DOCUSATE SODIUM

(CAS #577-11-7)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: October 16, 2023

Expiration Date: October 16, 2028

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GreenScreen® Executive Summary for Docusate Sodium (CAS #577-11-7)

Docusate sodium is a member of the sulfosuccinates chemical category. This chemical is used as a wetting agent in industrial, pharmaceutical, cosmetic, and food applications. It is also used as a dispersing and solubilizing agent in foods and is the active ingredient of leading emollient-based stool softeners.

Docusate sodium exists as white wax at room temperature that decomposes at temperatures >200°C. It has a low vapor pressure, indicating low potential to form a vapor, and is highly soluble in water. Its partition coefficient is estimated at 1.998, indicating it is more soluble in the organic phase than in water; however, interpretation of this value is difficult due to the surface active properties of the compound.

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
    - Very High Group II Human Toxicity (eye irritation-IrE)

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

ToxServices' original GreenScreen® assessment was performed in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017 and a version 1.4 update in 2022. In the current GreenScreen® assessment, ToxServices maintained the BM-2 score with a version 1.4 update.

New Approach Methodologies (NAMs) used in this GreenScreen® comprise *in silico* modeling for respiratory sensitization and *in vitro* testing for genotoxicity and endocrine activity. 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 docusate sodium's NAMs dataset include the lack of sufficient data for endocrine activity and respiratory sensitization, and a lack of validated test methods for respiratory sensitization. Docusate sodium's Type II (extrapolation output) uncertainties include limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism and focusing on a few events in the process of mutagenicity, the uncertain *in vivo* relevance of *in vitro* high throughput assays of receptor binding activities, the incomplete coverage of Tox21 EDSP assays on critical endocrine pathways, the lack of defined applicability domains for respiratory sensitization structural alerts in OECD Toolbox, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of docusate sodium'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 Docusate Sodium

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**	**M**	DG	**M**	**L**	**L**	*L*	**L**	*L*	*L*	**H**	**vH**	**H**	*M*	**L**	**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 Docusate sodium (CAS #577-11-7)

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

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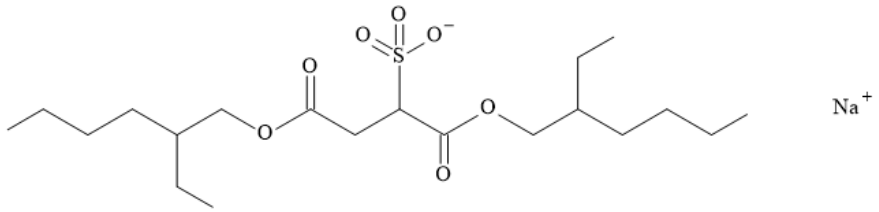
Date: August 28, 2023; October 16, 2023

Expiration Date: October 16, 2028[2]

Chemical Name: Docusate sodium

CAS Number: 577-11-7

Chemical Structure(s):



[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).

Also called:
Aerosol OT; Colace; DEH Na SS; DEH-Na-SS; diethylhexyl sodium sulfosuccinate; Dioctyl Sulfosuccinate; Dioctyl Sulfosuccinate, Sodium; Dioctyl Sulfosuccinates; Dioctyl Sulfosuccinic Acid; Dioctyl Sulfosuccinic Acid, Ammonium Salt; Dioctyl Sulfosuccinic Acid, Barium Salt; Dioctyl Sulfosuccinic Acid, Calcium Salt; Dioctyl Sulfosuccinic Acid, Magnesium Salt; Dioctyl Sulfosuccinic Acid, Potassium Salt; Dioctyl Sulfosuccinic Acid, Sodium Salt; Dioctylsulfosuccinate; Dioctylsulphosuccinate, Sodium; Docusate; Docusate Calcium; Docusate Potassium; Docusate Sodium; DOSS; Sodium Bis(2-ethylhexyl)sulfosuccinate; Sodium Dioctyl Sulfosuccinate; Sodium Dioctylsulphosuccinate; Sodium Sulfosuccinate, Diethylhexyl; Sulfosuccinate, Diethylhexyl Sodium; Sulfosuccinate, Dioctyl; Sulfosuccinates, Dioctyl; Sulfosuccinic Acid bis(2-Ethylhexyl) Ester (PubChem 2023)

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A relatively complete dataset was identified for docusate sodium. No surrogates were identified with data sufficient to fill the data gaps for docusate sodium. Therefore, the use of a surrogate was not possible for this assessment.

Identify Applications/Functional Uses:
1. Wetting agent
2. Food additive
3. Dispersant
4. Emulsifier
5. Stool softener
(HSDB 2001, U.S. EPA 2009)

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

GreenScreen® Summary Rating for Docusate Sodium[3,4 5,6]: Docusate sodium was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
  - Very High Group II Human Toxicity (eye irritation-IrE)

A data gap (DG) exists for endocrine activity-E. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), docusate sodium meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gap. In a worst-case scenario, if docusate sodium were assigned a High score for the data gap E, it would be categorized as a Benchmark 2 Chemical.

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

Figure 1: GreenScreen® Hazard Summary Table for Docusate Sodium

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	M	DG	M	L	L	*L*	L	*L*	*L*	H	vH	H	*M*	L	vL	*L*	L

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

Environmental Transformation Products

As shown in Table 1, below, OECD Toolbox (2023) identified four hydrolysis products under basic and acidic conditions, and two hydrolysis products under neutral conditions. Only one compound was identified in the Pharos database. 2-Ethyl-1-hexanol (CAS #104-76-7) is a Benchmark 2 chemical. As this compound is not a Benchmark 1 or LT-1, and the remaining compounds are not in the Pharos database, the benchmark score of the parent chemical is not modified.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[7,8]
N/A	Hydrolysis (acidic, basic, neutral)	2-Ethyl-1-hexanol	104-76-7	Y	Y	BM-2
N/A	Hydrolysis (acidic, basic)	Sodium; 2-sulfobutanedioic acid	N/A	Y	Y	Not in Pharos database
N/A	Hydrolysis (acidic, basic)	4-(2-Ethylhexoxy)-4-oxo-3-sulfo-butanoic acid; sodium	N/A	Y	Y	Not in Pharos database
N/A	Hydrolysis (acidic, basic, neutral)	4-(2-Ethylhexoxy)-4-oxo-2-sulfo-butanoic acid; sodium	N/A	Y	Y	Not in Pharos database

Introduction

Docusate sodium is a non-flammable, non-volatile white waxy solid that is a member of the sulfosuccinates chemical category. It is produced by the reaction of 2-ethylhexanol with maleic anhydride, followed by the addition of sodium bisulfite (HSDB 2001, U.S. EPA 2009).
ToxServices assessed docusate sodium against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2021).

[7] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[8] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

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

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

Docusate sodium is not listed on the U.S. EPA SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[9] 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 Docusate sodium can be found in Appendix C.

- Docusate sodium is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Docusate sodium is not listed on the U.S. DOT list.
- Docusate sodium is on the following lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.
  - German FEA – Substances Hazardous to Waters – Class 2 – Hazard to Waters
  - Environment Canada (EC) – CEPA Domestic Substances List (DSL) – Inherently Toxic to Humans (iTH)

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for docusate sodium. Self-classifications by its REACH registration dossier authors are shown in Table 2. General personal protective equipment (PPE) recommendations are presented in Table 3, below. No occupational exposure limits (OELs) were identified.

Table 2: GHS H Statements for Docusate Sodium (CAS #577-11-7) (ECHA 2023)

H Statement	H Statement Details
H315	Causes skin irritation
H318	Causes serious eye damage

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Docusate Sodium (CAS #577-11-7)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respiratory: breathing mask when there is inadequate ventilation	ECHA 2023	None identified	
Hands: Viton (0.7 mm), >480 min			
Eyes: protective goggles			

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

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Docusate Sodium (CAS #577-11-7)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Skin: suitable protective clothing			

Physicochemical Properties of Docusate Sodium

Docusate sodium exists as white wax at room temperature that decomposes at temperatures >200°C. It has a low vapor pressure, indicating low potential to form a vapor, and is highly soluble in water. Its partition coefficient is estimated at 1.998, indicating it has a low potential to bioaccumulate; however, interpretation of this estimate is difficult due to the surface active properties of the compound.

Table 4: Physical and Chemical Properties of Docusate Sodium (CAS #577-11-7)		
Property	**Value**	**Reference**
Molecular formula	$C_{20}H_{37}NaO_7S$	PubChem 2023
SMILES Notation	CCCCC(CC)COC(=O)CC(C(=O)OCC(CC)CCCC)S(=O)(=O)[O-].[Na+]	PubChem 2023
Molecular weight	444.6 g/mol	PubChem 2023
Physical state	Solid	PubChem 2023
Appearance	White, wax-like	PubChem 2023
Melting point	≥165 - ≤170°C	PubChem 2023
Boiling point	>200°C (decomposes)	ECHA 2023
Vapor pressure	2.17×10^{-11} mm Hg at 25ºC (estimated); $<7.5 \times 10^{-6}$ mm Hg (negligible)	PubChem 2023 U.S. EPA 2009
Water solubility	8.17 g/L at 20°C	ECHA 2023
Dissociation constant	pKa = -0.75 at 20°C (calculation)	ECHA 2023
Density/specific gravity	1.146 g/cm^3 at 27.4°C	ECHA 2023
Partition coefficient	Log K_{ow} = 1.998 at 20°C (calculation) Log K_{ow} = 3.95 (estimated)	ECHA 2023 U.S. EPA 2009

Toxicokinetics

Absorption, excretion, and metabolism of docusate sodium has been evaluated in rats, rabbits, dogs, and humans. Docusate sodium is highly absorbed via the oral route of exposure based on similar fraction of administered dose in the urine after oral and intravenous administration in rats and rabbits (90% radioactivity found in the urine). In dogs, however, the oral absorption is much lower (71% of radioactivity in the urine). In humans, an oral dose of 200 mg resulted in peak concentration of docusate sodium in the serum after 2 hours, and the peak concentration is similar in humans and dogs. Also similar to dogs, excreted metabolites in the urine in humans only accounted for a small fraction of administered docusate sodium. Dermal absorption is possible based on the physicochemical properties of the compound, but modeled data and skin irritation studies suggest that docusate sodium is more active at or in the dermis than through the dermis (i.e., absorbed). Physicochemical properties suggest inhalation absorption is also low. Distribution and metabolism occur rapidly within 24 hours in experimental animals. Docusate sodium does not accumulate in tissues based on experimental data. It is expected to be metabolized to 2-ethylhexanol forming compounds, and is mainly excreted via urine within 24 hours after dosing in rats and rabbits. In humans and dogs, most of the administered docusate sodium is excreted in the feces after oral and/or intravenous dosing (ECHA 2023).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Docusate sodium was assigned a score of Low for carcinogenicity based on a lack of evidence of carcinogenicity in a two-year feeding study in rats and a subcutaneous carcinogenesis study in rats focused on assessing tumors in the gastrointestinal system. 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 the studies have limited reliability.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - In a carcinogenicity study conducted in a manner similar to OECD Guideline 451 (GLP-status not reported), male Osborne-Mendel rats (12/dose) received diets containing docusate sodium at 0.25%, 0.5%, or 1.0% (contributing doses of 125, 250, and 500 mg/kg/day, respectively according to the authors) for two years. There were no mortalities or clinical signs reported. Treatment with 1.0% docusate sodium caused significant decrease in weight gain compared to control. No effects were reported in the 0.25% or 0.5% groups, and no abnormalities were reported for gross pathology and histopathology for any treated groups. Treatment with docusate sodium showed no carcinogenic potential (Klimisch 3, not reliable, due to limited information available on materials and methods).
  - In a model for colon carcinogenesis, 84 male Fisher 344 rats were administered 0 or 1% docusate sodium in the diet for 20 weeks and given a subcutaneous injection of 20 mg/kg 1,2-dimethylhydrazine once weekly. Animals (20/time point) were sacrificed at 3, 4, 5 and 6 months. The duodenum, small intestine, colon, and rectum were dissected and evaluated for tumors. There was no statistically significant difference between the test and control groups in the percentage of rats bearing tumors, and the number of tumors per rat increased progressively throughout the study. At 5 and 6 months, there were fewer gastrointestinal tumors of all histologic types combined at all organ sites in treated rats. This difference was statistically significant for the duodenum, colon, rectum, and total number of gastrointestinal tumors at 5 months (Klimisch 4, not assignable, due to limited information available on materials and methods).

Mutagenicity/Genotoxicity (M) Score (H, M, or L): L
Docusate sodium was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* and *in vivo* mutagenicity and clastogenicity assays. 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 experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023, CIR 1998
  - *In vitro:* Docusate sodium was negative in a GLP-compliant Ames bacterial reverse mutation assay according to OECD Guideline 471 in *Salmonella typhimurium* test strains TA98, TA100, TA102, TA1535, and TA1537. Two experiments were performed. In

experiment 1, cells were exposed to the test substance (>97% purity; acetone vehicle) at concentrations of 1.6, 8, 40, 200, and 1,000 µg/plate without metabolic activation, and concentrations of 4, 20, 100, 500, 2,500 µg/plate with metabolic activation (Aroclor 1254 induced male Sprague-Dawley rat liver S9 fraction). In experiment 2, cells were exposed to the test substance at concentrations of 62.5, 125, 250, 500, and 1,000 µg/plate without metabolic activation, and concentrations of 156.25, 312.5, 625, 1,250, and 2,500 µg/plate with metabolic activation. The positive controls were 2-nitrofluorene, sodium azide, 9-aminoacridine, glutaraldehyde, and 2-aminoanthracene. Positive, negative, and vehicle controls were reported as valid. There were no increases in the frequency of revertants observed in any strain at any concentration with or without metabolic activation (Klimisch 1, reliable without restrictions).

- *In vitro:* Docusate sodium produced ambiguous results in a GLP-compliant chromosomal aberration assay according to OECD Guideline 473 in Chinese hamster ovary (CHO) cells. Two experiments were performed. In experiment 1, cells were exposed to the test substance (>97% purity; acetone vehicle) at concentrations of 27.09, 38.71, and 55.29 µg/mL (20 hr + 0 hr recovery) without metabolic activation, and 100, 110, and 120 µg/mL (2hr + 18hr recovery) with metabolic activation (Aroclor 1254 induced male Sprague-Dawley rat liver S9 fraction). In experiment 2, cells were exposed to concentrations of 60, 70, and 80 µg/mL (20 hr + 0 hr recovery) or 60 µg/mL (44hr + 0hr recovery) without metabolic activation and 110, 120, and 130 µg/mL (2 hr + 18 hr recovery) or 120, 125, and 130 µg/mL (2 hr + 18 hr recovery) with metabolic activation. Cytotoxicity was observed at 55.29 and 120 µg/mL (experiment 1; without and with metabolic activation, respectively) and 80 µg/mL (experiment 2; without metabolic activation). There were no significant increases in the frequency of cells with aberrations at any concentration in the absence of metabolic activation. A significant increase in the frequency of cells with aberrations was observed at the cytotoxic concentration of 120 µg/mL with metabolic activation in experiment 1; however, a significant increase was not seen at this concentration in experiment 2. Yet, a small but statistically significant increase in cells with aberrations were seen at both 125 and 130 µg/mL. The authors considered this to be of marginal biological significance as the number of aberrant cells fell outside the normal range in only a single replicate. Therefore, as the observed effect was only seen following treatment in the presence of S9 and only at concentrations very close to the threshold of toxicity, the authors concluded it is likely that aberration induction involved an indirect mechanism (Klimisch 1, reliable without restrictions).
- *In vivo:* Docusate sodium was negative in a GLP-compliant micronucleus assay according to OECD Guideline 474. Male and female Crl: CD(SD) rats (5/sex/dose) were administered docusate sodium (purity not reported, tap water vehicle) at 500, 1,000, and 2,000 mg/kg/day via gavage twice. A positive control of cyclophosphamide was used. There were no increases in the incidence of micronucleated polychromatic erythrocytes at any dose level. Positive, negative, and vehicle controls were valid (Klimisch 1, reliable without restrictions).

- U.S. EPA 2009
  - *In vitro:* Docusate sodium was negative in an Ames reverse mutation assay in *S. typhimurium* test strains TA98, TA100, TA102, TA1535, and TA1537 in the presence and absence of metabolic activation at concentrations up to 2,500 µg/plate. Cytotoxicity was reported at 500, 1,000, and 2,500 µg/plate. Positive and negative controls were valid. There were no increases in the frequency of revertants observed in any strain at any dose level with or without metabolic activation.
    - *ToxServices notes that this may be the same as the first study described under ECHA*

2023.

- *In vitro:* Docusate sodium was negative in a chromosome aberration assay in CHO cells with and without metabolic activation at concentrations up to 470 µg/mL. Positive and negative controls were valid. The authors noted that chromosomal aberrations were noted only at cytotoxic concentrations.

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

Docusate sodium was assigned a score of Low for reproductive toxicity based on a lack of effects to reproductive parameters in two three-generation studies in rats and a two-generation reproduction and developmental toxicity study in rats. 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 reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS Japan: H361 – Suspected of damaging fertility or the unborn child (Toxic to reproduction – Category 2)
- CIR 1998, U.S. EPA 2009, ECHA 2023
  - *Oral:* In a GLP-compliant three-generation reproductive toxicity study similar to OECD Guideline 416, male and female Crl:DC(SD)BR rats (30/sex/group) received 0, 0.1, 0.5, or 1% docusate sodium (reported as equivalent to 0, 100, 500, and 1,000 mg/kg/day) in their diet during premating, mating (males and females), and during gestation for three generations (F0, F1, F2) until weaning of the third generation (F3). Treatment with 1.0% caused decreased body weights in F1 males and females and decreased final weights of F1 and F2 males and females. Treatment with 0.5% caused decreased body weights of F2 males. Treatment with 1.0% caused decreased mean birth weights of male and female pups. Treatment with 0.5% and 1.0% caused decreased body weights on day 21 in males and females of all three generations. However, the reduced body weights did not interfere with growth and development or reproductive performance, and the test substance had no adverse effects on reproductive function (mating, fertility, or gestation indices) of either sex in any generation up to 1% in the diet. The authors reported a dose-dependent increase in the absence of milk in the abdomen on lactation day 4 of F2 and F3 pups. Treatment had no effect on the total number of pups or litters, litter size, or sex ratio. Treatment did not affect pup survival. No treatment-related mortality or microscopic observations were reported. A reproductive NOAEL of 100 mg/kg/day and LOAEL of 500 mg/kg/day was identified by the U.S. EPA based on decreased fetal body weight and effects on lactation. ECHA dossier authors identified a reproductive NOAEL of 1% based on the lack of effects (Klimisch 2, reliable with restrictions).
- CIR 2016, ECHA 2023
  - *Oral:* In a two- to three-generation reproductive toxicity study similar to OECD Guideline 416 (pre-dates GLP), male and female albino rats (16/sex/dose) received 0.5 or 1.0% of a test substance containing 50% docusate sodium in the diet. Dosing began at weaning of F0 rats; F0 rats were mated twice to produce F1a and F1b and the F1b were mated to produce the F2 generation; the F2 generation was mated twice to produce F3a and F3b. F1a and F3b pups were weaned directly to the test diets. F1b, F2, and F3a pups received the test material after weaning. Necropsy of pups was performed on the F3a pups that died or were killed at weaning only. Parental males of the F0 had slightly decreased body weights until the F2 generation. There were no effects on fertility, gestation and viability, of the first and second matings of the F0 generation, however, the lactation index was down. There was a reduced

number of offspring surviving from day 5 until weaning in the first mating. The lactation index was also decreased in the F3b generation. The number of pups weaned and average body weight of those pups was decreased in the F1a generation. F3a pups receiving the test substance had reduced viability index. There were no abnormalities or variations observed in pups of any generation. It was concluded that diets containing 1% docusate sodium had no adverse effect on the reproduction and lactation performance of rats, and the lowered survival rate and mean body weights of the F1a and F3b pups is attributed to an impairment of nutrition as a result of the taste which is believed to have been secreted into the milk of the dams (Klimisch 2, reliable with restrictions).

- CIR 2016
  - *Oral:* In a reproduction and developmental toxicity study, female rats (30/dose, strain not specified) were administered 0, 16, 80, or 400 mg/kg/day of a test substance containing 0.4% docusate sodium via gavage starting at 14 days prior to mating with untreated males. Half the animals from each group were dosed until gestation day (GD) 13 and sacrificed, the remaining animals were dosed until parturition and were not sacrificed. No effects on reproductive parameters, fertility, or pup weight and condition were reported. The NOAEL for both maternal toxicity, reproductive, and developmental toxicity was 400 mg/kg/day (1.6 mg/kg/day active substance).
- Based on the weight of evidence, a score of Low was assigned. In the three-generation reproductive study, the authors reported a dose-dependent decrease in milk transfer to F2 and F3 pups. The second two- to three-generation study also reported a reduced survival rate and body weights attributable to impairment of nutrition from the test articles presence in the milk. GreenScreen® guidance (CPA 2018b) reports effects via lactation under the developmental toxicity endpoint; therefore, these effects are evaluated in the developmental toxicity endpoint below. As there were no effects on reproductive parameters (e.g., mating, fertility, gestation) in the three studies described above, ToxServices assigned a score of Low for this endpoint.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): M
Docusate sodium was assigned a score of Moderate for developmental toxicity based on effects via lactation in two three-generation reproductive toxicity studies in rats and an increase in fetal resorptions, malformations, and skeletal anomalies observed in developmental toxicity studies with rats at high doses that are also maternally toxic. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when there is limited or marginal evidence of developmental toxicity (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS Japan: H362 – May cause harm to breast-fed children
- CIR 1998, U.S. EPA 2009, ECHA 2023
  - *Oral:* In a GLP-compliant three-generation reproductive toxicity study similar to OECD Guideline 416, male and female Crl:DC(SD)BR rats (30/sex/group) received 0, 0.1, 0.5, or 1% docusate sodium (equivalent to 0, 100, 500, and 1,000 mg/kg/day) in their diet during premating, mating (males and females), and during gestation for three generations (F0, F1, F2) until weaning of the third generation (F3). Treatment with 1.0% caused decreased body weights in F1 males and females and decreased final weights of F1 and F2 males and females. Treatment with 0.5% caused decreased body weights of F2 males. Treatment with 1.0% caused decreased mean birth weights of male and female pups. Treatment with 0.5% and 1.0% caused decreased body weights on day 21 in males and females of all three generations. However, the reduced body weights did not interfere with growth and

development or reproductive performance, and the test substance had no adverse effects on reproductive function (mating, fertility, or gestation indices) of either sex in any generation up to 1% in the diet. The authors reported a dose-dependent increase in the absence of milk in the abdomen on lactation day 4 of F2 and F3 pups. Treatment had no effect on the total number of pups or litters, litter size, or sex ratio. Treatment did not affect pup survival. No treatment-related mortality or microscopic observations were reported. A reproductive NOAEL of 100 mg/kg/day and LOAEL of 500 mg/kg/day was identified by the U.S. EPA based on decreased fetal body weight and effects on lactation (Klimisch 2, reliable with restrictions).

- *Oral:* In a non-GLP prenatal developmental toxicity study similar to OECD Guideline 414, female Sprague-Dawley rats (treated = 20-22/dose; control = 43) received 0, 1, or 2% docusate sodium (reported in REACH dossier as equivalent to 1,074 and 1,988 mg/kg/day, respectively) in their diet on GD 6 through 15. Animals were sacrificed on GD 21. Treatment with 2% caused significantly reduced weight gain in dams, a significant increase in fetal resorptions, and a significant increase in externally malformed fetuses. The malformation was primarily exencephaly. Treatment also caused incomplete ossification of various cranial bones and curved or open vertebral columns. The authors identified a maternal toxicity and developmental NOAEL of 1% (1,074 mg/kg/day) and a LOAEL of 2% (1,988 mg/kg/day) based on reduced weight gain in dams, a significant increase in fetal resorptions, and a significant percentage of externally malformed fetuses. Authors concluded the developmental effects to be secondary to maternal toxicity (Klimisch 2, reliable with restrictions).

- CIR 2016, ECHA 2023
  - *Oral:* In a two- to three-generation reproductive toxicity study similar to OECD Guideline 416 (pre-dates GLP), male and female albino rats (16/sex/dose) received 0.5 or 1.0% of a test substance containing 50% docusate sodium in the diet. Dosing began at weaning of F0 rats; F0 rats were mated twice to produce F1a and F1b and the F1b were mated to produce the F2 generation; the F2 generation was mated twice to produce F3a and F3b. F1a and F3b pups were weaned directly to the test diets. F1b, F2, and F3a pups received the test material after weaning. Necropsy of pups was performed on the F3a pups that died or were killed at weaning only. Parental males of the F0 had slightly decreased body weights until the F2 generation. There were no effects on fertility, gestation and viability, of the first and second matings of the F0 generation, however, the lactation index was down. There was a reduced number of offspring surviving from day 5 until weaning in the first mating. Lactation index was also decreased in the F3b generation. The number of pups weaned and average body weight of those pups was decreased in the F1a generation. F3a pups receiving the test substance had reduced viability index. There were no abnormalities or variations observed in pups of any generation. It was concluded that diets containing 1% docusate sodium had no adverse effect on the reproduction and lactation performance of rats, and the lowered survival rate and mean body weights of the F1a and F3b pups is attributed to an impairment of nutrition as a result of the taste which is believed to have been secreted into the milk of the dams (Klimisch 2, reliable with restrictions).
- U.S. EPA 2009
  - *Oral:* Female Sprague-Dawley rats received 0 or 2% docusate sodium (equivalent to 0 or 1,000 mg/kg/day) in their diet on GD 6-16. Treatment with 1,000 mg/kg/day caused a significant decrease in maternal body weight, food consumption, and weight gain. Treatment caused decreased fetal weight, decreased crown-rump length, and increased skeletal anomalies (unossified sternebra). The authors identified a maternal toxicity and

developmental LOAEL of 1,000 mg/kg/day (only dose tested) based on decreased fetal body weight, decreased crown-rump length, and increased skeletal anomalies.

- CIR 2016
    - *Oral:* In developmental toxicity studies in rats (20/dose) and mice (20/dose), animals were administered 0, 16, 80, or 400 mg/kg/day of a test substance containing 0.4% docusate sodium. Mice were dosed on GD 6-15 and rats were dosed on GD 5 to 19. The NOAEL for both maternal toxicity and developmental toxicity was 400 mg/kg/day (1.6 mg/kg/day active substance) for both species.
    - *Oral:* In a reproduction and developmental toxicity study, female rats (30.dose, strain not specified) were administered 0, 16, 80, or 400 mg/kg/day of a test substance containing 0.4% docusate sodium via gavage starting at 14 days prior to mating with untreated males. Half the animals from each group were dosed until GD 13 and sacrificed, the remaining animals were dosed until parturition and were not sacrificed. No effects on reproductive parameters, fertility, or pup weight and condition were reported. The NOAEL for both maternal toxicity, reproductive, and developmental toxicity was 400 mg/kg/day (1.6 mg/kg/day active substance).
- Based on the weight of evidence, a score of Moderate was assigned. In the three-generation reproductive study, the authors reported a dose-dependent decrease in milk transfer to F2 and F3 pups. A second two- to three-generation study also reported a reduced survival rate and body weights attributable to impairment of nutrition from the test articles present in the milk. However, study authors attributed the effects to the aversion of taste due to the test substance appearing in the milk. Therefore, although effects on or via lactation warrants a High score for developmental toxicity under GreenScreen® criteria, the effect observed with docusate sodium is secondary rather than primary. Therefore, ToxServices reduced the level of concern to Moderate. Additionally, treatment with docusate sodium on GD 6-15 or 16 caused a significant increase in fetal resorptions, malformations, and skeletal anomalies in prenatal developmental toxicity studies in rats. These occurred at high maternal doses and ECHA dossier authors attributed them to maternal toxicity. However, authoritative bodies such as U.S. EPA and CIR did not provide such determination. Therefore, ToxServices considers it to be limited evidence of developmental toxicity that warrant a Moderate score.

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

Docusate sodium was assigned a score of Data Gap for endocrine activity based on insufficient data identified for this endpoint. Docusate sodium demonstrated activity in high throughput screening assays for estrogen, androgen, and thyroid receptor binding, but no effects were observed in previously described 3-generation or 2-generation reproductive or developmental toxicity studies. Therefore, the relevance of the positive *in vitro* tests is uncertain.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2023b
    - Docusate sodium was active in 4/21 estrogen receptor (ER) assays, 6/16 androgen receptor (AR) assays, 2/2 steroidogenesis assays, and 12/21 thyroid receptor assays performed as part of the of the Tox 21 high throughput *in vitro* assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program in the 21st Century (EDSP21) (Appendix D).

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.4 Benchmark system (the asterisk indicates repeated exposure). For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints. See GreenScreen® Guidance v1.4, Annex 2 for more details.

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): M

Docusate sodium was assigned a score of Moderate for acute toxicity based on the lowest identified oral LD_{50} of 650 mg/kg in guinea pigs. GreenScreen® criteria classify chemicals as a Moderate hazard for acute toxicity when oral LD_{50} values are >300 to 2,000 mg/kg (CPA 2018b). The confidence in the score is high based on reliable experimental data for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2009, CIR 2016
  - *Oral:* LD_{50} = 2,643 mg/kg in male albino ARS/ICR mice
- CIR 1998
  - *Oral:* LD_{50} = 1,900 mg/kg in female albino rats
- ECHA 2023
  - *Oral:* LD_{50} > 2,100 mg/kg in male and female WISW (SPF TNO) rats (non-GLP, OECD Guideline 401) (Klimisch 1, reliable without restrictions)
  - *Oral:* LD_{50} > 1,320 mg/kg in male and female Sprague-Dawley rats (GLP, OECD Guideline 401) (Klimisch 2, reliable with restrictions)
  - *Oral:* LD_{50} > 1,400 mg/kg in male and female TNO Wistar rats (non-GLP, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2009, ECHA 2023
  - *Oral:* LD_{50} = 4,200 mg/kg in male Sprague-Dawley rats (non-GLP, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions)
  - *Oral:* LD_{50} = 3,080 mg/kg in male CF Nelson rats (non-GLP, similar to OECD Guideline 401) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2009, CIR 2016, ECHA 2023
  - *Dermal:* LD_{50} > 10,000 mg/kg in male New Zealand White rabbits (non-GLP, similar to OECD Guideline 402) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2009
  - *Oral:* LD_{50} = ~2,000 mg/kg in female Wistar rats
- CIR 1998
  - *Oral:* LD_{50} = 3,690 mg/kg in rats (sex and strain not reported) for a product containing 84% docusate sodium
  - *Oral:* LD_{50} = 4,800 mg/kg in male and female Harlan albino mice for a product containing unspecified amount of docusate sodium
- CIR 2016
  - *Oral:* LD_{50} = 650 mg/kg in guinea pigs (sex and strain not reported)

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

Docusate sodium was assigned a score of Low for systemic toxicity (single dose) based on a lack of systemic toxicity below the guidance value of 2,000 mg/kg in oral studies with rats and mice and a dermal study with rabbits. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when there are not adverse systemic effects at oral and dermal values below 2,000

mg/kg/day (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral:* In a non-GLP acute toxicity study according to OECD Guideline 401, male and female WISW (SPF TNO) rats (5/sex) received 3,000 mg/kg docusate sodium as a 70% solution (2,100 mg/kg active ingredient) via gavage, and were observed for 14 days. There were no mortalities. Twenty to thirty minutes after treatment all animals had red/brown lips. One animal had diarrhea three to seven hours after treatment. Twenty-four hours after treatment, the skin was harsh, four animals had diarrhea, and 3 animals had dirty brown skin. Forty-eight hours later, the skin was still harsh and after 72 hours, animals had no symptoms. Dissection after the study found one animal with a partial bulge of the stomach mucosa (Klimisch 1, reliable without restrictions).
  - *Oral:* In a GLP-compliant acute oral toxicity study according to OECD Guideline 401, male and female Sprague-Dawley rats (5/sex) received 2,000 mg/kg docusate sodium as a 66% solution (1,320 mg/kg active ingredient) via gavage and were observed for 14 days. There were no deaths and no treatment-related clinical signs. Treatment did not alter body weight or cause macroscopic changes (Klimisch 2, reliable with restrictions).
  - *Oral:* In a non-GLP acute oral toxicity study similar to OECD Guideline 401, male and female TNO Wistar rats (2/sex) orally received 2,000 mg/kg docusate sodium as a 70% solution (1,400 mg/kg active ingredient), and were observed for 14 days. There were no mortalities. Treatment caused reversible harsh skin and diarrhea (Klimisch 2, reliable with restrictions).
- U.S. EPA 2009, ECHA 2022
  - *Oral:* In a non-GLP oral acute toxicity study similar to OECD Guideline 401, six male Sprague-Dawley rats orally received approximately 2,820, 3,560, 4,480, or 5,040 mg/kg docusate sodium (>97% purity). Animals were prostrate and lethargic. Necropsy found yellow fluid in the gastrointestinal tract of dead animals. No further details were reported.
  - *Oral:* In a non-GLP acute oral toxicity study similar to OECD Guideline 401, five male CF Nelson albino rats received 625, 1,250, 2,500, or 5,000 mg/kg docusate sodium (>97% purity) via gavage, and were observed for 14 days. Treatment caused clinical signs of depression and diarrhea at all doses, with recovery after 4 days. There were no adverse changes to body weights and no abnormalities at necropsy (Klimisch 2, reliable with restrictions).
  - *Dermal:* In a non-GLP acute dermal toxicity study similar to OECD Guideline 402, a dose of 10,000 mg/kg docusate sodium (>97% purity) was applied to clipped unabraded skin of five male New Zealand White rabbits for 24 hours under occlusive conditions. Treatment caused skin irritation but no signs of systemic toxicity (Klimisch 2, reliable with restrictions).
- U.S. EPA 2009
  - *Oral:* In an acute oral toxicity study, male ARS/ICR mice (10/sex) received 2,340, 2,520, 2,690, 2,880, 3,090, 3,310, 3,550, or 3,825 mg/kg docusate sodium via gavage and were observed for 14 days. There were no treatment-related clinical signs reported and no toxicity at necropsy described. An LD_{50} > 2,643 mg/kg was identified.
- Based on the weight of evidence, a score of Low was assigned. Docusate sodium is considered to have low oral and dermal toxicity (U.S. EPA 2009). Single-dose exposure to docusate sodium does

not cause significant toxic effects, and none were observed below the oral and dermal guidance value of 2,000 mg/kg; therefore, a GHS classification is not warranted and a score of Low was assigned.

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

Docusate sodium was assigned a score of Low for systemic toxicity (repeated dose) based on the lowest identified oral LOAEL of 500 mg/kg/day in a 26-week study in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when the oral LOAEL value is greater than 100 mg/kg/day in a 90-day study (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2009
  - *Oral:* Male Osborne-Mendel rats (5/dose) received 0, 2, 4, or 8% (equivalent to approximately 2,000, 4,000, and 8,000 mg/kg/day) docusate sodium in their diet for 16 weeks. All animals exposed to 8,000 mg/kg/day died within one week of treatment. One animal exposed to 4,000 mg/kg/day survived the duration of the study. Treatment with 2,000 mg/kg/day caused gastrointestinal irritation and animals gained less weight than controls. The authors identified a LOAEL of 2,000 mg/kg/day based on decreased body weight and gastrointestinal irritation.
- U.S. EPA 2009, CIR 2016
  - *Oral:* Rats (strain not specified) (12/sex/dose) received 0, 0.5, 1, and 1.5% (equivalent to approximately 250, 500, and 750 mg/kg/day) docusate sodium in their diet for 26 weeks. Four animals (sex not specified) treated with 750 mg/kg/day and two controls died prior to the end of the study. Two of the four dead animals treated with 750 mg/kg/day had hemorrhagic gastroenteritis. No other treatment related effects were reported. However, the authors identified a LOAEL of 500 mg/kg/day based on low weight gain and hemorrhagic gastroenteritis and a NOAEL of 250 mg/kg/day.
  - *Oral:* Beagle dogs (4/sex/dose) received 0 or 30 mg/kg/day docusate sodium via oral tablet 7 days per week for one year. Treatment did not produce gastric irritation. No adverse-treatment related effects were reported. The authors identified a NOAEL of 30 mg/kg/day (only dose tested) based on the absence of adverse effects.
- ECHA 2023
  - *Oral:* In a GLP-compliant 90-day oral toxicity study according to OECD Guideline 408, male and female Crl:CD(SD) rats (10/sex/dose) were administered docusate sodium (purity not reported) in the feed at 0, 100, 300, and 1,000 mg/kg/day. Recovery groups of 5/animals/sex were included for the control, mid and high dose groups for a 28-day treatment free period. There were no mortalities and no adverse clinical signs reported. High dose males had slightly decreased body weight and an increase in liver weight was reported in high dose animals of both sex however, these effects were reversed in the recovery period. There were no adverse treatment related effects on hematology, clinical chemistry, urinalysis, or ophthalmologic examination. There were no adverse effects reported upon gross pathological or histopathological examination. The authors identified a NOAEL of 1,000 mg/kg/day, the highest dose tested, for this study due to the lack of significant adverse treatment related effects (Klimisch 1, reliable without restrictions).
- CIR 1998, ECHA 2023

  - *Oral:* Male and female Wistar rats (5/sex/dose) received 0, 250, 500, 750, 1,000 and 1,250 mg/kg/day docusate sodium (actual doses based on consumption of 190, 370, 550, 750, and 870 mg/kg/day) in their diet for 24 weeks. The only clinical effect was diarrhea. There were no mortalities, no adverse effects to body weights, no effects to erythrocytes and leukocyte counts, and no lesions at necropsy. Neutrophils were increased and lymphocytes were decreased (doses not specified). ECHA dossier authors identified a NOAEL of 750 mg/kg/day for this study (Klimisch 4, not assignable, due to the limited materials and methods available).
  - *Oral:* Dogs (3/dose) received 100 or 250 mg/kg/day docusate sodium in their diet for 24 weeks. There were no mortalities and no lesions at necropsy. Body weight decreases were not considered to be toxicologically significant. ECHA dossier authors identified a NOAEL of 250 mg/kg/day for this study (Klimisch 4, not assignable, due to the limited materials and methods available).
  - *Oral:* Monkeys (3/dose) received 125 mg/kg/day docusate sodium in their diet for 24 weeks. There were no mortalities and no lesions at necropsy. ECHA dossier authors identified a NOAEL of 125 mg/kg/day for this study (Klimisch 4, not assignable, due to the limited materials and methods available).
  - *Dermal:* Female Sprague-Dawley rats (8/dose) were exposed to 0.00126% docusate sodium applied at a dose of 4 mL/kg 5 days/week for 67 days. There were no significant adverse effects on body weight, survival, urinalysis, hematological and clinical chemistry parameters, or organ weights. One animal had fluid filled kidneys (Klimisch 4, not assignable, due to being from a secondary source).
  - *Inhalation:* Male and female Sprague-Dawley rats (12/sex/dose) were exposed to docusate sodium aerosol at a concentration of 4.2 mg/m^3 4 hours/day, 5 days/week for 13 weeks. At 7 weeks, two rats were sacrificed and necropsied. There were no adverse effects on body weights, survival, clinical signs, or urinalysis and there were no lesions at necropsy. Some changes to hematological and clinical chemistry parameters were reported. Male rats had changes to relative brain, liver, and testes weights; females had changes to absolute heart weight. One male rat had scattered foci of neutrophils and an increase in free alveolar macrophages in the lungs (Klimisch 4, not assignable, due to insufficient documentation).
- CIR 2016, ECHA 2023
  - *Oral:* Male and female Charles river albino rats (20/sex/dose) received 0 or 1% docusate sodium (100% purity, reported to be an actual ingested dose of 750 mg/kg/day) in their diet for 90 days. There were no mortalities, no adverse effects to body weights or organ weights, no changes to hematological, clinical chemistry, or urinalysis parameters, and no lesions at necropsy. ECHA dossier authors identified a NOAEL of 750 mg/kg/day for this study (Klimisch 2, reliable with restrictions).

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Docusate sodium was assigned a score of Low for neurotoxicity (single dose) based on no clinical signs or gross necropsy findings indicative of neurotoxicity in standard acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and negative (CPA 2018b). The confidence in the score is low as there were no comprehensive neurobehavioral examinations conducted.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023

  - *Oral:* In a non-GLP acute toxicity study according to OECD Guideline 401, male and female WISW (SPF TNO) rats (5/sex) received 3,000 mg/kg docusate sodium as a 70% solution (2,100 mg/kg active ingredient) via gavage, and were observed for 14 days. There were no mortalities. Twenty to thirty minutes after treatment all animals had red/brown lips. One animal had diarrhea three to seven hours after treatment. Twenty-four hours after treatment, the skin was harsh, four animals had diarrhea, and 3 animals had dirty brown skin. Forty-eight hours later, the skin was still harsh and after 72 hours, animals had no poisoning symptoms. Dissection after the study found one animal with a partial bulge of the stomach mucosa (Klimisch 1, reliable without restrictions).
  - *Oral:* In a GLP-compliant acute oral toxicity study according to OECD Guideline 401, male and female Sprague-Dawley rats (5/sex) received 2,000 mg/kg docusate sodium as a 66% solution (1,320 mg/kg active ingredient) via gavage and were observed for 14 days. There were no deaths and no treatment-related clinical signs were reported. Treatment did not alter body weight or cause macroscopic changes (Klimisch 2, reliable with restrictions).
  - *Oral:* In a non-GLP acute oral toxicity study similar to OECD Guideline 401, male and female TNO Wistar rats (2/sex) orally received 2,000 mg/kg docusate sodium as a 70% solution (1,400 mg/kg active ingredient), and were observed for 14 days. There were no mortalities reported. Treatment caused reversible harsh skin and diarrhea (Klimisch 2, reliable with restrictions).
- U.S. EPA 2009, ECHA 2023
  - *Oral:* In a non-GLP oral acute toxicity study similar to OECD Guideline 401, six male Sprague-Dawley rats orally received approximately 2,820, 3,560, 4,480, or 5,040 mg/kg docusate sodium (>97% purity). Animals were prostrate and lethargic. Necropsy found yellow fluid in the gastrointestinal tract of dead animals. No further details were reported (Klimisch 2, reliable with restrictions).
  - *Oral:* In a non-GLP acute oral toxicity study similar to OECD Guideline 401, five male CF Nelson albino rats received 625, 1,250, 2,500, or 5,000 mg/kg docusate sodium (>97% purity) via gavage, and were observed for 14 days. Treatment caused clinical signs of depression and diarrhea at all doses, with recovery after 4 days. There were no adverse changes to body weights and no abnormalities at necropsy (Klimisch 2, reliable with restrictions).
  - *Dermal:* In a non-GLP acute dermal toxicity study similar to OECD Guideline 402, a dose of 10,000 mg/kg docusate sodium (>97% purity) was applied to clipped unabraded skin of five male New Zealand White rabbits for 24 hours under occlusive conditions. Treatment caused skin irritation but no signs of systemic toxicity (Klimisch 2, reliable with restrictions).
- U.S. EPA 2009
  - *Oral:* In an acute oral toxicity study, male ARS/ICR mice (10/sex) received 2,340, 2,520, 2,690, 2,880, 3,090, 3,310, 3,550, or 3,825 mg/kg docusate sodium via gavage and were observed for 14 days. There were no treatment-related clinical signs reported and no toxicity at necropsy described. An LD_{50} > 2,643 mg/kg was identified.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Docusate sodium was assigned a score of Low for neurotoxicity (repeated dose) based on a lack of neurotoxic effects in a neurobehavioral examination conducted as part of a 90-day study in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when the NOAEL is greater than 100 mg/kg/day in 90-day oral studies (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists

  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - *Oral:* In a GLP-complaint 90-day oral toxicity study according to OECD Guideline 408, male and female Crl:CD(SD) rats (10/sex/dose) were administered docusate sodium (purity not reported) in the feed at 0, 100, 300, and 1,000 mg/kg/day. Recovery groups of 5/animals/sex were included for the control, mid and high dose groups for a 28-day treatment free period. A neurobehavioral examination was conducted at the end of exposure and at the end of the recovery period. Authors conducted a screening of sensory reactivity to stimuli (e.g., auditory, visual, and proprioceptive stimuli), an assessment of grip strength, and a motor activity assessment. Observational screening included righting reflex, body temperature, salivation, startle response, respiration, mouth breathing, urination, convulsions, pilo-erection, diarrhea, pupil size, pupil response, lacrimation, stereotypy, toe pinch, tail pinch, wire maneuver, hind leg splay, positional passivity, tremors, positive geotropism, limb rotation, and auditory functions. There were no toxicological relevant adverse effects on any of the parameters tested. A neurotoxicity NOAEL of 1,000 mg/kg/day, the highest dose tested, can be established for this study (Klimisch 1, reliable without restrictions).

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

Docusate sodium was assigned a score of Low for skin sensitization based on negative results in a repeated insult patch tests in human volunteers. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as the highest tested concentration was only 2.5%.

- 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 2016, ECHA 2023
  - Docusate sodium was negative in a non-GLP Modified Draize-Shelanski Repeat Insult Patch Test in male and female humans (n=100). An induction dose of 300 mg of 2.5% docusate sodium (100% purity) in petrolatum was applied under occlusion to 15 mm patch sites on the back or volar forearms for 10 alternate-day 24 hour long periods. Following a seven-day rest period, challenge patches containing 300 mg of 1% docusate sodium in petrolatum were applied in the same manner for 24 hours. Challenge patches were read after 24 hours. Treatment caused mild skin irritation in 19 subjects but there was no evidence of sensitization (Klimisch 2, reliable with restrictions).
- CIR 1998
  - In a repeated insult patch test (RIPT) in 100 human volunteers, 0.42% docusate sodium was applied as nine induction patches over three weeks. After a 2-week rest period, the challenge patch was applied. There were no sensitization reactions to the challenge patch.
  - An additional five RIPTs tested 0.21% docusate sodium in 119 volunteers, 0.21% in 117 volunteers, 0.21% in 97 volunteers, 0.1% docusate sodium (84% pure) in 99 volunteers, and 0.1% docusate sodium (84% pure) in 94 volunteers. After challenge, 2, 3, 5, 1, and 0 subjects, respectively, had no more than mild reactions to the challenge patches. The test articles were not considered to be sensitizers (Klimisch scores not reported).

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Docusate sodium was assigned a score of Low for respiratory sensitization based on lack of dermal sensitization potential according to ECHA's guidelines. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative and 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
  - Docusate sodium does not contain any structural alerts for respiratory sensitization (Appendix E)
- 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 docusate sodium 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 docusate sodium, and as docusate sodium does not contain any structural alerts for respiratory sensitization (OECD 2023), docusate sodium is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): H
Docusate sodium was assigned a score of High for skin irritation/corrosivity based on results from a skin irritation study in rabbits classifying it as GHS Category 2. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when a chemical is classified as GHS Category 2 (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data, supported by screening lists.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS – Japan – H315 – Causes skin irritation [Skin corrosion/irritation – Category 2].
  - *Screening:* GHS – Australia – H315 – Causes skin irritation [Skin corrosion/irritation – Category 2].
  - *Screening:* GHS – New Zealand – Skin irritation Category 2.
- U.S. EPA 2009
  - 10 mg of test substance was applied to rabbit skin (not specified if under occlusion) for 24 hours. Treatment caused moderate irritation. No further details were provided.
- ECHA 2023
  - Docusate sodium caused skin irritation in a non-GLP acute dermal irritation study performed according to OECD Guideline 404. Docusate sodium as a 70% solution (15% water and 15% ethanol) was applied to shaved skin of 3 male White Russian rabbits under occlusion for 4 hours. The mean overall irritation score for 1, 24, 48 and 72 hours was 7.8 (max 8). The mean (24, 48, and 72 hour) erythema and edema scores were both 4 in all three tested

animals. Effects were not fully reversible in 14 days. The authors classified docusate sodium as a Category 2 irritant (Klimisch 2, reliable with restrictions).
    - *GHS Guidance classifies chemicals as Category 2 when mean erythema scores are ≥ 2.3 and ≤ 4.0 in at least 2 of 3 treated animals at 24, 48, and 72 hours after treatment (UN 2021).*
- CIR 2016, ECHA 2023
    - In a non-GLP acute dermal irritation study performed according to FHSA procedure 16 CFR 1500.41, docusate sodium (>97% purity) was applied to intact and abraded skin of New Zealand White rabbits (6 animals, sex not specified) under occlusive conditions for 24 hours. The mean erythema scores were 2.33 and 1.66 at 24 and 72 hours, respectively, for intact skin, and 2.5 and 1.66 at 24 and 72 hours, respectively, for abraded skin. The mean edema scores were 2.5 and 1.0 at 24 and 72 hours, respectively, for intact skin and 2.5 and 1.16 at 24 and 72 hours, respectively for abraded skin. The primary dermal irritation score was 3.83 (max 4) after 72 hours (Klimisch 2, reliable with restrictions).
- CIR 1998
    - In a dermal irritation study, rabbits (number not reported) were exposed to 0.5 mL of a 2% docusate sodium solution on intact and abraded skin. The average (24 and 72 hours) irritation scores were 3.7/8 and 1.7/8 for intact and abraded skin, respectively.
    - In a single insult occlusive patch test in rabbits (number not reported), a 10% solution of a product containing 84% docusate sodium in propylene glycol produced minimal irritation.
    - In four 4-day mini-cumulative irritation clinical tests, primary irritation indices (PIIs) of 0.25, 0.3, 0.8, and 0.38 were reported for a product containing 2.94% docusate sodium; PIIs of 1.78 and 1.85 were reported for a product containing 0.25% of 84% docusate sodium; and a PII of 0.04 for a product containing 0.1% of 84% docusate sodium.
    - A 21-day cumulative irritation test in human volunteers (n=7) applied 1.13% solution containing 84% docusate sodium under occlusion. The total irritation score was 324/578 with an average score per panelist of 46.3/84.

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

Docusate sodium was assigned a score of Very High for eye irritation/corrosivity based on irreversible cornea turbidity in rabbits. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when a GHS Category 1 classification is warranted (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data supported by screening lists.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* GHS – Australia – H318 – Causes serious eye damage [Serious eye damage/eye irritation – Category 1].
    - *Screening:* GHS – New Zealand – Serious eye damage Category 1.
    - *Screening:* GHS – Japan – H319 – Causes serious eye irritation [Serious eye damage/eye irritation – Category 2].
- U.S. EPA 2009
    - Instillation of 250 µg of docusate sodium into rabbit eyes (strain not specified) caused mild irritation. No further details were provided.
    - Instillation of 1% docusate sodium into rabbit eyes (strain not specified) caused severe irritation. No further details were provided.
- ECHA 2023
    - Docusate sodium caused irreversible damage to the eye in a non-GLP acute eye irritation study performed according to OECD Guideline 405. Docusate sodium as a 70% solution

(15% water and 15% ethanol) was instilled into the right eye of three male White Russian rabbits for 72 hours. Treatment caused cornea turbidity, iritis, and conjunctival redness in all animals; turbidity of the cornea was irreversible. The mean overall irritation score for 1-72 hours was 46.67 (max 110). The mean (24, 48, and 72 hour) cornea opacity scores were 1.67, 1.67, and 1.66, the mean iris scores were 1, 1, and 1, the mean conjunctiva scores were 3, 3, and 3, and the mean chemosis scores were 1, 1, and 1. The authors classified docusate sodium as a Category 1 irritant (Klimisch 2, reliable with restrictions).

- CIR 2016, ECHA 2023
    - In a non-GLP acute eye irritation study performed according to FHSA procedure 16 CFR 1500.42, instillation of docusate sodium (>97% purity) into the eye of New Zealand White rabbits (3 animals, sex not specified) caused changes to the cornea, iris, and conjunctiva for up to 72 hours. At 24, 48, and 72 hours, the mean cornea score was 11.66, 12.5, and 4.16, respectively; the mean iris score was 1.66, 1.66, and 1.66, respectively; and the mean conjunctivae score was 5.33, 4.33, and 1.66, respectively. A mean irritation score of 14.9 (max 110) was reported, and the authors concluded docusate sodium to be moderately irritating (Klimisch 2, reliable with restrictions).
- CIR 1998
    - In an ocular irritation study in rabbits (number not specified), 0.1 mL of 0.5%, 2% and 2% solutions of docusate sodium were instilled into the eye and irritation was assessed at 1 hour and 24 hours. For the 0.5%, 2%, and 10% solutions, irritation scores were 4, 9, and 26, respectively, at 1 hour and 2, 2, and 24, respectively, at 24 hours.
    - A 10% solution of a product containing 84% docusate sodium produced minimal irritation in rabbits using the Draize classification. No further details were reported.
    - In an ocular irritation assay, 0.1, 0.25, 0.5, 1, and 100% docusate sodium was instilled into rabbit eyes as either a single instillation of two drops or in repeated dosing of two drops four times a day for 6 days (undiluted groups received 1 dose a day for 6 days). At 0.1% a single application produced no effects, repeated application caused mild conjunctival injection that resolved in 24 hours. At 0.5%, conjunctival hyperemia, edema, loosening of the epithelium, and corneal staining occurred after single and repeated applications. Effects resolved withing 48 hours. At 1%, conjunctival hyperemia, edematous loosening of the epithelium, blepharospasm, and corneal haziness occurred after single and repeated applications. These effects resolved withing 72 hours. Undiluted test substance caused conjunctival injection, edema, sloughing of the epithelium, corneal haziness, and staining.
    - In an ocular irritation assay in rabbits (3/group), 1%, 5%, and 25% docusate sodium was instilled into both eyes of the animals; the right eye was rinsed after 30 seconds and the left eye was left unrinsed. At 1% there was slight to no irritation in both rinsed and unrinsed eyes. At 5%, a slight effect, that resolved within 1 week, as reported in both rinsed and unrinsed eyes. At 25% the rinsed eye showed similar effects to the 5% concentration, however, the unrinsed eye had severe effects, including corneal injury and impairment of vision.
- Based on the weight of evidence, a score of Very High was assigned. In an OECD Guideline 405 study, docusate sodium caused irreversible turbidity of the cornea. GHS Guidance classifies chemicals as Category 1 when treatment produces, in at least one animal, effects on the cornea, iris, or conjunctiva that are not expected to reverse or not fully reversible within an observation period of 21 days (UN 2021).

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): H
Docusate sodium was assigned a score of High for acute aquatic toxicity based on an EC_{50} value of 6.6 mg/L in daphnia. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when acute aquatic toxicity values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* GHS – Japan – H402 – Harmful to aquatic life [Hazardous to the aquatic environment (acute) – Category 3]
- ECHA 2023
  - 96-hr LC_{50} = 49 mg/L (*Danio rerio,* fish) (GLP, EU Method C.1) (Klimisch 1, reliable without restrictions)
  - 96-hr LC_{50} = 17.3 mg/L (*Pimephales promelas,* fish) (GLP, EPA OTS 797.1400) (Klimisch 2, reliable with restrictions)
  - 48-hr EC_{50} = 6.6 mg/L (*Daphnia magna,* daphnia) (GLP, EU Method C.2) (Klimisch 2, reliable with restrictions)
  - 72-hr EC_{50} = 82.5 mg/L (growth rate) and 39.3 mg/L (biomass) (*Scenedesmus subspicatius,* algae) (GLP, EU Method C.3) (Klimisch 2, reliable with restrictions)
- U.S. EPA 2009, ECHA 2023
  - 96-hr LC_{50} = 28 mg/L (nominal), 27.2 mg/L (measured) (*Oncorhynchus mykiss,* fish) (GLP, OECD Guideline 203) (Klimisch 2, reliable with restrictions)
  - 96-hr LC_{50} = 37 mg/L (nominal), 35.9 mg/L (measured) (*Lepomis macrochirus,* fish) (GLP, OECD Guideline 203) (Klimisch 2, reliable with restrictions)
  - 48-hr EC_{50} = 36.2 mg/L (nominal), 34.9 mg/L (measured) (*D. magna,* daphnia) (GLP not specified, similar to OECD Guideline 202) (Klimisch 2, reliable with restrictions)
- Based on the weight of evidence, a score of High was assigned. The measured 96-hr LC_{50} values in fish ranged from 17.3 mg/L to 49 mg/L, the measured 48-hr EC_{50} values in daphnia ranged from 6.6 mg/L to 36.2 mg/L, and the measured 72-hr growth rate EC_{50} value in algae was 82.5 mg/L.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
Docusate sodium was assigned a score of Moderate for chronic aquatic toxicity based on a measured EC_{10} of 9 mg/L in daphnia, and an estimated chronic value (ChV) of 2.66 mg/L in fish. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are between 1 and 10 mg/L (CPA 2018b). The confidence in the score is low as data were not available for all three trophic levels and the value for fish is estimated using acute-to-chronic ratios.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
  - *Other:* GHS – Japan – H412 – Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) – Category 3].
- ECHA 2023
  - 21-day EC_{10} = 9 mg/L (mortality) and 9.8 mg/L (reproduction) (*D. magna*, daphnia) (GLP, OECD Guideline 211) (Klimisch 1, reliable without restrictions)
  - 72-hr EC_{10} = 22 mg/L (growth rate) and 12.4 mg/L (biomass) (*S. subspicatius,* algae) (GLP, EU Method C.3) (Klimisch 2, reliable with restrictions)

- U.S. EPA 2013
    - As limited chronic data were identified, ToxServices applied the acute-to-chronic (ATC) ratios to derive the chronic values. Docusate sodium belongs to the chemical class of anionic surfactants, which has ATC ratios of 6.5, 6.5 and 4 for fish, daphnia and green algae.
        - ChV (fish) = lowest 96h EC_{50} /6.5 = 17.3 mg/L / 6.5 = 2.66 mg/L
        - ChV (daphnia) = lowest 48h EC_{50} / 6.5 = 6.6 mg/L / 6.5 = 1.02 mg/L
        - ChV (algae) = lowest EC_{50} / 4 = 82.5 mg/L / 4 = 20.63 mg/L
- Modeling of the target chemical using ECOSAR was not presented because docusate sodium has surfactant properties, and therefore, it may be out of the model applicability domain of ECOSAR.

Environmental Fate (Fate)

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

Docusate sodium was assigned a score of Low for persistence based on several biodegradation studies demonstrating it meets the GHS classification of rapidly biodegradable. GreenScreen® criteria classify chemicals as a Low hazard for persistence when they are considered to be rapidly biodegradable (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2009
    - Fugacity (Level III) modeling predicts docusate sodium will partition 59.9% to soil, 37.3% to water, 1.55% to air, and 1.33% to sediment.
    - Docusate sodium was 66.4% degraded after 28 days in a ready biodegradation test (OECD 301D or E, study summary did not specify which test was performed). Docusate sodium was not readily biodegradable.
- ECHA 2023
    - Docusate sodium was readily biodegradable in a GLP-compliant Ready Biodegradability – CO2 in Sealed Vessels (Headspace Test) according to ISO 14593 and similar to OECD Guideline 310. In this test, 10 mg/L of the test substance (98% purity) was exposed to aerobic, domestic, non-adapted, activated sludge for 28 days. Docusate sodium was 91.2% degraded after 28 days (Klimisch 1, reliable without restrictions).
    - Docusate sodium was readily biodegradable in a non-GLP Ready Biodegradability: Manometric Respirometry Test according to OECD Guideline 301F. In this test, 107 mg/L of the test substance (98.5% purity) was exposed to aerobic, non-adapted, activated sludge for 28 days. Docusate sodium was 100% degraded after 28 days based on DOC removal and 73.6-78.3% degraded in 28 days based on daily BOD determinations (Klimisch 1, reliable without restrictions).
    - Docusate sodium was readily biodegradable in a GLP-compliant Ready Biodegradability: CO2 Evolution Test according to OECD Guideline 301B. In this test, 20 mg/L of the test substance (76.4% purity) was exposed to aerobic, non-adapted, activated sludge for 29 days. Docusate sodium was 83.5-103.6% degraded after 29 days (Klimisch 2, reliable with restrictions).
    - Docusate sodium was readily biodegradable in a non-GLP Ready Biodegradability: Closed Bottle Test according to OECD Guideline 301D. In this test, 3 mg/L of the test substance (85% purity) was exposed to aerobic, non-adapted, domestic sewage for 30 days. Docusate sodium was 93% degraded after 28 days (Klimisch 2, reliable with restrictions).

    - Docusate sodium was readily biodegradable in a non-GLP Ready Biodegradability Test according to ISO 11735. In this test, 5 mg/L of the test substance (70% purity) was exposed to aerobic, non-adapted, predominately domestic sewage for 19 days. Docusate sodium was 95% degraded after 19 days (Klimisch 2, reliable with restrictions).
- Modeling of the target chemical using EPI Suite™ was not presented because docusate sodium has surfactant properties, and therefore, it may be out of the model applicability domain of EPI Suite™. Information on the 10-day window was not provided for any of the studies identified. Meeting the pass levels within the 10-day window in OECD Guideline 301 tests qualify a Very Low score. Therefore, the available information does not support a Very Low score. According to GHS criteria, when no information on the 10-day window is available, the percentage of degradation reached (> 70% for DOC, or 60% for oxygen depletion of CO2 generation) after 28 days may be used to determine rapid degradability as a pragmatic approach (UN 2021). Therefore, the available data support the rapid degradability of docusate sodium. This translates to a Low score in a GreenScreen®.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Docusate sodium was assigned a score of Very Low for bioaccumulation based on measured BCF values < 9.33 in carp. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are less than 100 (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2009, ECHA 2023
    - BCF values of < 0.891 and 9.33 were measured in carp (*Cyprinus carpio*) when docusate sodium was tested at concentrations of 0.5 mg/L and 0.05 mg/L, respectively (non-GLP, no guideline specified) (Klimisch 2, reliable with restrictions).
- ECHA 2023
    - Log K_{ow} = 1.998
        - *This value was calculated based on EU Method A.8; typical experimental methods for log K_{ow} determination, such as the shake flask and HPLC methods, are not applicable to surface active materials. Therefore, the saturation concentrations in water and n-octanol were determined in separate experiments, and the value of the partition coefficient was calculated using the solubilities of the test substance in the pure solvents.*

<u>Physical Hazards (Physical)</u>

Reactivity (Rx) Score (vH, H, M, or L): *L*
Docusate sodium was assigned a score of Low for reactivity based on the lack of oxidizing and explosive properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and not GHS classified (CPA 2018b). The confidence in the score is low due to the lack of measured data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023

- Docusate sodium was determined to have no oxidizing properties based on examination of its structure.
- Docusate sodium was determined to be non-explosive based on examination of its structure.

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

Docusate sodium was assigned a score of Low for flammability based on results from a flammability test. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023
  - Docusate sodium was determined to be non-flammable in an EU Method A.10 Flammability (Solids) assay. The combustion speed was >240 seconds for 200 mm. Therefore, the test was stopped after the pre-test and docusate sodium is considered to be not highly flammable (Klimisch 1, reliable without restrictions).
  - Docusate sodium was determined to have no measurable self-ignition in an EU Method A.16 Relative Self-Ignition Temperature for Solids assay. There was no measurable self-ignition below 180°C.

Use of New Approach Methodologies (NAMs)[10] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 5, Type I (input data) uncertainties in docusate sodium's NAMs dataset include the lack of sufficient data for endocrine activity and respiratory sensitization, and a lack of validated test methods for respiratory sensitization. Docusate sodium's Type II (extrapolation output) uncertainties include limitations of *in vitro* genotoxicity tests in mimicking *in vivo* metabolism and focusing on a few events in the process of mutagenicity, the uncertain *in vivo* relevance of *in vitro* high throughput assays of receptor binding activities, the incomplete coverage of Tox 21 EDSP assays on critical endocrine pathways, the lack of defined applicability domains for respiratory sensitization structural alerts in OECD Toolbox, and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of docusate sodium's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** There are no *in vivo* data that measure hormone levels required by the GreenScreen® criteria. **Respiratory sensitization**: No experimental data are available, and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[11]. The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal

[10] 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).

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

	aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[12]. **Endocrine activity:** The *in vivo* relevance of receptor binding activity is not clear due to lack of toxicokinetic considerations. The Tox21 EDSP has limited coverage of critical endocrine pathways. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro data:* High throughput screening assays
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	
Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	N	
Bioaccumulation	N	

[12] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Docusate Sodium (CAS #577-11-7)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / **Chemical Name** / **CAS#**	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Docusate sodium / 577-11-7	*L*	L	L	M	DG	M	L	L	*L*	L	*L*	*L*	H	vH	H	*M*	L	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	Yes	Yes	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Docusate sodium	2

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

Table 6

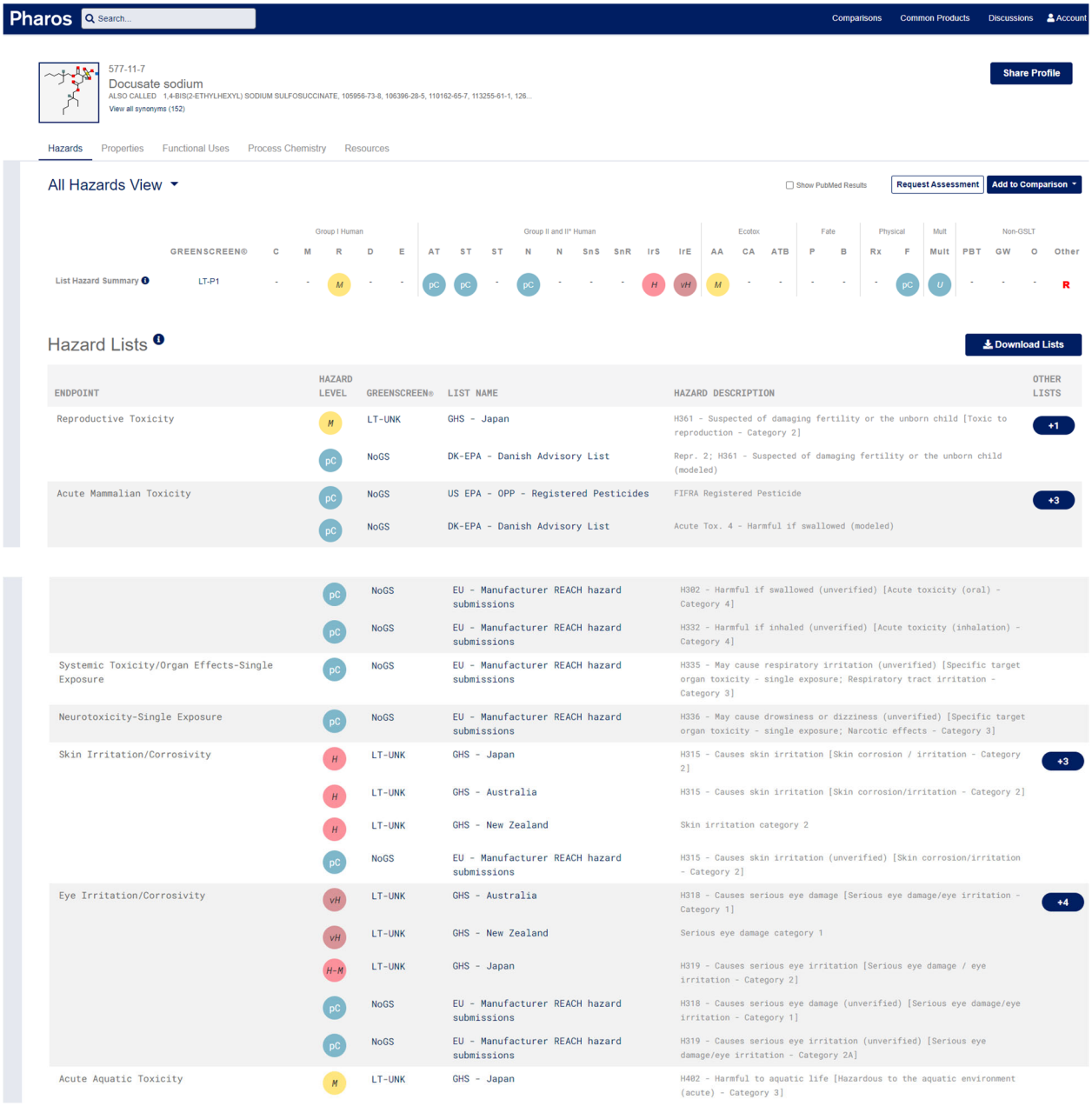
Chemical Name	Final GreenScreen® Benchmark Score
Docusate sodium	2

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

Table 5: Data Gap Assessment Table

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

APPENDIX C: Pharos Output for Docusate Sodium (CAS #577-11-7)



Flammability	pC	NoGS	EU - Manufacturer REACH hazard submissions	H226 - Flammable liquid and vapour (unverified) [Flammable liquids - Category 3]
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	EC - CEPA DSL	Inherently Toxic to Humans (iTH)
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - Japan	H412 - Harmful to aquatic life with long lasting effects [Hazardous to the aquatic environment (chronic) - Category 3] +2
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H413 - May cause long lasting harmful effects to aquatic life (unverified) [Hazardous to the aquatic environment (chronic) - Category 4]
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters

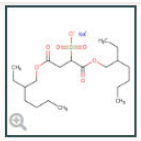
Restricted Substance Lists (3)

- 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 (3)

- Cosmetic Ingredient Review (CIR): Safe with Qualifications
- GB 9685 National Food Safety Standard (2016): GB 9685 National Food Safety Standard (2016)
- Inventory of Existing Cosmetic Ingredients in China (IECIC 2015): Cosmetic Ingredients

APPENDIX D: EDSP Tox21 Endocrine Receptor Binding Assay Results for Docusate Sodium (CAS #577-11-7)



Docusate sodium

577-11-7 | DTXSID8022959

Searched by CASRN

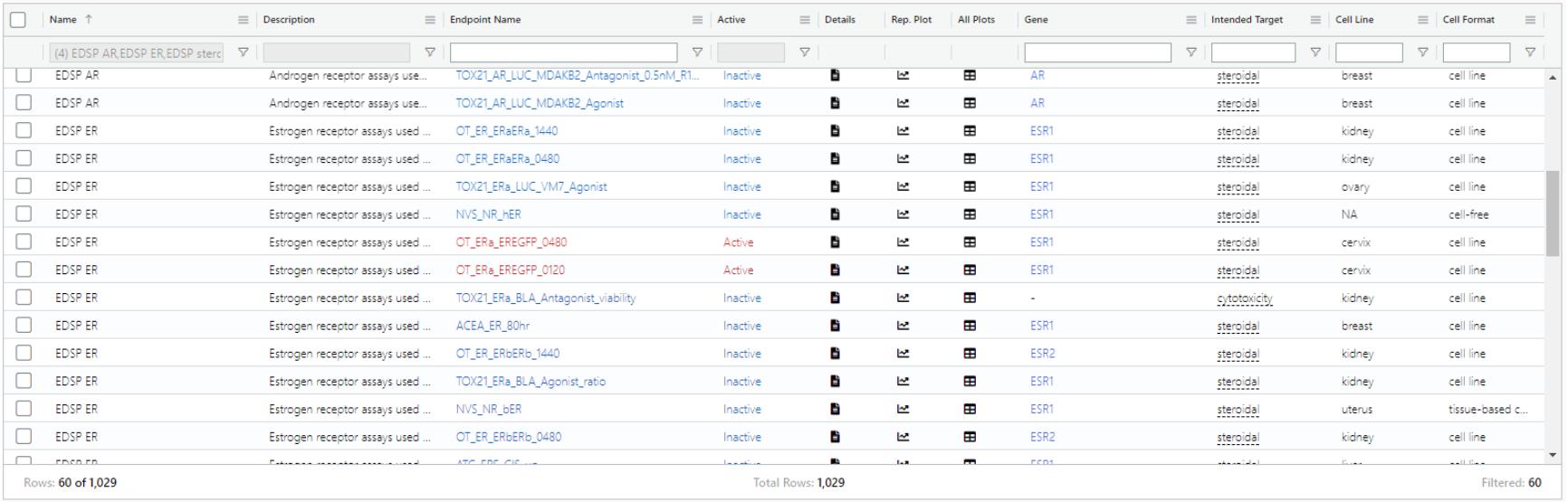
Concentration Response Data

Analytical Data on Tox21 Browser

EXPORT

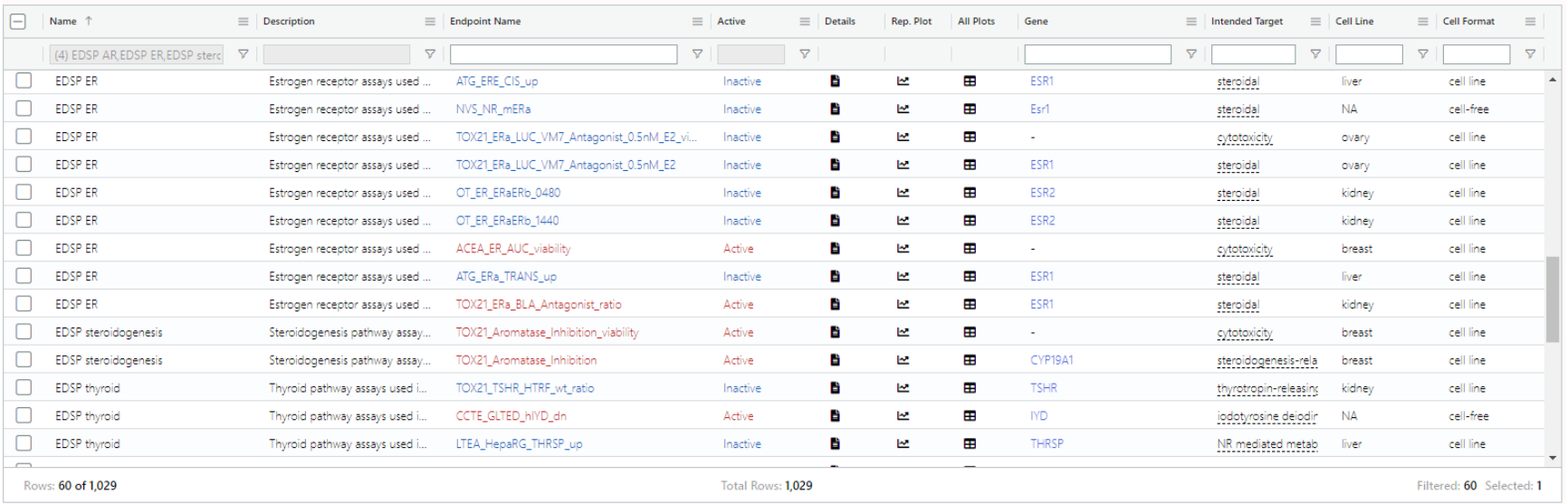
Name	Description	Endpoint Name	Active	Details	Rep. Plot	All Plots	Gene	Intended Target	Cell Line	Cell Format
(4) EDSP AR,EDSP ER,EDSP steroi										
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_R1...	Inactive				-	cytotoxicity	breast	cell line
EDSP AR	Androgen receptor assays use...	NVS_NR_rAR	Active				Ar	steroidal	prostate	tissue-based c...
EDSP AR	Androgen receptor assays use...	OT_AR_ARSRC1_0480	Active				AR	steroidal	kidney	cell line
EDSP AR	Androgen receptor assays use...	UPITT_HCI_U2OS_AR_TIF2_Nucleoli_Agonist	Inactive				AR	steroidal	bone	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Antagonist_viability	Active				-	cytotoxicity	kidney	cell line
EDSP AR	Androgen receptor assays use...	OT_AR_ARSRC1_0960	Inactive				AR	steroidal	kidney	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Antagonist_ratio	Inactive				AR	steroidal	kidney	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_10nM_R1...	Inactive				-	cytotoxicity	breast	cell line
EDSP AR	Androgen receptor assays use...	OT_AR_ARELUC_AG_1440	Inactive				AR	steroidal	ovary	cell line
EDSP AR	Androgen receptor assays use...	ATG_AR_TRANS_up	Inactive				AR	steroidal	liver	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_10nM_R1...	Inactive				AR	steroidal	breast	cell line
EDSP AR	Androgen receptor assays use...	UPITT_HCI_U2OS_AR_TIF2_Nucleoli_Antagonist	Active				AR	steroidal	bone	cell line
EDSP AR	Androgen receptor assays use...	NVS_NR_cAR	Active				AR	steroidal	NA	cell-free
EDSP AR	Androgen receptor assays use...	TOX21_AR_BLA_Agonist_ratio	Active				AR	steroidal	kidney	cell line

Rows: 60 of 1,029 Total Rows: 1,029 Filtered: 60



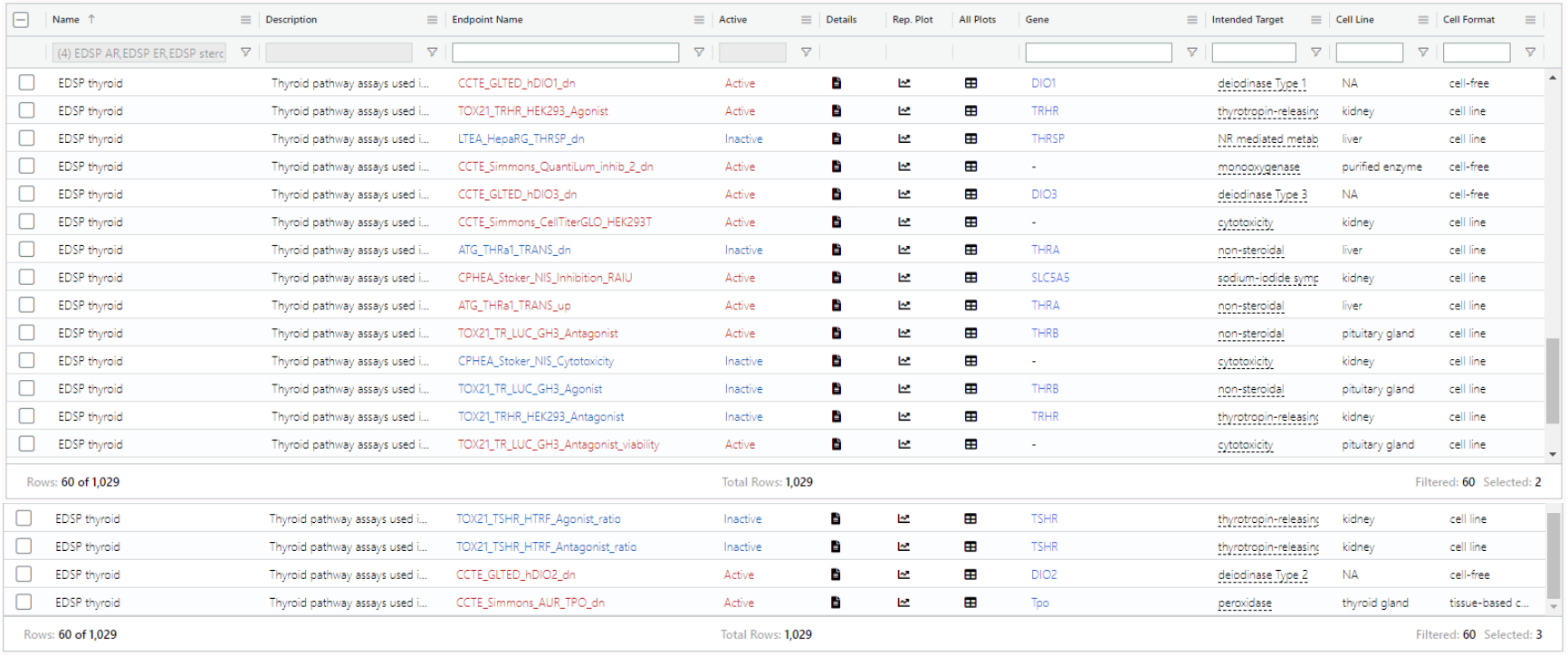
Name	Description	Endpoint Name	Active	Details	Rep. Plot	All Plots	Gene	Intended Target	Cell Line	Cell Format
(4) EDSP AR,EDSP ER,EDSP sterc										
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Antagonist_0.5nM_R1...	Inactive				AR	steroidal	breast	cell line
EDSP AR	Androgen receptor assays use...	TOX21_AR_LUC_MDAKB2_Agonist	Inactive				AR	steroidal	breast	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERaERa_1440	Inactive				ESR1	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERaERa_0480	Inactive				ESR1	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_LUC_VM7_Agonist	Inactive				ESR1	steroidal	ovary	cell line
EDSP ER	Estrogen receptor assays used ...	NVS_NR_hER	Inactive				ESR1	steroidal	NA	cell-free
EDSP ER	Estrogen receptor assays used ...	OT_ERa_EREGFP_0480	Active				ESR1	steroidal	cervix	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ERa_EREGFP_0120	Active				ESR1	steroidal	cervix	cell line
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_BLA_Antagonist_viability	Inactive				-	cytotoxicity	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	ACEA_ER_80hr	Inactive				ESR1	steroidal	breast	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERbERb_1440	Inactive				ESR2	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_BLA_Agonist_ratio	Inactive				ESR1	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	NVS_NR_bER	Inactive				ESR1	steroidal	uterus	tissue-based c...
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERbERb_0480	Inactive				ESR2	steroidal	kidney	cell line

Rows: 60 of 1,029 Total Rows: 1,029 Filtered: 60



Name	Description	Endpoint Name	Active	Details	Rep. Plot	All Plots	Gene	Intended Target	Cell Line	Cell Format
(4) EDSP AR,EDSP ER,EDSP sterc										
EDSP ER	Estrogen receptor assays used ...	ATG_ERE_CIS_up	Inactive				ESR1	steroidal	liver	cell line
EDSP ER	Estrogen receptor assays used ...	NVS_NR_mERa	Inactive				Esr1	steroidal	NA	cell-free
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_LUC_VM7_Antagonist_0.5nM_E2_vi...	Inactive				-	cytotoxicity	ovary	cell line
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_LUC_VM7_Antagonist_0.5nM_E2	Inactive				ESR1	steroidal	ovary	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERaERb_0480	Inactive				ESR2	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	OT_ER_ERaERb_1440	Inactive				ESR2	steroidal	kidney	cell line
EDSP ER	Estrogen receptor assays used ...	ACEA_ER_AUC_viability	Active				-	cytotoxicity	breast	cell line
EDSP ER	Estrogen receptor assays used ...	ATG_ERa_TRANS_up	Inactive				ESR1	steroidal	liver	cell line
EDSP ER	Estrogen receptor assays used ...	TOX21_ERa_BLA_Antagonist_ratio	Active				ESR1	steroidal	kidney	cell line
EDSP steroidogenesis	Steroidogenesis pathway assay...	TOX21_Aromatase_Inhibition_viability	Active				-	cytotoxicity	breast	cell line
EDSP steroidogenesis	Steroidogenesis pathway assay...	TOX21_Aromatase_Inhibition	Active				CYP19A1	steroidogenesis-rela	breast	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_wt_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	CCTE_GLTED_hIYD_dn	Active				IYD	iodotyrosine deiodir	NA	cell-free
EDSP thyroid	Thyroid pathway assays used i...	LTEA_HepaRG_THRSP_up	Inactive				THRSP	NR mediated metab	liver	cell line

Rows: 60 of 1,029 Total Rows: 1,029 Filtered: 60 Selected: 1

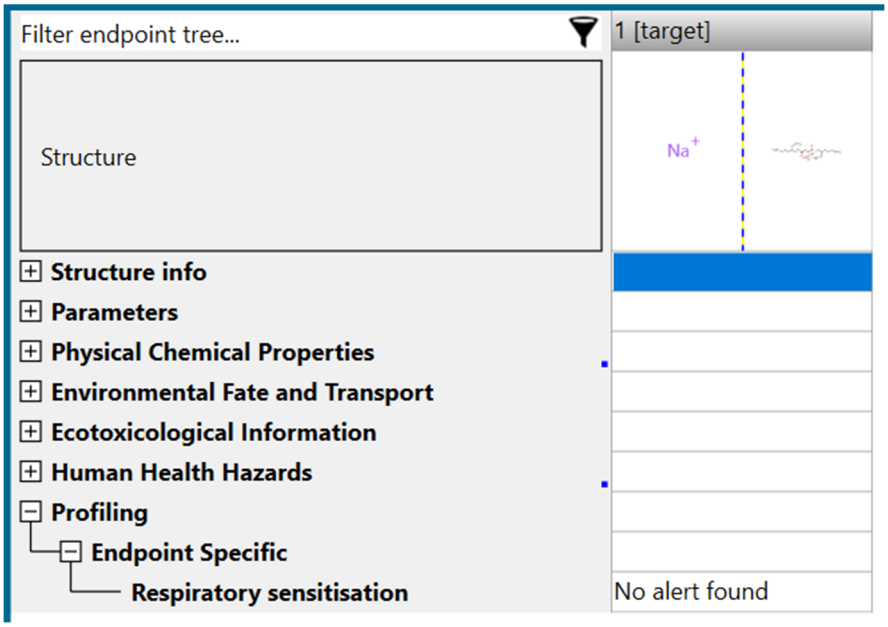


Name	Description	Endpoint Name	Active	Details	Rep. Plot	All Plots	Gene	Intended Target	Cell Line	Cell Format
(4) EDSP AR,EDSP ER,EDSP sterc										
EDSP thyroid	Thyroid pathway assays used i...	CCTE_GLTED_hDIO1_dn	Active				DIO1	deiodinase Type 1	NA	cell-free
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TRHR_HEK293_Agonist	Active				TRHR	thyrotropin-releasing	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	LTEA_HepaRG_THRSP_dn	Inactive				THRSP	NR mediated metab	liver	cell line
EDSP thyroid	Thyroid pathway assays used i...	CCTE_Simmons_QuantiLum_inhib_2_dn	Active				-	monooxygenase	purified enzyme	cell-free
EDSP thyroid	Thyroid pathway assays used i...	CCTE_GLTED_hDIO3_dn	Active				DIO3	deiodinase Type 3	NA	cell-free
EDSP thyroid	Thyroid pathway assays used i...	CCTE_Simmons_CellTiterGLO_HEK293T	Active				-	cytotoxicity	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	ATG_THRa1_TRANS_dn	Inactive				THRA	non-steroidal	liver	cell line
EDSP thyroid	Thyroid pathway assays used i...	CPHEA_Stoker_NIS_Inhibition_RAIU	Active				SLC5A5	sodium-iodide symp	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	ATG_THRa1_TRANS_up	Active				THRA	non-steroidal	liver	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Antagonist	Active				THRB	non-steroidal	pituitary gland	cell line
EDSP thyroid	Thyroid pathway assays used i...	CPHEA_Stoker_NIS_Cytotoxicity	Inactive				-	cytotoxicity	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Agonist	Inactive				THRB	non-steroidal	pituitary gland	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TRHR_HEK293_Antagonist	Inactive				TRHR	thyrotropin-releasing	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TR_LUC_GH3_Antagonist_viability	Active				-	cytotoxicity	pituitary gland	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_Agonist_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	TOX21_TSHR_HTRF_Antagonist_ratio	Inactive				TSHR	thyrotropin-releasing	kidney	cell line
EDSP thyroid	Thyroid pathway assays used i...	CCTE_GLTED_hDIO2_dn	Active				DIO2	deiodinase Type 2	NA	cell-free
EDSP thyroid	Thyroid pathway assays used i...	CCTE_Simmons_AUR_TPO_dn	Active				Tpo	peroxidase	thyroid gland	tissue-based c...

Rows: 60 of 1,029 Total Rows: 1,029 Filtered: 60 Selected: 2

Rows: 60 of 1,029 Total Rows: 1,029 Filtered: 60 Selected: 3

APPENDIX E: OECD Toolbox Respiratory Sensitization Results for Docusate Sodium (CAS #577-11-7)



APPENDIX F: Change in Benchmark Score

Table 6 provides a summary of changes to ToxServices' GreenScreen® Benchmark™ for docusate sodium. ToxServices performed the original GreenScreen® assessment in 2014 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score was maintained with a version 1.3 update in 2017 and a version 1.4 update in 2022. In the current GreenScreen® assessments in 2003, ToxServices maintained the BM-2 score with a version 1.4 update.

Table 6: Change in GreenScreen® Benchmark™ for Docusate Sodium

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
September 8, 2014	BM-2	v. 1.2	Original GreenScreen® assessment.
September 7, 2017	BM-2	v. 1.3	No change in BM score. The GreenScreen® assessment was updated with a v.1.3 template. Reclassification of respiratory sensitization endpoint from Data Gap (DG) to *Low* (low confidence) and chronic aquatic toxicity endpoint from DG to *Moderate* (low confidence).
September 7, 2022	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template. Reclassification of reproductive toxicity endpoint from *Moderate* (low confidence) to **Low** (high confidence), the neurotoxicity (single dose) endpoint from DG to *Low* (low confidence), the neurotoxicity (repeated dose) endpoint from DG to **Low** (high confidence), the skin sensitization endpoint from **Low** (high confidence) to *Low* (low confidence), and the persistence endpoint from *Very Low* (low confidence) to **Low** (high confidence).
August 28, 2023	BM-2	v. 1.4	No change in BM score. The GreenScreen® assessment was updated with a v.1.4 template.
October 16, 2023	BM-2	v. 1.4	No change in BM score. The confidence of acute mammalian toxicity score was revised from low to high confidence. Additional minor edits were made to fix typos in response to Washington Department of Ecology's comments.

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