/F. Adopted September 20, 2019. Available:

<https://echa.europa.eu/documents/10162/039eb0b3-d5a4-c474-915e-0cf4ed07ccba>

European Chemicals Agency (ECHA). 2024. Information on chemicals. Available:

<https://echa.europa.eu/information-on-chemicals>

European Commission (EC). 2024. Sodium citrate (CAS #68-04-2 / 6132-04-3). CosIng database.

Available: <https://ec.europa.eu/growth/tools-databases/cosing/details/37816>

European Food Safety Authority (EFSA). 2018. Guidance on uncertainty analysis in scientific assessments. *EFSA J.* 16(1): e05123. Available:

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7009727/>

Gad, S. 2016. QSAR Tools for Drug Safety. Chapter 10. In, Drug Safety Evaluation. Third Edition. New York: Wiley. 209-224.

Hazardous Substances Data Bank (HSDB). 2002. Trisodium citrate (CAS #68-04-2). United States National Library of Medicine. Available via ToxPlanet: <https://chemical-search.toxplanet.com/#/login>

Madden, J.C., S.J. Enoch, A. Paini, and M.T.D. Cronin. 2020. A review of *in silico* tools as alternatives to animal testing: principles, resources, and applications. *Alt. Lab. Animals*. 1-27. Available: <https://journals.sagepub.com/doi/pdf/10.1177/0261192920965977>

Organisation for Economic Co-operation and Development (OECD). 2020. Overview of Concepts and Available Guidance related to Integrated Approaches to Testing and Assessment (IATA), Series on Testing and Assessment, No. 329, Environment, Health and Safety, Environment Directorate. Available: <https://www.oecd.org/chemicalsafety/risk-assessment/concepts-and-available-guidance-related-to-integrated-approaches-to-testing-and-assessment.pdf>

Organisation for Economic Co-operation and Development (OECD). 2023. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 4.6. Available: https://www.oecd.org/chemicalsafety/risk-assessment/oecd-qsar-toolbox.htm#Download_qsar_application_toolbox

Pharos. 2024. Pharos chemical and material library. Available: <http://www.pharosproject.net/material/>.

PubChem. 2024. Explore chemistry database. United States National Library of Medicine. Available: <https://pubchem.ncbi.nlm.nih.gov/>

Sahigara, F. 2007. Defining the Applicability Domain of QSAR models: An overview. Available: http://www.molecularDescriptors.eu/tutorials/T7_molecularDescriptors_ad.pdf

ToxServices. 2021. SOP 1.37: GreenScreen® Hazard Assessments. Dated: May 24, 2021.

Toxtree. 2018. Estimation of Toxic Hazard- A Decision Tree Approach v3.1.0. Available: <http://toxtree.sourceforge.net>.

United Nations (UN). 2023. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Tenth revised edition.

United Nations Environmental Programme (UNEP). 2004. Screening Information Data Set (SIDS) dossier for citric acid (CAS #77-92-9). Organization for Economic Cooperation and Development (OECD) SIDS. Published July 2004. Available: https://hpvchemicals.oecd.org/UI/SIDS_Details.aspx?id=EE84E16E-D3E9-456F-907C-E1CCE3CFB138

United States Department of Transportation (U.S. DOT). 2008a. Chemicals Listed with Classification. 49 CFR § 172.101. Available: <http://www.gpo.gov/fdsys/pkg/CFR-2008-title49-vol2/pdf/CFR-2008-title49-vol2-sec172-101.pdf>.

United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl

United States Environmental Protection Agency (U.S. EPA). 2015. Safer Choice Standard. Available: <https://www.epa.gov/saferchoice/standard>

United States Environmental Protection Agency (U.S. EPA). 2017. Estimation Programs Interface (EPI) Suite™ Web, v4.11, Washington, DC, USA. Available: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm>.

United States Environmental Protection Agency (U.S. EPA). 2019. OncoLogic™. Version 8.0.16
Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2020. New Approach Methods Workplan.
Office of Research and Development. Office of Chemical Safety and Pollution Prevention. EPA
615B20001. June 2020. Available: https://www.epa.gov/sites/default/files/2020-06/documents/epa_nam_work_plan.pdf

United States Environmental Protection Agency (U.S. EPA). 2021. OncoLogic™. Version 9.0
Washington, DC, USA.

United States Environmental Protection Agency (U.S. EPA). 2022. ECOSAR 2.2. Washington, DC,
USA. Available: <http://www.epa.gov/oppt/newchems/tools/21ecosar.htm/>.

United States Environmental Protection Agency (U.S. EPA). 2024a. CompTox Dashboard. Available:
<https://comptox.epa.gov/dashboard>

United States Environmental Protection Agency (U.S. EPA). 2024b. Safer Chemical Ingredients List
(SCIL). Available: <https://www.epa.gov/saferchoice/safer-ingredients>

United States Environmental Protection Agency (U.S. EPA). 2024c. High Production Volume
Information System (HPVIS) entry for citric acid, anhydrous (CAS #77-92-9). Available:
<https://chemview.epa.gov/chemview#>


United States Food and Drug Administration (U.S. FDA). 2023. Trisodium citrate (CAS #68-04-2).
Substances Added to Food (formerly EAFUS). Available:
<https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=TRISODIUMCITRATE>

Virtual Models for Evaluating the Properties of Chemicals within a Global Architecture (VEGA). 2023.
Predictive Model Platform version 1.2.3. Available: <https://www.vegahub.eu/download/vega-qsar-download/>

APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

- (AA) Acute Aquatic Toxicity**
- (AT) Acute Mammalian Toxicity**
- (B) Bioaccumulation**
- (C) Carcinogenicity**
- (CA) Chronic Aquatic Toxicity**
- (D) Developmental Toxicity**
- (E) Endocrine Activity**
- (F) Flammability**
- (IrE) Eye Irritation/Corrosivity**
- (IrS) Skin Irritation/Corrosivity**
- (M) Mutagenicity and Genotoxicity**
- (N) Neurotoxicity**
- (P) Persistence**
- (R) Reproductive Toxicity**
- (Rx) Reactivity**
- (SnS) Sensitization- Skin**
- (SnR) Sensitization- Respiratory**
- (ST) Systemic/Organ Toxicity**

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)






Table 1: Hazard Table

Group I Human

Carcinogenicity

Mutagenicity/Genotoxicity

Reproductive Toxicity

Developmental Toxicity

Endocrine Activity

Group II and II* Human

Acute Toxicity

Systemic Toxicity

Neurotoxicity

Skin Sensitization *

Respiratory Sensitization *

Skin Irritation

Eye Irritation

Ecotox

Acute Aquatic Toxicity

Chronic Aquatic Toxicity

Fate

Persistence

Bioaccumulation

Physical

Reactivity

Flammability

Table 2: Chemical Details

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

Sodium Citrate

69-04-2, 994-36-5, 6132-04-3

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

Sodium Citrate

4

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

Table 6

Chemical Name

Final GreenScreen® Benchmark Score

Sodium 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

APPENDIX C: Pharos Output for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)



68-04-2

Sodium citrate anhydrous

ALSO CALLED [183748-56-3] 1,2,3-PROPANETRICARBOXYLIC ACID, 2-HYDROXY-, TRISODIUM SALT (primary CASRN is 68-04-2)...

View all synonyms (50)

Share Profile

Hazards Properties Functional Uses Resources

All Hazards View ▾

☐ Show PubMed Results

Request Assessment

Add to Comparison ▾

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

Hazard Lists ⓘ

Download Lists

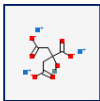
ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Acute Tox. 4 - Harmful if swallowed (modeled)	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause 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]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

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 (5)

- 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): Preservatives-Antioxidants - Green Circle (Verified Low Concern)
- US EPA - DfE Safer Chemicals Ingredients list (SCIL): Processing Aids-Additives - Green Circle (Verified Low Concern)



994-36-5
Sodium Citrate
 ALSO CALLED [6132-04-3] Sodium citrate, 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monosodium salt, 1,2,3-Prop...
[View all synonyms \(23\)](#)

[Share Profile](#)

[Hazards](#)
[Properties](#)
[Functional Uses](#)
[Resources](#)

All Hazards View ▾

☐ Show PubMed Results

[Request Assessment](#)

[Add to Comparison ▾](#)

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

Hazard Lists ⓘ

[Download Lists](#)

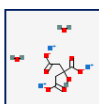
ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Acute Tox. 4 - Harmful if swallowed (modeled) *	
Systemic Toxicity/Organ Effects-Single Exposure	pC	NoGS	EU - Manufacturer REACH hazard submissions	H335 - May cause 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] *	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters *	

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 (5)

- 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): Preservatives-Antioxidants - Green Circle (Verified Low Concern)
- US EPA - DfE Safer Chemicals Ingredients list (SCIL): Processing Aids-Additives - Green Circle (Verified Low Concern)



6132-04-3
Sodium citrate
ALSO CALLED [18996-35-5] Sodium citrate, [994-36-5] Sodium Citrate, [68-04-2] Sodium citrate anhydrous, 200-675-...
[View all synonyms \(13\)](#)

[Share Profile](#)

[Hazards](#) [Properties](#) [Functional Uses](#) [Resources](#)

All Hazards View ▾

☐ Show PubMed Results

[Request Assessment](#)

[Add to Comparison ▾](#)

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

Hazard Lists ⓘ

[Download Lists](#)

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Acute Mammalian Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Acute Tox. 4 - Harmful if swallowed (modeled) *	
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] *	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	

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 (5)

- 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): Preservatives-Antioxidants - Green Circle (Verified Low Concern)
- US EPA - DfE Safer Chemicals Ingredients list (SCIL): Processing Aids-Additives - Green Circle (Verified Low Concern)

APPENDIX D: Toxtree Carcinogenicity Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

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

File Edit Chemical Compounds Toxic Hazard Method Help

Chemical identifier [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O Go

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
Q5AR13 applicable?	NO
Q5AR6,8 applicable?	NO
SA10_gen	NO
SA11_gen	NO
SA12_gen	NO

Structure diagram

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

QSA310_nogen.Halogenated PAH (naphthalenes, biphenyls, diphenyls) (Nongenotoxic carcinogens) **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA31c_nogen.Halogenated dibenzodioxins (Nongenotoxic carcinogens) **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA39_gen_and_nogen.Steroidal estrogens **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA40_nogen.substituted phenoxyacid **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA41_nogen.substituted n-alkylcarboxylic acids **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA42_nogen.phthalate diesters and monoesters **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA43_nogen.Perfluorooctanoic acid (PFOA) **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA44_nogen.Trichloro (or fluoro) ethylene and Tetrachloro (or fluoro) ethylene **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA45_nogen.indole-3-carbinol **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA46_nogen.pentachlorophenol **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA47_nogen.o-phenylphenol **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA48_nogen.quercetin-type flavonoids **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA49_nogen.imidazole and benzimidazole **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA50_nogen.dicarboximide **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA51_nogen.dimethylpyridine **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA52_nogen.Metals, oxidative stress **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA53_nogen.Benzensulfonic ethers **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA54_nogen.1,3-Benzodioxoles **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA55_nogen.Phenoxo herbicides **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QSA56_nogen.alkyl halides **No** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

QNongenotoxic alert? At least one alert for nongenotoxic carcinogenicity fired? **No** Class **Negative for nongenotoxic carcinogenicity** [Na+].[Na+].[Na+].OC(CC([O-])=O)(CC([O-])=O)C([O-])=O

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



Carcinogenicity model (CAESAR) 2.1.10

page 1



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p> EXPERIMENTAL DATA</p> <p>E xperimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).</p>
--	---

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

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



	<p>Compound #1 CAS: 77-92-9 Dataset id:173 (Training Set) SMILES: <chem>O=C(O)CC(O)(C(=O)O)CC(=O)O</chem> Similarity: 1 Experimental value : NON-Carcinogen Predicted value : Carcinogen</p>
	<p>Compound #2 CAS: 69-65-8 Dataset id:421 (Training Set) SMILES: <chem>OCC(O)C(O)C(O)C(O)CO</chem> Similarity: 0.817 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #3 CAS: 50-81-7 Dataset id:58 (Training Set) SMILES: <chem>O=C1C(O)=C(O)OC1C(O)CO</chem> Similarity: 0.802 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #4 CAS: 139-13-9 Dataset id:498 (Training Set) SMILES: <chem>O=C(O)CN(CC(=O)O)CC(=O)O</chem> Similarity: 0.8 Experimental value : Carcinogen Predicted value : Carcinogen</p>
	<p>Compound #5 CAS: 30310-80-6 Dataset id:593 (Training Set) SMILES: <chem>O=NN1CC(O)CC1(C(=O)O)</chem> Similarity: 0.758 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #6 CAS: 10318-26-0 Dataset id:213 (Training Set) SMILES: <chem>OC(CBr)C(O)C(O)C(O)CBr</chem> Similarity: 0.755 Experimental value : Carcinogen Predicted value : NON-Carcinogen</p>

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..

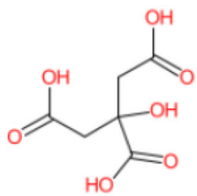

Symbols explanation:

- 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.



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p> EXPERIMENTAL DATA</p> <p>Experimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).</p> <p>The following alerts have been found: SA41 Substituted n-alkylcarboxylic acids</p>
---	--

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

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



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

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.

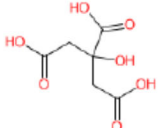
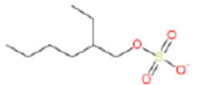
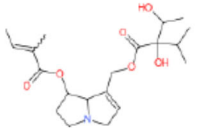


The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning: Relevant Chemical Fragments and Moieties



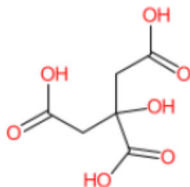

(Molecule 0) Reasoning on fragments/structural alerts :.

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.	
	<p>CAS: 77-92-9 Dataset id:829 (Training Set) SMILES: <chem>O=C(O)CC(O)(C(=O)O)CC(=O)O</chem> Similarity: 1</p> <p>Experimental value : NON-Carcinogen Predicted value : Carcinogen</p> <p>Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids</p>
	<p>CAS: 126-92-1 Dataset id:77 (Training Set) SMILES: <chem>O=S(=O)([O-])OCC(CC)CCCC</chem> Similarity: 0.675</p> <p>Experimental value : Carcinogen Predicted value : Carcinogen</p> <p>Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids</p>
	<p>CAS: 22571-95-5 Dataset id:486 (Training Set) SMILES: <chem>O=C(OC2CCN1CC=C(COC(=O)C(O)(C(O)C)C(C)C)C12)C(=CC)C</chem> Similarity: 0.616</p> <p>Experimental value : Carcinogen Predicted value : Carcinogen</p> <p>Alerts (found also in the target): SA41 Substituted n-alkylcarboxylic acids</p> <p>Alerts (not found also in the target): SA37 Pyrrolizidine Alkaloids</p>



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p> EXPERIMENTAL DATA</p> <p>Experimental value is NON-Carcinogen. Model prediction is Possible NON-Carcinogen (GOOD reliability).</p>
---	--

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

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



	<p>Compound #1 CAS: 77-92-9 Dataset id:745 (Training Set) SMILES: <chem>O=C(O)CC(O)(C(=O)O)CC(=O)O</chem> Similarity: 1 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #2 CAS: 69-65-8 Dataset id:69 (Training Set) SMILES: <chem>OCC(O)C(O)C(O)C(O)CO</chem> Similarity: 0.817 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #3 CAS: 50-81-7 Dataset id:25 (Training Set) SMILES: <chem>O=C1C(O)=C(O)OC1C(O)CO</chem> Similarity: 0.802 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #4 CAS: 139-13-9 Dataset id:167 (Training Set) SMILES: <chem>O=C(O)CN(CC(=O)O)CC(=O)O</chem> Similarity: 0.8 Experimental value : Carcinogen Predicted value : Carcinogen</p>
<p>Alerts (not found also in the target): Carcinogenity alert no. 34</p>	
	<p>Compound #5 CAS: 6381-77-7 Dataset id:943 (Training Set) SMILES: <chem>O=C1OC(C(O)=C1(O))C(O)C[O-]</chem> Similarity: 0.767 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #6 CAS: 10318-26-0 Dataset id:369 (Training Set) SMILES: <chem>OC(CBr)C(O)C(O)C(O)CBr</chem> Similarity: 0.755 Experimental value : Carcinogen Predicted value : Possible NON-Carcinogen</p>

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.

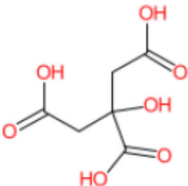



The feature has a bad assessment, model is not reliable regarding this aspect.



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p> EXPERIMENTAL DATA</p> <p>Experimental value is NON-Carcinogen. Model prediction is Carcinogen (LOW reliability).</p> <p>The following relevant fragments have been found: Carcinogenicity alert no. 21</p>
---	--

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: Carcinogenicity alert no. 21

Reliability: The predicted compound is outside the Applicability Domain of the model

Remarks:

none

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values

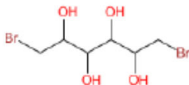


	<p>Compound #1</p> <p>CAS: 77-92-9 Dataset id:173 (Training Set) SMILES: <chem>O=C(O)CC(O)(C(=O)O)CC(=O)O</chem> Similarity: 1 Experimental value : NON-Carcinogen Predicted value : Carcinogen</p>
<p>Alerts (found also in the target): Carcinogenicity alert no. 21</p>	
	<p>Compound #2</p> <p>CAS: 69-65-8 Dataset id:421 (Training Set) SMILES: <chem>OCC(O)C(O)C(O)C(O)CO</chem> Similarity: 0.817 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #3</p> <p>CAS: 50-81-7 Dataset id:58 (Training Set) SMILES: <chem>O=C1C(O)=C(O)OC1C(O)CO</chem> Similarity: 0.802 Experimental value : NON-Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #4</p> <p>CAS: 139-13-9 Dataset id:498 (Training Set) SMILES: <chem>O=C(O)CN(CC(=O)O)CC(=O)O</chem> Similarity: 0.8 Experimental value : Carcinogen Predicted value : Possible NON-Carcinogen</p>
	<p>Compound #5</p> <p>CAS: 30310-80-6 Dataset id:593 (Training Set) SMILES: <chem>O=NN1CC(O)CC1C(=O)O</chem> Similarity: 0.758 Experimental value : NON-Carcinogen Predicted value : Carcinogen</p>
	<p>Alerts (not found also in the target): Carcinogenicity alert no. 8; Carcinogenicity alert no. 11; Carcinogenicity alert no. 15; Carcinogenicity alert no. 46; Carcinogenicity alert no. 47; Carcinogenicity alert no. 50; Carcinogenicity alert no. 51; Carcinogenicity alert no. 54; Carcinogenicity alert no. 55; Carcinogenicity alert no. 63</p>

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): Carcinogenicity alert no. 58; Carcinogenicity alert no. 59




3.2 Applicability Domain:

Measured Applicability Domain Scores



	<p>Global AD Index</p> <p>AD index = 0</p> <p>Explanation: The predicted compound is outside the Applicability Domain of the model.</p>
	<p>Similar molecules with known experimental value</p> <p>Similarity index = 1</p> <p>Explanation: Strongly similar compounds with known experimental value in the training set have been ..</p>
	<p>Accuracy of prediction for similar molecules</p> <p>Accuracy index = 0</p> <p>Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..</p>
	<p>Concordance for similar molecules</p> <p>Concordance index = 0</p> <p>Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..</p>
	<p>Atom Centered Fragments similarity check</p> <p>ACF index = 1</p> <p>Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..</p>

Symbols explanation:

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

4.1 Reasoning: Relevant Chemical Fragments and Moieties



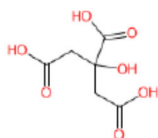
(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: Carcinogenicity alert no. 21



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

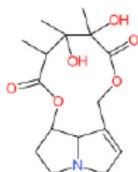
Following, the most similar compounds from the model's dataset having the same fragment.



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): Carcinogenicity alert no. 21

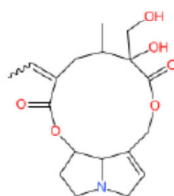


CAS: 315-22-0
 Dataset id:488 (Test Set)
 SMILES: O=C1OC3CCN2CC=C(COC(=O)C(O)(C)C(O)(C)C1C)C23
 Similarity: 0.653

Experimental value : Carcinogen
 Predicted value : Carcinogen

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

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

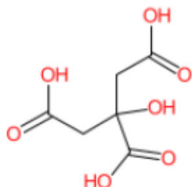


Alerts (found also in the target): Carcinogenicity alert no. 21

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



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p>Prediction:  Reliability: </p> <p>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:</p> <ul style="list-style-type: none">- 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

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



	<p>Compound #1</p> <p>CAS: 124-04-9 Dataset id:541 (Training Set) SMILES: <chem>O=C(O)CCCC(=O)O</chem> Similarity: 0.816 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #2</p> <p>CAS: 145-73-3 Dataset id:494 (Training Set) SMILES: <chem>O=C(O)C2C1OC(CC1)C2(C(=O)O)O</chem> Similarity: 0.78 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #3</p> <p>CAS: 77182-82-2 Dataset id:528 (Training Set) SMILES: <chem>O=C(O)C(N)CCP(=O)(O)C</chem> Similarity: 0.765 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #4</p> <p>CAS: 1596-84-5 Dataset id:88 (Training Set) SMILES: <chem>O=C(O)CCC(=O)NN(C)C</chem> Similarity: 0.753 Experimental value : Carcinogen Predicted value : Carcinogen</p>
	<p>Compound #5</p> <p>CAS: 1071-83-6 Dataset id:531 (Training Set) SMILES: <chem>O=C(O)CNC(=O)COP(=O)(O)O</chem> Similarity: 0.744 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #6</p> <p>CAS: 115-02-6 Dataset id:27 (Training Set) SMILES: <chem>N#[N+]C=C([O-])OCC(N)C(=O)O</chem> Similarity: 0.74 Experimental value : Carcinogen Predicted value : NON-Carcinogen</p>

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.

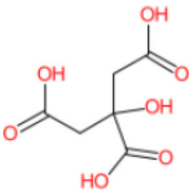




The feature has a bad assessment, model is not reliable regarding this aspect.



1. Prediction Summary

Prediction for compound Molecule 0 -

	<p>Prediction:  Reliability: </p> <p>Prediction is NON-Carcinogen, but the result shows some critical aspects, which require to be checked:</p> <ul style="list-style-type: none">- 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

3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



	<p>Compound #1</p> <p>CAS: 124-04-9 Dataset id:517 (Training Set) SMILES: <chem>O=C(O)CCCC(=O)O</chem> Similarity: 0.816 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #2</p> <p>CAS: 139-13-9 Dataset id:178 (Training Set) SMILES: <chem>O=C(O)CN(CC(=O)O)CC(=O)O</chem> Similarity: 0.8 Experimental value : Carcinogen Predicted value : Carcinogen</p>
	<p>Compound #3</p> <p>CAS: 145-73-3 Dataset id:466 (Training Set) SMILES: <chem>O=C(O)C2C1OC(CC1)C2(C(=O)O)</chem> Similarity: 0.78 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #4</p> <p>CAS: 77182-82-2 Dataset id:503 (Training Set) SMILES: <chem>O=C(O)C(N)CCP(=O)(O)C</chem> Similarity: 0.765 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen</p>
	<p>Compound #5</p> <p>CAS: 1596-84-5 Dataset id:74 (Training Set) SMILES: <chem>O=C(O)CCC(=O)NN(C)C</chem> Similarity: 0.753 Experimental value : Carcinogen Predicted value : Carcinogen</p>
	<p>Compound #6</p> <p>CAS: 115-02-6 Dataset id:24 (Training Set) SMILES: <chem>O=C(O)C(N)COC(=O)C=[N+]=N</chem> Similarity: 0.749 Experimental value : Carcinogen Predicted value : Carcinogen</p>

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.

APPENDIX F: OncoLogic™ Carcinogenicity Results for Sodium Citrate
(CAS #68-04-2, 994-36-5, 6132-04-3)

 OncoLogic 9.0

Target Report

Coded by  Help

 Chemical class	Level of concern
<div>This class of chemicals is not supported in the current version of OncoLogic</div>	

© 2005 U.S. Environmental Protection Agency

APPENDIX G: Danish QSAR Carcinogenicity Results for Sodium Citrate
(CAS #68-04-2, 994-36-5, 6132-04-3)

	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

APPENDIX H: OECD Toolbox Respiratory Sensitization Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

QSAR Toolbox 4.6 [Document 1]

QSAR TOOLBOX

► Input ► Profiling ► Data ► Category definition ► Data Gap Filling

01010
01 0
10100

Profiling Custom profile

Apply View New Delete

Documents

Document 1
[C: 1;Md: 0;P: 0] CAS: 68042

Profiling methods

Options ▾ 1 Selected

f Select All Unselect All Invert

☒ **Predefined**

- ☐ Database Affiliation
- ☐ Inventory Affiliation
- ☐ OECD HPV Chemical Categories
- ☐ Substance type
- ☐ US-EPA New Chemical Categories

Metabolism/Transformations

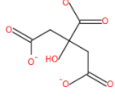
Options ▾ 0 Selected

f Select All Unselect All Invert

Filter endpoint tree... 1 [target]

Structure

Na⁺ **Na⁺**

Na⁺ 

Structure info

Parameters

Physical Chemical Properties

Environmental Fate and Transport

Ecotoxicological Information

Human Health Hazards

Profiling

Endpoint Specific

Respiratory sensitisation

No alert found

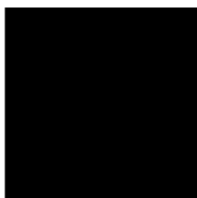
APPENDIX I: ECOSAR Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
68042	1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt	[O-]C(=O)CC(O)(C(=O)[O-])CC(=O)[O-]

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
----------	----------	-----------	----------------------	-------------	-------

Class Results:	
----------------	--

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	3.14E06	5	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	

APPENDIX J: EPI Suite™ Modeling Results for Sodium Citrate (CAS #68-04-2, 994-36-5, 6132-04-3)

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

CAS Number: 68-04-2

SMILES : O([Na])C(=O)CC(O)(C(=O)O([Na]))CC(=O)O([Na])

CHEM : 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, trisodium salt

MOL FOR: C6 H5 O7 Na3

MOL WT : 258.07

----- 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): 1.2e+005

log Kow used: -0.28 (estimated)

no-melting pt equation used

Water Sol (Exper. database match) = 4.34e+005 mg/L (deg C)

Exper. Ref: MERCK INDEX (1996); approx.

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 : 8.43E-018 atm-m3/mole (8.54E-013 Pa-m3/mole)

Group Method: Incomplete

For Henry LC Comparison Purposes:

User-Entered Henry LC: not entered

Henry's LC [via VP/WSol estimate using User-Entered or Estimated values]:

HLC: 5.914E-018 atm-m³/mole (5.992E-013 Pa-m³/mole)

VP: 2.09E-012 mm Hg (source: MPBPVP)

WS: 1.2E+005 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:

Log Kow used: -0.28 (KowWin est)

Log Kaw used: -15.463 (HenryWin est)

Log Koa (KOAWIN v1.10 estimate): 15.183

Log Koa (experimental database): None

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 deg C)[AEROWIN v1.00]:

Vapor pressure (liquid/subcooled): 2.64E-008 Pa (1.98E-010 mm Hg)

Log Koa (Koawin est): 15.183

Kp (particle/gas partition coef. (m³/ug)):

Mackay model : 114

Octanol/air (Koa) model: 374

Fraction sorbed to airborne particulates (phi):

Junge-Pankow model : 1

Mackay model : 1

Octanol/air (Koa) model: 1

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:

Hydroxyl Radicals Reaction:

OVERALL OH Rate Constant = 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)

1 (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)
 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) = -2.9529 days (HL = 0.001114 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: 8.43E-018 atm-m³/mole (estimated by Bond SAR Method)
 Half-Life from Model River: 1.116E+014 hours (4.649E+012 days)
 Half-Life from Model Lake : 1.217E+015 hours (5.071E+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	1.73e-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	1.73e-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)
Air	1.85e-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			

APPENDIX K: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups


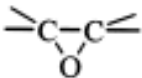
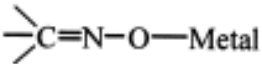
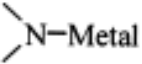
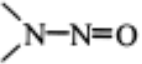
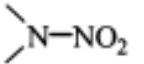
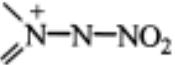
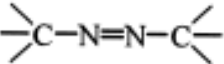
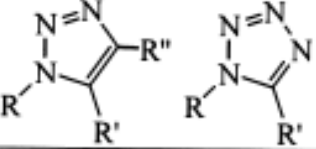
- Not classified if no chemical groups associated with explosivity, e.g.

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

© CHCS Module 17
CLP - Substances
31

Explosivity – Full List


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

Chemical group	Chemical Class
-C≡C-	Acetylenic Compounds
-C≡C-Metal	Metal Acetylides
-C≡C-Halogen	Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO ₂	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO ₂	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or <i>aci</i> -Nitro Salts
	N-Metal Derivatives (especially heavy metals)
 	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
(ArN=N) ₂ O, (ArN=N) ₂ S	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C} \\ \backslash \\ \text{OOR}' \end{array}$ [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, $\begin{array}{c} \text{O} \\ \parallel \\ \text{---C} \\ \backslash \\ \text{OO}^- \text{Metal}^+ \end{array}$ [2]	Metal peroxides, Peroxoacids salts
-N ₃	Azides e.g. PbN ₆ , CH ₃ N ₃
$\text{}^-\text{O} \text{---} \text{C} \text{---} \text{N}_2^+$	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. perchlorates, bromates, etc
NX ₃ e.g. NCl ₃ , RNCI ₂	N-Halogen Compounds

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

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

© CHCS Module 17

CLP - Substances

53

APPENDIX L: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for sodium citrate. This is a new GreenScreen® assessment.

Table 5: Change in GreenScreen® Benchmark™ for Sodium Citrate			
Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
March 18, 2024	BM-3 _{DG}	v. 1.4	New GreenScreen® assessment.

Licensed GreenScreen® Profilers

Sodium Citrate GreenScreen® Evaluation Prepared by:

SIGNATURE
BLOCK

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

Sodium Citrate GreenScreen® Evaluation QC'd by:

SIGNATURE
BLOCK

Jennifer Rutkiewicz, Ph.D.
Senior Toxicologist
ToxServices LLC