SINAPIC ACID

(CAS #530-59-6)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: May 16, 2024

Expiration Date: May 16, 2029

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GreenScreen® Executive Summary for Sinapic Acid (CAS #530-59-6)

Sinapic acid is a non-flammable, non-volatile light yellow powder at standard temperature and pressure. It is a hydroxy-methoxy derivative of cinnamic acid that is used as a food additive and skin conditioning agent. It also occurs naturally in foods such as beer, soybeans, and wine.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (carcinogenicity-C)

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, skin sensitization, respiratory sensitization, aquatic toxicity, persistence, and bioaccumulation; and *in vitro* assays for genotoxicity, skin sensitization, skin irritation, and eye irritation. 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 sinapic acid's NAMs dataset include lack of or limited experimental data for carcinogenicity, skin sensitization, respiratory sensitization, skin irritation, eye irritation, aquatic toxicity, persistence, and bioaccumulation, and lack of established test methods for respiratory sensitization. Sinapic acid's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of individual and/or combination of *in vitro* skin and/or eye irritation assays to determine all GHS categories, inability of *in vitro* skin sensitization assays to identify pro- and pre-haptens, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization.

GreenScreen® Hazard Summary Table for Sinapic Acid

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

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

GreenScreen® Chemical Assessment for Sinapic Acid (CAS #530-59-6)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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Title: Toxicologist
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Date: March 14, 2024

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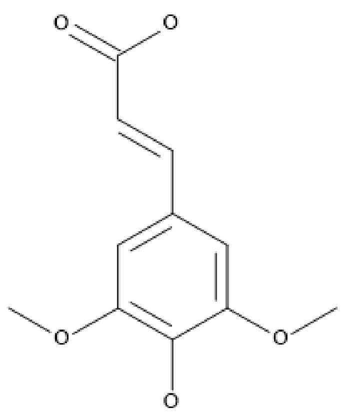
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: May 16, 2024

Expiration Date: May 16, 2029[2]

Chemical Name: Sinapic acid

CAS Number: 530-59-6

Chemical Structure(s):

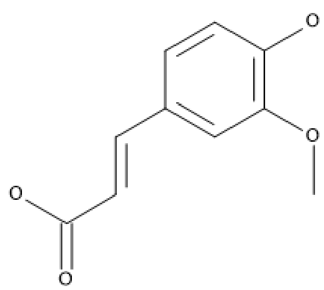


Also called:
(2E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propenoic acid; (2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylic acid; (2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid; (E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propenoic acid; (E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acrylic acid; (E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid; (E)-Sinapic acid; 2-Propenoic acid, 3-(4-hydroxy-3,5-dimethoxyphenyl)-; 2-propenoic acid, 3-(4-hydroxy-3,5-dimethoxyphenyl)-, (2E)-; 2-Propenoic acid, 3-(4-hydroxy-3,5-dimethoxyphenyl)-, (E)-; 3-(4-Hydroxy-3,5-dimethoxyphenyl)-(2E)-2-Propenoic acid; 3-(4-Hydroxy-3,5-dimethoxyphenyl)-(E)-2-propenoic acid; 3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-Propenoic acid; 3-(4-Hydroxy-3,5-dimethoxyphenyl)acrylic acid; 3-(4-Hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid; 3,5-Dimethoxy-4-hydroxycinnamic acid; 3,5-Dimethoxy-4-hydroxy-trans-cinnamic acid; 4-Hydroxy-3,5-dimethoxy-(E)-Cinnamic acid; 4-Hydroxy-3,5-

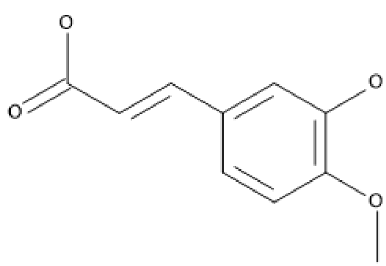
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment expires three years from the date of completion if completed before January 1, 2019 (CPA 2018a).

dimethoxycinnamic acid; Cinnamic acid, 4-hydroxy-3,5-dimethoxy-; Cinnamic acid, 4-hydroxy-3,5-dimethoxy-, (E)-; Sinapate; sinapic acid, (E)-; Sinapic acid, trans-; Sinapinate; Sinapinic acid; Synapoic acid; trans-3,5-Dimethoxy-4-hydroxycinnamic acid; trans-sinapic acid; trans-sinapinic acid (PubChem 2024)

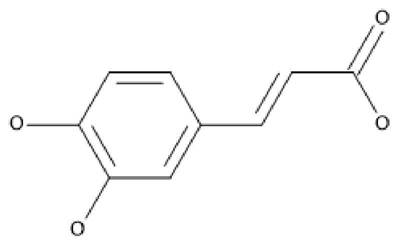
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Minimal data were identified for sinapic acid, therefore, ToxServices searched for structurally similar chemicals to fill data gaps. ToxServices identified ferulic acid (CAS #1135-24-6), isoferulic acid (CAS #537-73-5), and caffeic acid (CAS #331-39-5) as substances with similar strucutre and functional groups to sinapic acid. Sinapic acid has maximum common substructure (MCS) Tanimoto coefficients of 0.875, 0.7647, and 0.8125 with ferulic acid, isoferulic acid, and caffeic acid, respectively, indicating a high degree of structural similarity with these surrogates (ChemMine 2024). When data were insufficient for these surrogates, ToxServices utilized data for cinnamic acid (CAS #621-82-9/140-10-3), as sinapic acid is a cinnamic acid derivative. However, as sinapic acid and cinnamic acid share a lower MCS Tanimoto coefficient of 0.6875 (ChemMine 2024), and sinapic acid contains additional functional groups not present on cinnamic acid (i.e., hydroxyl and methoxy substituents on the benzene ring), cinnamic acid was considered to be a weak surrogate and scores based on data for cinnamic acid are reported with low confidence. The ChemMine Tanimoto coefficients output can be found in Appendix D.



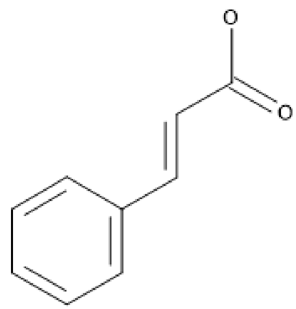
Ferulic Acid (CAS #1135-24-6)



Isoferulic Acid (CAS #537-73-5)



Caffeic Acid (CAS #331-39-5)



Cinnamic Acid (CAS #621-82-9/140-10-3)

Identify Applications/Functional Uses: (PubChem 2024)
1. Food additive – flavoring agent
2. Skin conditioning agent

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

<u>GreenScreen® Summary Rating for Sinapic Acid</u>[4,5 6,7]: Sinapic acid 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:

- Benchmark 2e
    - Moderate Group I Human Toxicity (carcinogenicity-C)

Data gaps (DG) exist for reproductive toxicity-R, endocrine activity-E, neurotoxicity (repeated dose)-Nr*, and respiratory sensitization-SnR*. As outlined in GreenScreen® Guidance (CPA 2018b) Section 11.6.2.1 and Annex 5 (Conduct a Data Gap Analysis), sinapic acid meets requirements for a GreenScreen Benchmark™ Score of 2 despite the hazard data gaps. In a worst-case scenario, if sinapic acid were assigned a High score for the data gaps R or E, it would be categorized as a Benchmark 1 Chemical.

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

Figure 1: GreenScreen® Hazard Summary Table for Sinapic Acid

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

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

Environmental Transformation Products

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

Introduction

Sinapic acid is a hydroxy-methoxy derivative of cinnamic acid that is used food additive and skin conditioning agent. It also occurs naturally in foods such as beer, soybeans, and wine (EFSA 2011).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2024a). 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).

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

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

- Sinapic acid is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Sinapic acid is not listed on the U.S. DOT list.
- Sinapic acid is not on any lists for multiple endpoints. Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

No European Union (EU) harmonized Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for sinapic acid. H Statements reported by the majority of self-notifiers to the European Chemicals Agency Classification and Labelling (ECHA C&L) Inventory are reported in Table 1. General personal protective equipment (PPE) recommendations are presented in Table 2, below. No occupational exposure limits (OELs) were identified.

Table 1: GHS H Statements for Sinapic Acid (CAS #530-59-6) (ECHA C&L, CAS #530-59-6, 2024)	
H Statement	**H Statement Details**
H315	Causes skin irritation (170/171 (99.4%) self-notifiers to C&L Inventory)
H319	Causes serious eye irritation (170/171 (99.4%) self-notifiers to C&L Inventory)
H335	May cause respiratory irritation (169/171 (98.8%) self-notifiers to C&L Inventory)

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Sinapic Acid (CAS #530-59-6)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
Safety glasses with shields; protective gloves and protective clothing; respiratory protection in exposure limits are exceeded	Santa Cruz Biotechnology 2016	None identified	N/A

Physicochemical Properties of Sinapic Acid

Sinapic acid is a light yellow powder at standard temperature and pressure. Its boiling point of 490°C and predicted vapor pressure of 1.18×10^{-7} mm Hg suggests it is not a volatile organic compound. It is predicted to be soluble in water and its estimated log K_{ow} of 1.24 indicates it is not likely to bioaccumulate.

Table 3: Physical and Chemical Properties of Sinapic Acid (CAS #530-59-6)		
Property	**Value**	**Reference**
Molecular formula	$C_{11}H_{12}O_5$	PubChem 2024
SMILES Notation	COC1=CC(=CC(=C1O)OC)/C=C/C(=O)O	PubChem 2024
Molecular weight	224.21 g/mol	PubChem 2024
Physical state	Solid	PubChem 2024
Appearance	Light yellow powder	PubChem 2024
Melting point	192°C; 202°C	PubChem 2024 Santa Cruz Biotechnology 2016
Boiling point	490°C	EFSA 2011
Vapor pressure	1.18×10^{-7} mm Hg at 25°C (estimated)	U.S. EPA 2017

Table 3: Physical and Chemical Properties of Sinapic Acid (CAS #530-59-6)		
Property	**Value**	**Reference**
Water solubility	1,830 mg/L at 25°C (estimated)	U.S. EPA 2017
Dissociation constant	Not identified	
Density/specific gravity	Not identified	
Partition coefficient	Log K_{ow} = 1.24 (estimated)	U.S. EPA 2017

Toxicokinetics

Toxicokinetic data for sinapic acid and structurally similar chemicals are limited. Sinapic acid is expected to be rapidly absorbed from the gastrointestinal tract following oral exposure. After entering the cell, sinapic acid is expected to behave similarly to cinnamic acid – be converted to acyl CoA esters and oxidized via the beta-oxidation pathway (EFSA 2011). However, because it contains several metabolically active sites, it has the potential to be transformed though various pathways to a large number of metabolites, depending on dose administered, route of administration, and animal species (EFSA 2011).

When male Wistar rats (n=5) were orally administered 50 mg/mL of the surrogate ferulic acid via gavage, 5.4 ± 4.1% of the administered dose was detected as unchanged compound and 5.1 ± 3.6% of the glucuronide conjugate was obtained in the urine, suggesting it is readily bioavailable via the oral route. The unaccounted part of the dose may be excreted via other roues or as unidentified metabolites (EFSA 2011).

When (^{14}C)-ferulic acid was administered to female Wistar rats via intraperitoneal injection at a dose of 38 mg (150-190 mg/kg), radioactivity was poorly incorporated in the rat organs and tissues at 24 hours after injection; 19.5% was recovered in the feces and 68% was recovered in the urine, both as free ferulic acid and as m-hydroxyphenylpropionic acid, followed by vanillic acid. Only 1.95% was found in respiratory CO_2, indicating very little ferulic acid was metabolized via beta-oxidation of the side-chain (EFSA 2011).

Human (1 male and 4 females) consumption of tomatoes (360-728 g as a single bolus), providing a mean of 30.1 g (21-44 g) ferulic acid, resulted in progressive excretion of ferulic acid 7-9 hours after administration, after which it showed no further excretion. With 4-5% of the ingested dose excreted as free ferulic acid over 24 hours; a considerable proportion was excreted as the glucuronide. The total recovery of ferulic acid in the urine, on the basis of total free ferulic acid and feruloyl glucuronide excreted, was 11 - 25% of the amount ingested (EFSA 2011).

Following human ingestion of ferulic acid, the 3-hydroxyphenyl and 3-methoxy-4-hydroxyphenyl acids were found to be excreted in urine (EFSA 2011).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Sinapic acid was assigned a score of Moderate for carcinogenicity based on mixed results from modeling programs and experimental data for the surrogate caffeic acid classifying it to IARC Group 2B. GreenScreen® criteria classify chemicals as a Moderate hazard for carcinogenicity when there is limited or marginal evidence of carcinogenicity in animals (CPA 2018b). The confidence in the score is low as the surrogate ferulic acid is reported to not exert a similar effect as caffeic acid and the modeling for sinapic acid produced mixed results.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- VEGA 2023
    - ToxServices predicted the carcinogenicity potential of sinapic acid using the following six VEGA v1.2.3 models: CAESAR v2.1.10, ISS v.1.0.3, IRFMN/ISSCAN-CGX v1.0.2, IRFMN/Antares v1.0.2, IRFMN oral classification v1.0.1, and IRFMN inhalation classification v1.0.1. If an external compound is beyond the defined scope of a given model, it is considered outside that model's applicability domain (AD) and cannot be associated with a reliable prediction (Sahigara 2007). Values for AD index (ADI) range from 0 (worst case) to 1 (best case). Generally, ADI values of > 0.70 indicate that the prediction has moderate or better predictivity (Gad 2016).
        - CAESAR v2.1.10 model predicts sinapic acid to be a carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix E).
        - ISS v1.0.3 model predicts sinapic acid to be a non-carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix E).
        - IRFMN/ISSCAN-CGX v1.0.2 model predicts sinapic acid to be a possible non-carcinogen with moderate confidence. The ADI is 0.618, indicating that the prediction is not reliable (Appendix E).
        - IRFMN/Antares v1.0.2 model predicts sinapic acid to be a carcinogen with moderate confidence. The ADI is 0.638, indicating that the prediction is not reliable (Appendix E).
        - IRFMN oral classification v1.0.2 model predicts sinapic acid to be a **non-carcinogen** with high confidence. The ADI is **0.879**, indicating that the prediction is reliable (Appendix E).
        - IRFMN inhalation classification v1.0.2 model predicts sinapic acid to be a carcinogen with low confidence. The ADI is 0, indicating that the prediction is not reliable (Appendix E).
- Toxtree 2018
    - Sinapic acid does not contain a structural alert for genotoxic or nongenotoxic carcinogenicity (Appendix F).
- DTU 2024
    - Danish (Q)SAR Database for the CAS number 530-59-6 reports that sinapic acid is in the domains of five of the seven of the E Ultra FDA RCA cancer databases and is predicted to be negative for carcinogenicity in all five databases (male rat, female rat, rat, female mouse, and rodent). Sinapic acid is in the domain of four of the seven Leadscope FDA RCA cancer databases, and is predicted it to be negative for carcinogenicity in one database (rat); it is predicted to be positive in the remaining three databases (male mouse, female mouse, and mouse). Regarding the liver specific cancer in rat or mouse model, sinapic acid is outside the domain of all three models (CASE Ultra, Leadscope, and SciQSAR) and the overall battery (Appendix G).
- U.S. EPA 2021
    - Attempts were made to evaluate the carcinogenic potential of sinapic acid using the most current version of OncoLogic (v9.0); however, OncoLogic indicated that its chemical class is not supported in the current version of software (Appendix H).
- IARC 1993

    - *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a carcinogenicity study, male and female B6C3F1 mice (30/sex/dose) were administered caffeic acid (≥98% purity) in the diet at 0% and 2% (reported to be 2,120 and 3,126 mg/kg/day in males and females, respectively) for 96 weeks. Squamous-cell papillomas and carcinomas occurred in the forestomachs of treated mice (4/30 papillomas and 3/30 carcinomas in males and 0/29 papillomas and 1/29 carcinomas in females). The incidences of epithelial hyperplasia of the forestomach were increased significantly ($p < 0.01$) in both treated males and females. Renal-cell adenomas were found in 8/29 ($p < 0.01$) females; one renal adenocarcinoma was seen in a treated male. There were significant increases in the incidence of renal tubular-cell hyperplasia in treated males and females. An increased incidence of alveolar type II-cell tumors (adenomas plus carcinomas) of the lung (8/30; $p < 0.05$) was reported in males but not in females.
    - *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a carcinogenicity study, male and female Fisher 344 rats (30/sex/dose) were administered caffeic acid (≥98% purity) in the feed at 0% and 2% (reported to be 678 and 814 mg/kg/day in males and females, respectively) for 104 weeks. Squamous-cell papillomas and carcinomas occurred in the forestomach in 23/30 (papillomas) and 17/30 (carcinomas) males and in 24/30 (papillomas) and 15/30 (carcinomas) females. The frequency of forestomach hyperplasia was also increased significantly in animals of each sex as compared to the control level ($p < 0.01$). There were renal tubular-cell adenomas in four treated males. There were significant increases in the incidence of renal tubular-cell hyperplasia in both treated males and females.
    - The International Agency for Research on Cancer (IARC) concluded there is sufficient evidence on experimental animals for the carcinogenicity of caffeic acid and classified it to Group 2B (possibly carcinogenic to humans).
- ILS 1998
    - *Surrogate: Ferulic Acid (CAS #113524-6):* Although caffeic acid is shown to induce rat forestomach carcinogenesis, the metabolite ferulic acid did not exert this effect when administered at 1% (10,000 ppm) in the diet for 52 weeks to male F344 rats pretreated with 1,2-dimethylhydrazine (DMH) and N-methyl-N-nitrosourea (MNU).
- Based on the weight of evidence, a score of Moderate was assigned. The surrogate caffeic acid was positive for carcinogenicity in chronic assays in rats and mice; however, ferulic acid did not exert a similar effect in a tumor promotion study of shorter duration (ILS 1998). Sinapic acid does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity according to Toxtree. One of the six models in VEGA produced a reliable prediction for carcinogenicity for sinapic acid, and it was predicted to be a non-carcinogen in this model. Danish QSAR modeling database gave ambiguous results, with both positive and negative in domain predictions for carcinogenicity. OncoLogic was unable to evaluate the carcinogenic potential of sinapic acid. The weight of evidence from surrogate experimental data and from rule-based (VEGA, Toxtree, and OncoLogic) and statistical-based (Danish QSAR) modeling programs indicates a carcinogenic concern for sinapic acid cannot be ruled out. Based on the IARC Group 2B classification for the surrogate caffeic acid, ToxServices assigned a score of Moderate for this endpoint.

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

Sinapic acid was assigned a score of Low for mutagenicity/genotoxicity based on negative results in bacterial reverse mutation assays, and *in vivo* genotoxicity assays for gene mutation and chromosomal aberration for the surrogate caffeic acid. 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 experimental data for a strong surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2011
  - *In vitro:* Sinapic acid was negative in a non-GLP mutation assay designed for the determination of effects on UV-induced mutagenesis in *Escherichia coli* B/r WP_2. Cells were exposed to the test substance at 1,000 µg/plate without metabolic activation. The assay was negative for both direct mutagenic activity and enhancement of UV-induced mutagenesis.
    - *ToxServices notes EFSA (2011) indicates the validity of this study cannot be evaluated due to limited reporting of experimental details and results.*
  - *In vitro: Surrogate: Ferulic Acid (CAS #1135-24-6):* Ferulic acid was negative in a non-GLP compliant Ames reverse mutation assay. *Salmonella typhimurium* strains TA98 and TA100 were exposed to the test substance at unreported concentrations with and without metabolic activation. The ozonation products of ferulic acid (and other structural components of humic substances) were also tested in this assay and gave positive results.
    - *ToxServices notes EFSA (2011) indicates the validity of this study cannot be evaluated due to limited reporting of experimental details and results.*
- EFSA 2011, ECHA, CAS #1135-24-6, 2024
  - *In vitro: Surrogate: Ferulic Acid (CAS #1135-24-6):* Ferulic acid was negative in a non-GLP mutation assay designed for the determination of effects on UV-induced mutagenesis in *E. coli* B/r WP_2. Cells were exposed to the test substance at 1,000 µg/plate without metabolic activation. The assay was negative for both direct mutagenic activity and enhancement of UV-induced mutagenesis.
    - *ToxServices notes EFSA (2011) indicates the validity of this study cannot be evaluated due to limited reporting of experimental details and results. Additionally, this study is reported in the ECHA REACH dossier with a Klimisch Score 4 (not assignable).*
  - *In vitro: Surrogate: Ferulic Acid (CAS #1135-24-6):* Ferulic acid was negative in a non-GLP sister chromatid exchange (SCE) assay. Chinese hamster ovary (CHO) cells were exposed to the test substance at 0, 3.3, 10, 33.3, 100, and 333 µM (0, 0.641, 1.94, 6.41, 19.4, and 64.1 µg/mL) with and without metabolic activation. The test substance did not influence cell cycle and spontaneous SCEs at the concentrations tested; however, post-treatment of mitomycin-treated cells with the test substance increased the frequency of SCEs in a dose-related manner, reaching statistical significance ($p<0.001$) at the two highest non-toxic concentrations. Additionally, The frequency of SCEs induced by UV was significantly increased by treatment at 10 ($0.001<p<0.01$), 33.3, and 100 µM ($p<0.001$) in a dose related manner; yet, X-ray induced SCEs were significantly reduced by treatment at 10 ($0.01<p<0.05$), 33.3, and 100 µM ($p<0.001$) also in a dose-related manner (Klimisch 2, reliable with restrictions).
- ILS 1998
  - *In vitro: Surrogate: Caffeic Acid (CAS #331-39-5):* Caffeic acid was negative in a bacterial reverse mutation assay in *S. typhimurium* strain TA98 at concentrations of 150 µg/plate with and without metabolic activation.
  - *In vitro: Surrogate: Caffeic Acid (CAS #331-39-5):* Caffeic acid was negative in a bacterial reverse mutation assay in *S. typhimurium* strain TA98 and TA100 at concentrations of 6 and

10 mg/plate with and without metabolic activation.
  - *In vitro: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was negative in a bacterial reverse mutation assay in *S. typhimurium* strain TA98 at concentrations of 1, 2, 3, 6 and 9 mg/mL with metabolic activation.
  - *In vitro: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was negative in a bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 at concentrations of 0.33-10 mg/plate with and without metabolic activation.
  - *In vitro: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* A mammalian cell gene mutation assay in mouse lymphoma L5178Y cells with caffeic acid was positive at a concentration of 307 µg/mL without metabolic activation, but was negative with metabolic activation.
  - *In vitro: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* An *in vitro* chromosomal aberration assay in CHO cells with caffeic acid was positive at a concentration of 250 µg/mL without metabolic activation.
  - *In vivo: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was negative in an *in vivo* micronucleus assay in which B6C3F1 mice were administered caffeic acid at a dose of 2,400 mg/kg in the diet.
  - *In vivo: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was negative in an *in vivo* micronucleus assay in which C56B1/6J mice were administered caffeic acid at a dose of 800 mg/kg in the diet.
  - *In vivo: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was negative in an *in vivo* micronucleus assay in which C56B1/6J mice were administered caffeic acid at a dose of 4,800 mg/kg in the diet.
- IARC 1993
  - *<u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* IARC concluded that caffeic acid was not mutagenic in bacteria or clastogenic in mice *in vivo*. However, it was mutagenic and clastogenic *in vitro* in cultured rodent cells.
- Bhalli et al. 2019
  - *In vivo: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* Caffeic acid was tested for *in vivo* genotoxicity based on three endpoints: micronucleus, Pig-a, and comet assay. Rats (strain unspecified, 6/group) were exposed to caffeic acid by gavage at 0, 500, or 2,000 mg/kg/day for 3 consecutive days. Animals were either sacrificed 3 hours after the last dose for the comet assay (blood and liver), or maintained for peripheral blood collection on Days 01, 14, and 30 for the Pig-a assay, and on Day 4 for the micronucleus assay. There was a statistically significant increase in micronucleus formation at 2,000 mg/kg/day. However, Pig-a mutation frequences were not increased on Days 14 or 30 in red blood cells or reticulocytes, and there were no increases in DNA strand breaks in the blood or liver in the comet assay.
- ECHA, CAS #140-10-3, 2024
  - *In vitro: <u>Surrogate: Cinnamic Acid (CAS #140-10-3):</u>* Cinnamic acid was negative for mutagenicity in a GLP-compliant OECD Guideline 471 bacterial reverse mutation assay. *S. typhimurium* strains TA1535, TA1537, TA98, and TA100, and *E. coli* WP_2 were exposed to the test substance (purity not reported) in DMSO at 1.5, 5, 15, 50, 150, 500, 1,500, and 5,000 µg/plate with and without metabolic activation. There were no increases in the frequency of revertants in any strain at any concentration with or without metabolic activation. Vehicle, untreated negative, and positive controls were reported to be valid (Klimisch 1, reliable without restriction).
- EFSA 2011
  - The European Food Safety Authority (EFSA)'s flavorant group aryl-substituted saturated

and unsaturated primary alcohol/aldehyde/acid/ester derivatives contains sinapic acid and the surrogate ferulic acid. In terms of the genotoxicity potential of the group, EFSA concluded that although available genotoxicity data on category members are insufficient for an adequate evaluation, such as lacking *in vivo* data, there are no indications of mutagenic activity in bacteria or clastogenic activity in mammalian cells based on data from category members and supporting substances.

- Based on the weight of evidence, a score of Low was assigned. The surrogate caffeic acid had the most data compared to other chemicals evaluated. IARC determined that it was positive for gene mutation in mammalian cells *in vitro*, and negative in bacterial reverse mutation assays and *in vivo* clastogenicity assays. More recently, a publication reported caffeic acid to be negative for gene mutation *in vivo* in rats in the comet assay and in the Pig-a test. Although the same study reported positive *in vivo* micronucleus results, at a high dose of 2,000 mg/kg/day provided on three consecutive days, this contradicts the negative results in multiple earlier *in vivo* micronucleus assays in rats and mice, and may be due to the high doses administered. Therefore, overall caffeic acid has a low potential for gene mutation and chromosomal aberration *in vivo.* Data on the sinapic acid and the surrogate ferulic acid are more limited and non-standard, but results are all negative for bacterial gene mutation, and SCE in mammalian cells. Despite the limitation in these data, EFSA did not raise a concern on the genotoxicity potential of these compounds.

Reproductive Toxicity (R) Score (H, M, or L): DG
Sinapic acid was assigned a score of Data Gap for reproductive toxicity based on a lack of data identified for this endpoint.

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

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Sinapic acid was assigned a score of Low for developmental toxicity based on a lack of developmental effects at oral doses up to 50 mg/kg/day in a study in rats with the surrogate cinnamic acid. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on limited data for a weak surrogate and the available study only tested up to 50 mg/kg/day.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2011, Bickers et al. 2005
  - *Oral:* *Surrogate: Cinnamic Acid (CAS #621-82-9/140-10-3):* In a non-GLP developmental toxicity study, pregnant female rats (14-15/dose) were administered the test substance at doses of 0, 5, and 50 mg/kg/day throughout pregnancy. There were no adverse effects reported on dams or offspring and maternal toxicity and developmental toxicity NOAELs of 50 mg/kg/day, the highest dose tested, were established. No further details were reported.

Endocrine Activity (E) Score (H, M, or L): DG
Sinapic acid was assigned a score of Data Gap for endocrine activity based on a lack of sufficient data identified for this endpoint. Predicted very weak reactivity toward estrogen receptor has uncertain toxicological significance.

- 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 2024b
  - ToxCast models predict sinapic acid to have very weak activity towards estrogen receptor agonism, antagonism, and binding (Appendix I).

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

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L
Sinapic acid was assigned a score of Low for acute toxicity based on oral LD_{50} values of 7,900 and 8,100 mg/kg in rats and mice, respectively, for the surrogate isoferulic acid, and oral and dermal LD_{50} values of >2,000 mg/kg in rats and >5,000 mg/kg in rabbits, respectively, for the surrogate cinnamic acid. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg (CPA 2018b). The confidence in the score is high as it is based on experimental data for a strong surrogate isoferulic acid.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- RTECS 2019
  - *Oral: <u>Surrogate: Isoferulic Acid (CAS #537-73-5):</u>* LD_{50} (rat, sex and strain not specified) = 7,900 mg/kg
  - *Oral: <u>Surrogate: Isoferulic Acid (CAS #537-73-5):</u>* LD_{50} (mouse, sex and strain not specified) = 8,100 mg/kg
- ECHA, CAS #140-10-3, 2024
  - *Oral: <u>Surrogate: Cinnamic Acid (CAS #140-10-3):</u>* LD_{50} (female Wistar rat) > 2,000 mg/kg (GLP, OECD Guideline 420) (Klimisch 1, reliable without restriction).
- Bickers et al. 2005
  - *Dermal: <u>Surrogate: Cinnamic Acid (CAS #140-10-3):</u>* LD_{50} (rabbits, sex and strain not reported) > 5,000 mg/kg.
- EFSA 2011
  - *Oral: <u>Surrogate: Cinnamic Acid (CAS #621-82-9):</u>* LD_{50} (rat, sex and strain not specified) = 3,570 µL/kg

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score (vH, H, M, or L): *M*
Sinapic acid was assigned a score of Moderate for systemic toxicity (single dose) based on its classification to GHS Category 3 with H335: may cause respiratory irritation by the majority of self-notifiers to the ECHA C&L Inventory. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 for respiratory irritation

(CPA 2018b). The confidence in the score is low as it is based on classification by self-notifiers with no supporting experimental data available.

- 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 C&L, CAS #530-59-6, 2024
    - A majority of the self-notifiers to the ECHA C&L Inventory (169/171 (98.8%)) classified sinapic acid GHS Category 3 with H335: may cause respiratory irritation.
- ECHA, CAS #140-10-3, 2024
    - *Oral: Surrogate: Cinnamic Acid (CAS #140-10-3):* In a GLP-compliant acute oral toxicity study conducted according to OECD Guideline 420, female Wistar rats (4/dose) were administered cinnamic acid (purity not reported) at 2,000 mg/kg in arachis oil via gavage. There were no mortalities, clinical signs of toxicity, adverse effects to body weight, or abnormalities at necropsy (Klimisch 1, reliable without restriction).

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

Sinapic acid was assigned a score of Low for systemic toxicity (repeated dose) based on the oral LOAEL of 406 mg/kg/day in a 10-week study in rats with the surrogate caffeic acid and the NOAEL of 2,000 mg/kg/day in a limited 4-week study in rats with the surrogate ferulic acid. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when the oral LOAEL is greater than 100 mg/kg/day for 90-day studies (CPA 2018b). The confidence in the score is low due to the limited reporting details and reliability of available studies.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- EFSA 2011, ECHA, CAS #1135-24-6, 2024
    - *Oral: Surrogate: Ferulic Acid (CAS #1135-24-6):* In a non-GLP subacute toxicity study male Fisher 344 rats (5/sex) were administered the test substance at doses of 0% and 2% in the diet (reported to be 0, and 2,000 mg/kg/day) for 4 weeks. A NOAEL of 2,000 mg/kg/day, the only dose tested, was established based on a lack of adverse effects. No further details were reported.
        - *ToxServices notes EFSA (2011) indicates this study is of limited quality as experimental details are insufficiently reported. Additionally, this study is reported in the ECHA REACH dossier with a Klimisch Score 4 (not assignable).*
- ILS 1998
    - *Oral: Surrogate: Caffeic Acid (CAS #331-39-5):* In a subacute study, male F344 rats (5/dose) were administered caffeic acid (>98% purity) in the diet at 2% (approximately 2,000 mg/kg/day[9]) for 4 weeks. Body and liver weights were not affected, however, treatment induced epithelial hyperplasia of the forestomach in all treated rats. No further details were available.
    - *Oral: Surrogate: Caffeic Acid (CAS #331-39-5):* In a subacute study, male Sprague-Dawley rats (10/dose) were administered caffeic acid (purity not reported) in the diet at 0.2 and 0.8% (estimated to be 40 and 60 mg/kg/day, respectively) for 6 weeks. There were no effects on food consumption, weight gain or final body weight, relative liver weight or plasma fatty acids composition, however, there was an increase in plasma and lipoprotein concentrations

[9] Based on food factor for male Fisher 344 rats in subchronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.1 kg feed/kg bw = 2,000 mg/kg/day

of alpha-tocopherol. The authors concluded caffeic acid demonstrated an antioxidant effect. No further details were available.

- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a subchronic study, female Balb/c mice (9-12/dose) were administered caffeic acid (purity not reported) in the diet at 0.2% (approximately 406 mg/kg/day[10]) for 10 weeks. There were no effects on body, liver, and intestine weights and there were no effects on glutathione S-transferase (GST) or cytochrome b5 and P-450 activity in the liver. However, aryl hydrocarbon hydroxylase (AHH) and UDP-glucuronosyl transferase (UDPGT) were reduced in the intestine. No further details were available.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a subchronic study, male F344 rats (10/dose) were administered caffeic acid (purity not reported) in the diet at 2% (approximately 2,000 mg/kg/day[11]) for 24 weeks. Treatment induced hyperplasia of the forestomach in all treated rats. No further details were available.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a subchronic study, male F344 rats (9/dose) were administered caffeic acid (>98% purity) in the diet at 2% (approximately 2,000 mg/kg/day[12]) for 24 weeks. Treatment induced papillary hyperplasia of the forestomach; 7/9 animals had mild basal cell hyperplasia and 1/9 animals had moderate basal cell hyperplasia. No further details were available.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a chronic study, male F344 rats (15/dose) were administered caffeic acid (>98% purity) in the diet at 1% (reported to be 160 mg/kg/day) for 51 weeks. Body weight was not affected by treatment but liver and kidney weights increased. Hyperplasia of the forestomach was reported in all treated rats. No further details were available.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a chronic study, male F344 rats (10/dose) were administered caffeic acid (>98% purity) in the diet at 2% (approximately 1,580 mg/kg/day[13]) for 48 weeks. There was moderate papillary hyperplasia of the forestomach in 20% of the treated animals and mild basal cell hyperplasia in 60% of animals. The authors concluded the papillary hyperplasia regressed after cessation of treatment but basal cell hyperplasia did not. No further details were available.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a chronic study, male F344 rats (30/dose) were administered caffeic acid (>98% purity) in the diet at 2% (approximately 1,580 mg/kg/day[14]) for 2 years. Treatment significantly induced hyperplasia of the kidney in 21/30 rats. No further details were reported.
- *Oral:* *Surrogate: Caffeic Acid (CAS #331-39-5):* In a chronic study, male F344/DuCrj rats (18/dose) were administered caffeic acid (purity not reported) in the diet at 2% (approximately 1,580 mg/kg/day[15]) for 2 years. Treatment significantly reduced body weights and increased relative liver weights. No further details were reported.

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[10] Based on food factor for female mice in subchronic study (TERA Undated): 0.2% = 2000 ppm = 2000 mg/kg feed * 0.203 kg feed/kg bw = 406 mg/kg/day

[11] Based on food factor for male Fisher 344 rats in subchronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.1 kg feed/kg bw = 2,000 mg/kg/day

[12] Based on food factor for male Fisher 344 rats in subchronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.1 kg feed/kg bw = 2,000 mg/kg/day

[13] Based on food factor for male Fisher 344 rats in chronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.079 kg feed/kg bw = 1,580 mg/kg/day

[14] Based on food factor for male Fisher 344 rats in chronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.079 kg feed/kg bw = 1,580 mg/kg/day

[15] Based on food factor for male Fisher 344 rats in chronic study (TERA Undated): 2% = 20,000 ppm = 20,000 mg/kg feed * 0.079 kg feed/kg bw = 1,580 mg/kg/day

- *Oral: <u>Surrogate: Caffeic Acid (CAS #331-39-5):</u>* In a subchronic study, male Syrian golden hamsters (15/dose) were administered caffeic acid (>98% purity) in the diet at 1% (approximately 948.5 mg/kg/day[16]) for 20 weeks. Treatment significantly increased incidences of mild (4/15) and moderate (10/15) hyperplasia of the forestomach. No further details were reported.
- Based on the weight of evidence, a score of Low was assigned. Only limited repeated dose toxicity study data were identified for sinapic acid and its surrogates. The surrogate caffeic acid induced hyperplasia of the forestomach and kidney at extremely high doses (≥ 1% in the diet) in subchronic and chronic studies in rats and hamsters. Administration of lower doses of caffeic acid in the diet did not result in evidence of forestomach or kidney hyperplasia in a 6-week study in rats (doses reported to be up to 60 mg/kg/day) or 10-week study in mice (approximately 406 mg/kg/day). The forestomach hyperplasia may be due to the irritating qualities of the surrogate caffeic acid. A 4-week study of limited quality with the surrogate ferulic acid reported no adverse effects following administration of doses up to 2% (2,000 mg/kg/day) in the diet in rats. Based on the LOAEL of 406 mg/kg/day in the 10-week study in rats with the surrogate caffeic acid and the NOAEL of 2,000 mg/kg/day in the limited 4-week study in rats with the surrogate ferulic acid, a score of Low was assigned.

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

Sinapic acid was assigned a score of Low for neurotoxicity (single dose) based on no signs of neurotoxicity in an acute oral toxicity study in rats with the surrogate cinnamic acid. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low as there were no specified neurotoxicity examinations and it is based on data for a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #140-10-3, 2024
  - *Oral: <u>Surrogate: Cinnamic Acid (CAS #140-10-3):</u>* In a GLP-compliant acute oral toxicity study conducted according to OECD Guideline 420, female Wistar rats (4/dose) were administered cinnamic acid (purity not reported) at 2,000 mg/kg in arachis oil via gavage. There were no mortalities, clinical signs of toxicity, or abnormalities at necropsy (Klimisch 1, reliable without restriction).

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

Sinapic acid was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of data identified for this endpoint.

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

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

Sinapic acid was assigned a score of Moderate for skin sensitization based on the presence of structural alerts for skin sensitization and mixed results from modeling programs. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when a GHS Category 1B classification is

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[16] Based on body weight and food consumption for male Syrian hamsters in subchronic study (U.S. EPA 1988): 1% = 10,000 ppm = 10,000 mg/kg feed * 0.0092 kg feed/day / 0.097 kg bw = 948.5 mg/kg/day

warranted and there is a low to moderate frequency of occurrence of sensitization reactions (CPA 2018b). The confidence in the score is low as it is based on modeling results and experimental data for a weak surrogate was negative.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #140-10-3, 2024
  - *In chemico: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was predicted to be negative for skin sensitization potential in a GLP-compliant Direct Peptide Reactivity Assay (DPRA) conducted according to OECD Guideline 442C. The mean cysteine and lysine peptide depletion values were -1.15 and -0.645, respectively, indicating cinnamic acid had no to minimal reactivity (Klimisch 1, reliable without restriction).
  - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was predicted to be negative for skin sensitization potential in a GLP-compliant ARE-Nrf2 Luciferase Test conducted according to OECD Guideline 442D. The Imax (concentration for induction of luciferase activity) values were 1.24 and 1.03 in the two replicates. As the Imax values were both less than 1.5 fold compared to the control, cinnamic acid had no response for luciferase induction (Klimisch 1, reliable without restriction).
  - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was predicted to be positive for skin sensitization potential in a GLP-compliant human cell line activation test (h-CLAT) assay conducted according to OECD Guideline 442E. The relative fluorescence intensity (RFI) of CD86 and CD54 were >150% and >200%, respectively, in two replicates indicating cinnamic acid activated THP-1 cells under the conditions of this assay (Klimisch 1, reliable without restriction).
  - *Surrogate: Cinnamic Acid (CAS #140-10-3): Based on negative results in two of three validated test methods for skin sensitization (OECD Guidelines 442C, 442D, and 442E), the surrogate cinnamic acid is predicted to be non-sensitizing.*
- Payne and Walsh 1994
  - Sinapic acid is predicted to be a skin sensitizer based on the presence of a known structural alert identified by Payne and Walsh (1994) – Michael addition electrophiles and precursors (Appendix J). ToxServices notes that the surrogate cinnamic acid also has the same structural alert.
- OECD 2023
  - Sinapic acid is predicted to not be a skin sensitizer using the OECD Toolbox model using the read-across methodology. Only one read-across chemical was selected, which does not share the structural alert of Michael acceptor as the target chemical (see Appendix K). Therefore, the reliability of this prediction is questionable.
- Toxtree 2018
  - Sinapic acid is predicted to be a skin sensitizer using the Toxtree model using decision tree methodology as it has been identified as a substrate for one of the 5 electrophilic mechanisms known to produce a skin sensitization reaction – Michael acceptor (see Appendix L). ToxServices notes that the surrogate cinnamic acid also has the same structural alert (Appendix L).
- VEGA 2023
  - ToxServices predicted the skin sensitization potential of sinapic acid using the following three VEGA v1.2.3 models: CAESAR v2.1.7, IRFMN-JRC v1.0.1, and NCSTOX v1.0.1.
    - CAESAR v2.1.7 model predicts sinapic acid to be a **sensitizer** with high confidence. The ADI is **0.918**, indicating that the prediction is reliable (Appendix M).

- IRFMN-JRC v1.0.1model predicts sinapic acid to be a sensitizer with moderate confidence. The ADI is 0.651, indicating that the prediction is not reliable (Appendix M).
- NCSTOX v1.0.1 model predicts sinapic acid to be a sensitizer with moderate confidence. The ADI is 0.649, indicating that the prediction is not reliable (Appendix M).

- LabMol 2020
  - The LabMol Pred-Skin platform predicts sinapic acid is not a skin sensitizer based on the Bayesian outcome prediction with high confiability. Pred-Skin estimates confiability (or degree of confidence in the prediction) by calculating the ratio of predictions made by internal models (trees in the random forest statistical model), the AD, and maps for the predicted fragment contribution of the structure (Borba et al. 2021). The Bayesian outcome is based on positive predictions from the DPRA and LLNA models, with a confiability scores of 90.4% and 99.9%, respectively, and negative predictions with the KeratinoSens, h-CLAT, and HRIPT/HMT models, with confiability scores of 94.6%, 57.7%, and 80.3%, respectively. It may be noted sinapic acid was in domain for all models except LLNA (Appendix N).
- Based on the weight of evidence, a score of Moderate was assigned. Sinapic acid contain structural alerts for skin sensitization as identified by Payne and Walsh (1994) and Toxtree; however, the surrogate cinnamic acid also has the same structural alert. The surrogate cinnamic acid was predicted to be non-sensitizing based on negative results in two of three validated test methods for skin sensitization (OECD Guidelines 442C, 442D, and 442E). Only one of the three models in VEGA produced a reliable prediction for skin sensitization for sinapic acid, and it was positive. In contrast, OECD Toolbox predicted sinapic acid to not be a skin sensitizer using the read-across methodology (with limited reliability), and LabMol also predicts sinapic acid is not a skin sensitizer with high confidence. Based on the presence of structural alerts and mixed results from modeling programs, a skin sensitization concern for sinapic acid cannot be ruled out. Therefore, ToxServices assigned a score of Moderate for this endpoint.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): DG
Sinapic acid was assigned a score of Data Gap for respiratory sensitization based on insufficient data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2023
  - Sinapic acid does not contain any structural alerts for respiratory sensitization (Appendix O).
- Toxtree 2018
  - Sinapic acid is identified as a substrate for one of the 5 electrophilic mechanisms known to produce a skin sensitization reaction – Michael acceptor (see Appendix L).
- COEH 2024
  - Sinapic acid has a predicted occupational asthma hazard index of 0.0142, indicating a low hazard; although it may still be hazardous (Appendix P).
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of sinapic acid according to ECHA's guideline (ECHA 2017), which 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). Sinapic acid does not contain any structural alerts, but may be a skin sensitizer based on mixed data. According to the ECHA guidance, the positive skin sensitization results in animals and lack of structural alerts and evidence of respiratory sensitization indicate that there is insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Centre for Occupational and Environmental Health's (COEH's) Chemical Asthma Hazard Assessment Program as well as Toxtree (skin sensitization alerts) to predict whether a screened substance has the potential to cause respiratory sensitization. Golden et al. (2021) compared these (Q)SAR models and found that Toxtree had superior performance for some structural alerts (such as Michael addition) and some categories of well-characterized skin sensitizers, while the COEH model had high accuracy in identifying sensitizers that lacked identified skin sensitization structural features. Sinapic acid has the Michael addition alert from Toxtree, but is predicted to have a low occupational asthma hazard by COEH. Therefore, data are still inconsistent. Due to the positive predictions for skin sensitization and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Data Gap was assigned.

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

Sinapic acid was assigned a score of High for skin irritation/corrosivity based on its classification to GHS Category 2 for skin irritation by the majority of the self-notifiers to the ECHA C&L Inventory. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are classified to GHS Category 2 for skin irritation (CPA 2018b). The confidence in the score is low as it is based on classification by self-notifiers and data for the weak surrogate cinnamic acid indicates it does not have skin irritation potential.

- 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 C&L, CAS #530-59-6, 2024
    - The majority of the self-notifiers to the ECHA C&L Inventory (170/171 (99.4%)) classified sinapic acid to GHS Category 2 with H315: causes skin irritation.
- ECHA, CAS #140-10-3, 2024
    - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was found to be non-corrosive to skin in a GLP-compliant *in vitro* Reconstructed Human Epidermis (RHE) test conducted according to OECD Guideline 431. Cells were exposed to 25 mg unchanged test substance (purity not reported) for 3 or 60 minutes. The mean tissue viability was 96.1% after the 3 minutes exposure and 94% after the 60 minutes exposure (Klimisch 1, reliable without restriction).
    - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was found to be a non-irritant in a GLP-compliant *in vitro* EPISKIN™ reconstructed human epidermis model test conducted according to OECD Guideline 439. Cells were exposed to 10 mg unchanged test substance (purity not reported) for 15 minutes. The mean tissue viability was 81.9% after the 15-minute exposure (Klimisch 1, reliable without restriction).

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

Sinapic acid was assigned a score of High for eye irritation/corrosivity based on its classification to GHS Category 2A for eye irritation with H319 by the majority of the self-notifiers to the ECHA C&L

Inventory. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A with H319 for ocular irritation (CPA 2018b). The confidence in the score is low as it is based on classification by self-notifiers with no available experimental data suitable for classification.

- 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, C&L Inventory, 2024
  - The majority of the self-notifiers to the ECHA C&L Inventory (170/171 (99.4%)) classified sinapic acid GHS Category 2 with H3195: causes serious eye irritation.
- ECHA, CAS #140-10-3, 2024
  - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was not corrosive to the eye in a GLP-compliant Bovine Corneal Opacity and Permeability (BCOP) test conducted according to OECD Guideline 437; however, no prediction on irritation potential could be made. Excised bovine corneas were exposed to 0.1970 g unchanged test substance (99% purity) for 240 minutes. The mean *in vitro* irritation score was 36.2 (Klimisch 1, reliable without restriction).
  - *In vitro: Surrogate: Cinnamic Acid (CAS #140-10-3):* Cinnamic acid was not corrosive to the eye in a GLP-compliant Isolated Chicken Eye (ICE) test conducted according to OECD Guideline 438; however, no prediction on irritation potential could be made. Treated eyes were exposed to 0.03 g unchanged test substance (purity not reported) for 10 seconds. The maximum mean corneal opacity score was 2, the mean fluorescein retention score was 0.7, and the mean percent corneal swelling score was 12.27 (Klimisch 1, reliable without restriction).

Ecotoxicity (Ecotox)

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

Sinapic acid was assigned a score of Moderate for acute aquatic toxicity based on an EC_{50} of 19 mg/L in aquatic plants for the surrogate cinnamic acid. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when acute aquatic toxicity values are > 10 to 100 mg/L (CPA 2018b). The confidence in the score is low as it is based on experimental data for a weak surrogate and modeling for the target compound suggest a lower order of toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #140-10-3, 2024
  - *Surrogate: Cinnamic Acid (CAS #140-10-3):* 48-hour mobility EC_{50} (*Daphnia magna,* daphnia) = 32 mg/L (measured) (GLP, OECD Guideline 202) (Klimisch 1, reliable without restriction)
  - *Surrogate: Cinnamic Acid (CAS #140-10-3):* 72-hour EC_{50} (*Pseudokirchnerella subcapitata,* green algae) = 19 mg/L (growth rate, measured) and 14 mg/L (yield, measured) (GLP, OECD Guideline 201) (Klimisch 1, reliable without restriction)
- U.S. EPA 2022
  - Sinapic acid belongs to the neutral organics and phenols ECOSAR chemical classes. The most conservative predicted acute E/LC_{50} values are 1,020 mg/L in fish (96h), 313 mg/L in daphnia (48h), and 1,250 mg/L in green algae (96h) (Appendix Q).
- Based on the weight of evidence, a score of Moderate was assigned. Modeling on sinapic acid

indicate L/EC_{50} values > 100 mg/L and a score of Low, while measured data on the weak surrogate cinnamic acid support a Moderate score. ToxServices also performed modeling on the surrogate cinnamic acid, and the predicted L/EC_{50} values are also > 100 mg/L, supporting a Low score (data not shown). Therefore, the ECOSAR modeling results for these chemicals may not be sufficiently conservative, and ToxServices relied on measured surrogate data to score this endpoint.

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
Sinapic acid was assigned a score of Moderate for chronic aquatic toxicity based on a NOEC of 9 mg/L in aquatic plants for the surrogate cinnamic acid. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are >1 to 10 mg/L (CPA 2018b). The confidence in the score is low as it is based on experimental data for a weak surrogate for only one trophic level, and modeling for the target compound suggest a lower order of toxicity.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA, CAS #140-10-3, 2024
  - <u>*Surrogate: Cinnamic Acid (CAS #140-10-3):*</u> 72-hour NOEC (*P. subcapitata,* green algae) = 9 mg/L (growth rate and yield, measured) (GLP, OECD Guideline 201) (Klimisch 1, reliable without restriction)
- U.S. EPA 2022
  - Sinapic acid belongs to the neutral organics and phenols ECOSAR chemical classes. The most conservative predicted chronic values (ChVs) are 93.3 mg/L in fish, 30 mg/L in daphnia, and 154 mg/L in green algae (Appendix Q).

<u>Environmental Fate (Fate)</u>

Persistence (P) Score (vH, H, M, L, or vL): *vL*
Sinapic acid was assigned a score of Very Low for persistence based on being predicted to be readily biodegradable, with the major environmental compartment being soil. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil is the dominant compartment and they meet the 10-day window in biodegradability studies (i.e., being readily biodegradable) (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that sinapic acid is expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 75.5% will partition to soil with a half-life of 30 days, 24.5% will partition to water with a half-life of 15 days, and 0.0749% will partition to sediment with a half-life of 135 days (Appendix R).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Sinapic acid was assigned a score of Very Low for bioaccumulation based on an estimated BCF of 3.162 and an estimated log K_{ow} of 1.24. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is less than 4 and the BCF is less than 100 (CPA 2018b). The confidence in the score is low as it is based on modeling.

- Authoritative and Screening Lists

    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2017
    - BCFBAF predicts a BCF of 3.162 L/kg wet-wt using the regression based model based on a modeled log K_{ow} of 1.24, and a BCF of 2.191 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix R).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Sinapic acid was assigned a score of Low for reactivity based on stability and physical hazard ratings of 0 from NFPA and HMIS reported on a safety data sheet. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and negative and they are 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.
- Santa Cruz Biotechnology 2016
    - An SDS for sinapic acid (>98% purity) has a stability rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and physical hazard rating of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").

Flammability (F) Score (vH, H, M, or L): *L*
Sinapic acid was assigned a score of Low for flammability based on flammability ratings of 0 from NFPA and HMIS reported on a safety data sheet. 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 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.
- Santa Cruz Biotechnology 2016
    - An SDS for sinapic acid (>98% purity) reports a flammability score of 0 under HMIS ("Materials that must be preheated before ignition will occur. Includes liquids, solids and semi solids having a flash point above 200°F (93°C)") and NFPA ("Materials that require considerable preheating, under all ambient temperature conditions, before ignition and combustion can occur (e.g. mineral oil). Includes some finely divided suspended solids that do not require heating before ignition can occur. Flash point at or above 93°C (200°F)").

Use of New Approach Methodologies (NAMs)[17] in the Assessment, Including Uncertainty Analyses of Input and Output

[17] 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).

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for carcinogenicity, skin sensitization, respiratory sensitization, aquatic toxicity, persistence, and bioaccumulation; and *in vitro* assays for genotoxicity, skin sensitization, skin irritation, and eye irritation. 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 4, Type I (input data) uncertainties in sinapic acid's NAMs dataset include lack of or limited experimental data for carcinogenicity, skin sensitization, respiratory sensitization, skin irritation, eye irritation, aquatic toxicity, persistence, and bioaccumulation, and lack of established test methods for respiratory sensitization. Sinapic acid's Type II (extrapolation output) uncertainties include limitation of *in vitro* genotoxicity assays in mimicking *in vivo* metabolism and their focusing on one or only a few types of genotoxicity events, the limitation of Toxtree and OECD Toolbox in identifying structural alerts without defining the applicability domains, the inability of individual and/or combination of *in vitro* skin and/or eye irritation assays to determine all GHS categories, inability of *in vitro* skin sensitization assays to identify pro- and pre-haptens, and the limitations in the examination of structural alerts for respiratory sensitization evaluation that does not account for non-immunologic mechanisms of respiratory sensitization. Some of sinapic acid's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Carcinogenicity:** Insufficient experimental data are available. **Skin irritation**: No *in vivo* studies are available. **Eye irritation**: No *in vivo* studies are available. **Skin sensitization**: No *in vivo* studies are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Acute and chronic aquatic toxicity**: Only limited experimental data are available for a weak surrogate. **Persistence**: No experimental data are available. **Bioaccumulation**: No experimental data are available.
Type II Uncertainty: Extrapolation Output	**Carcinogenicity**: Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). The one model in VEGA that produced a reliable (i.e., Global AD index >0.7) prediction, the read-across chemicals used in this model has additional/fewer functional groups than the target compound, limiting the confidence of the prediction from this model. **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[18]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e., the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[19] The *in vitro* chromosome aberration assay (OECD Guideline 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[20]. The *in vitro* SCE assay (as defined in OECD Guideline 479, a guideline deleted in 2014) detects reciprocal exchange of DNA without providing the underlying mechanism of action[21]. **Skin sensitization:** The *in silico* and *in vitro* assays evaluating key events in the skin sensitization adverse outcome pathway (AOP) don't typically include metabolism or abiotic transformation to address chemicals that are pro-haptens or pre-haptens, respectively. Further, each test has their applicable domain such as limitations in test substance solubility or log K_{ow}.[22] Toxtree only identifies structural alerts (SAs), and no applicability domain can be defined (Toxtree 2018). **Skin irritation**: The OECD Guideline 431 test is only used to identify corrosive substances (GHS Category 1)[23]; and OECD Guideline 439 test is only used to identify irritating substances (GHS Category 2) and non-irritating substances (no category), and does not allow the classification as a mild skin irritant (GHS Category 3)[24]. **Eye irritation**: The BCOP (OECD Guideline 437) test is not recommended for identifying GHS Category 2A or 2B irritants[25]. The OECD Guideline 438 test method could not be used to identify chemicals that are irritating to the eyes (i.e., GHS Categories 2A and 2B). As it uses enucleated chicken eyes, it is not a true non-animal test[26]. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains.

[18] https://www.oecd-ilibrary.org/docserver/9789264071247-en.pdf?expires=1614097593&id=id&accname=guest&checksum=89925F80B9F4BD2FFC6E90F94A0EE427
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[25] https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1614095760&id=id&accname=guest&checksum=1613168F64BDB3558225572BDD75FC8D
[26] https://www.oecd-ilibrary.org/docserver/9789264203860-en.pdf?expires=1657729772&id=id&accname=guest&checksum=05C34780720727D92856887CAD43C8DD

	Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.

Endpoint	NAMs Data Available and Evaluated? (Y/N)	Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)
Carcinogenicity	Y	*In silico* modeling: VEGA/Toxtree/OncoLogic™/Danish QSAR
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay/*in vitro* SCE assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	N	
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	Y	*In silico* modeling: VEGA/Payne and Walsh (1994) structural alerts/ VEGA/ Toxtree/ OECD Toolbox/ LabMol *In vitro* data: OECD Guideline 442C, 442D, and 442E
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/COEH/Toxtree
Skin irritation	Y	*In vitro* tests: OECD Guideline 431 and 439 Tests
Eye irritation	Y	*In vitro* tests: OECD Guideline 437 and 438 Tests
Acute aquatic toxicity	Y	*In silico* modeling: ECOSAR
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Sinapic Acid (CAS #530-59-6)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

Table 2: Chemical Details

			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
									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	Sinapic Acid	530-59-6	*M*	L	DG	*L*	DG	L	*M*	*L*	*L*	DG	*M*	DG	*H*	*H*	*M*	*M*	*vL*	*vL*	*L*	*L*

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Sinapic Acid	2

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

Table 6

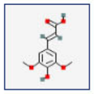
Chemical Name	Final GreenScreen® Benchmark Score
Sinapic Acid	2

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 Sinapic Acid (CAS #530-59-6)



530-59-6
SINAPIC ACID
ALSO CALLED (2E)-3-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propenoic acid, (2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)acryl...
View all synonyms (41)

Share Profile

Hazards Properties Functional Uses Resources

All Hazards View

Show PubMed Results Request Assessment Add to Comparison

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

Hazard Lists

Download Lists

ENDPOINT	HAZARD LEVEL	GREENSCREEN®	LIST NAME	HAZARD DESCRIPTION	OTHER LISTS
Skin Sensitization	pC	NoGS	DK-EPA - Danish Advisory List	Skin Sens. 1 - May cause an allergic skin reaction (modeled)	

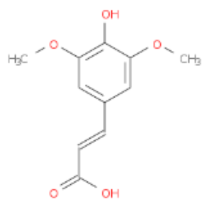
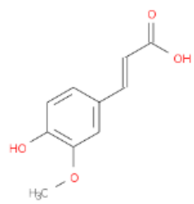
APPENDIX D: ChemMine Tanimoto Coefficients between Sinapic Acid (CAS #530-59-6) and Surrogates

Compound Similarity

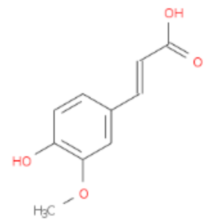
6 compound(s) in workbench

Select two compounds to compare from the grid below.

Selected Compounds

unspecified_084751	unspecified_786031
	
remove	remove

AP Tanimoto: 0.598485
MCS Tanimoto: 0.8750
MCS Size: 14
MCS Min: 1.0000
MCS Max: 0.8750
SMILES:
c1(c(ccc(/C=C/C(=O)O)c1)O)OC
unspecified_084751

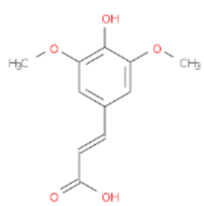
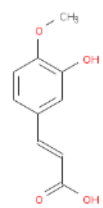


Compound Similarity

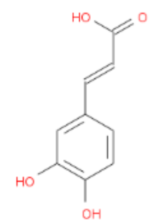
6 compound(s) in workbench

Select two compounds to compare from the grid below.

Selected Compounds

unspecified_084751	unspecified_420875
	
remove	remove

AP Tanimoto: 0.425676
MCS Tanimoto: 0.7647
MCS Size: 13
MCS Min: 0.9286
MCS Max: 0.8125
SMILES:
c1(c(cc(cc1)/C=C/C(=O)O)O)O
unspecified_084751

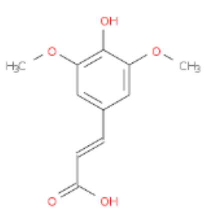
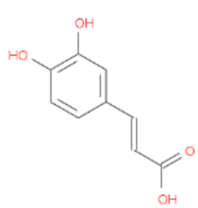


Compound Similarity

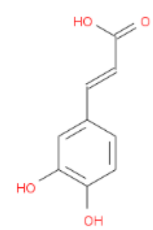
6 compound(s) in workbench

Select two compounds to compare from the grid below.

Selected Compounds

unspecified_084751	unspecified_937251
	
remove	remove

AP Tanimoto: 0.414286
MCS Tanimoto: 0.8125
MCS Size: 13
MCS Min: 1.0000
MCS Max: 0.8125
SMILES:
c1(c(cc(cc1)/C=C/C(=O)O)O)O
unspecified_084751



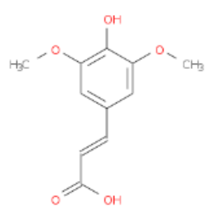
Compound Similarity

6 compound(s) in workbench

Select two compounds to compare from the grid below.

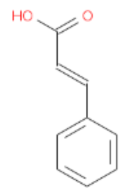
Selected Compounds

unspecified_084751



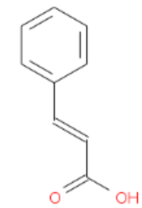
remove

unspecified_053286



remove

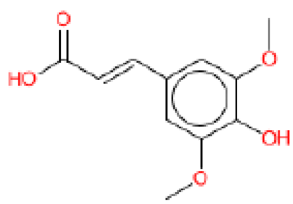
AP Tanimoto: 0.232394
MCS Tanimoto: 0.6875
MCS Size: 11
MCS Min: 1.0000
MCS Max: 0.6875
SMILES:
c1(ccccc1)/C=C/C(=O)O
unspecified_084751



APPENDIX E: VEGA Carcinogenicity Results for Sinapic Acid (CAS #530-59-6)

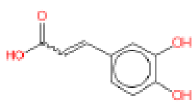
1. Prediction Summary

Prediction for compound Molecule 0 -

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

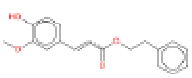
Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Carcinogen activity: Carcinogen
P(Carcinogen): 0.538
P(NON-Carcinogen): 0.462
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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



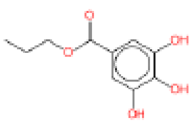
Compound #1

CAS: 331-39-5
Dataset id:121 (Test Set)
SMILES: O=C(O)C=Cc1ccc(O)c(O)c1
Similarity: 0.908
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



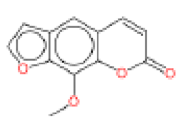
Compound #2

CAS: 71835-85-3
Dataset id:649 (Training Set)
SMILES: O=C(OCCc1ccccc1)C=Cc2ccc(O)c(OC)c2
Similarity: 0.839
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



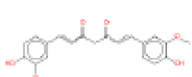
Compound #3

CAS: 121-79-9
Dataset id:673 (Training Set)
SMILES: O=C(OCCC)c1cc(O)c(O)c(O)c1
Similarity: 0.821
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



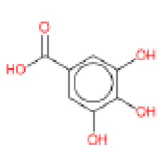
Compound #4

CAS: 298-81-7
Dataset id:441 (Training Set)
SMILES: O=C1Oc2c(OC)c3occc3(cc2(C=C1))
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : Carcinogen



Compound #5

CAS: 458-37-7
Dataset id:788 (Training Set)
SMILES: O=C(C=Cc1ccc(O)c(OC)c1)CC(=O)C=Cc2ccc(O)c(OC)c2
Similarity: 0.812
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen



Compound #6

CAS: 149-91-7
Dataset id:344 (Training Set)
SMILES: O=C(O)c1cc(O)c(O)c(O)c1
Similarity: 0.806
Experimental value : NON-Carcinogen
Predicted value : NON-Carcinogen

3.2 Applicability Domain:

Measured Applicability Domain Scores

✗	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.869 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✗	Accuracy of prediction for similar molecules Accuracy index = 0.477 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
⚠	Concordance for similar molecules Concordance index = 0.523 Explanation: some similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..
✗	Model class assignment reliability Pos/Non-Pos difference = 0.077 Explanation: model class assignment is uncertain..
⚠	Neural map neurons concordance Neurons concordance = 0.75 Explanation: predicted value disagrees with experimental values of training set compounds laying in the same neuron..

Symbols explanation:

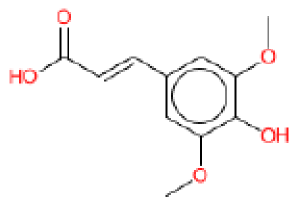
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

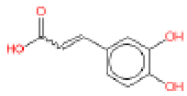
Prediction for compound Molecule 0 -

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

Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Carcinogen activity: NON-Carcinogen
Structural Alerts: -
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

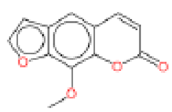
3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



Compound #1

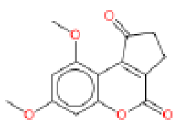
CAS: 331-39-5
Dataset id:813 (Training Set)
SMILES: O=C(O)C=Cc1ccc(O)c(O)c1
Similarity: 0.908
Experimental value : Carcinogen
Predicted value : NON-Carcinogen



Compound #2

CAS: 298-81-7
Dataset id:610 (Training Set)
SMILES: O=C1Oc2c(OC)c3occc3(cc2(C=C1))
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : Carcinogen

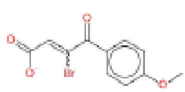
Alerts (not found also in the target): SA30 Coumarins and Furocoumarins



Compound #3

CAS: 1150-42-1
Dataset id:866 (Training Set)
SMILES: O=C2Oc1cc(OC)cc(OC)c1C=3C(=O)CCC2=3
Similarity: 0.803
Experimental value : Carcinogen
Predicted value : Carcinogen

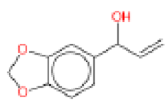
Alerts (not found also in the target): SA10 alfa, beta unsaturated carbonyls; SA30 Coumarins and Furocoumarins



Compound #4

CAS: 21739-91-3
Dataset id:46 (Training Set)
SMILES: O=C([O-])C=C(C(=O)c1ccc(OC)cc1)Br
Similarity: 0.794
Experimental value : Carcinogen
Predicted value : Carcinogen

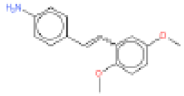
Alerts (not found also in the target): SA10 alfa, beta unsaturated carbonyls; SA38 Alkenylbenzenes



Compound #5

CAS: 5208-87-7
Dataset id:427 (Training Set)
SMILES: OC(C=C)c1ccc2OCOc2(c1)
Similarity: 0.78
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA38 Alkenylbenzenes; SA54 1,3-Benzodioxoles



Compound #6

CAS: 5803-51-0
Dataset id:865 (Training Set)
SMILES: O(c2ccc(OC)c(C=Cc1ccc(N)cc1)c2)C
Similarity: 0.779
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): SA28 Primary aromatic amine, hydroxyl amine and its derived esters (with restrictions)

3.2 Applicability Domain:
Measured Applicability Domain Scores

✗	Global AD Index AD index = 0 Explanation: The predicted compound is outside the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.857 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✗	Accuracy of prediction for similar molecules Accuracy index = 0.47 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✗	Concordance for similar molecules Concordance index = 0 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

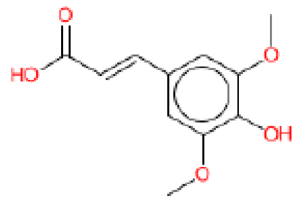
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

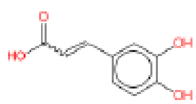
1. Prediction Summary

Prediction for compound Molecule 0 -

	Prediction: Reliability: Prediction is Possible NON-Carcinogen, but the result shows some critical aspects, which require to be checked: - Accuracy of prediction for similar molecules found in the training set is not optimal - similar molecules found in the training set have experimental values that disagree with the predicted value

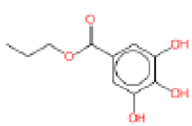
Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Carcinogenic activity: Possible NON-Carcinogen
No. alerts for carcinogenicity: 0
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



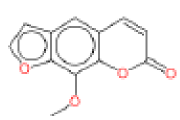
Compound #1

CAS: 331-39-5
Dataset id:613 (Training Set)
SMILES: O=C(O)C=Cc1ccc(O)c(O)c1
Similarity: 0.908
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #2

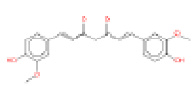
CAS: 121-79-9
Dataset id:976 (Training Set)
SMILES: O=C(OCCC)c1cc(O)c(O)c(O)c1
Similarity: 0.821
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

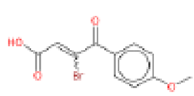
CAS: 298-81-7
Dataset id:507 (Training Set)
SMILES: O=C1Oc2c(OC)c3occc3(cc2(C=C1))
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 2



Compound #4

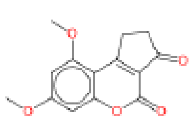
CAS: 8024-37-1
Dataset id:985 (Training Set)
SMILES: O=C(C=Cc1ccc(O)c(OC)c1)CC(=O)C=Cc2ccc(O)c(OC)c2
Similarity: 0.812
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #5

CAS: 21739-91-3
Dataset id:37 (Training Set)
SMILES: O=C(O)C=C(C(=O)c1ccc(OC)cc1)Br
Similarity: 0.809
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 16; Carcinogenity alert no. 37



Compound #6

CAS: 1150-42-1
Dataset id:770 (Training Set)
SMILES: O=C2Oc1cc(OC)cc(OC)c1C3=C2C(=O)CC3
Similarity: 0.803
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 37

3.2 Applicability Domain:
Measured Applicability Domain Scores

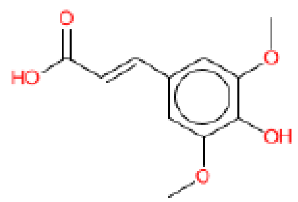
⚠	Global AD Index AD index = 0.618 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.843 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
⚠	Accuracy of prediction for similar molecules Accuracy index = 0.64 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
✖	Concordance for similar molecules Concordance index = 0.32 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

1. Prediction Summary

Prediction for compound Molecule 0 -



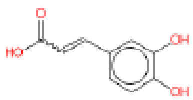
Prediction: Reliability:

Prediction is Carcinogen, but the result shows some critical aspects, which require to be checked:
- Accuracy of prediction for similar molecules found in the training set is not optimal
- similar molecules found in the training set have experimental values that disagree with the predicted value

The following relevant fragments have been found: Carcinogenity alert no. 17

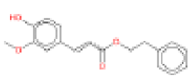
Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Carcinogenic activity: Carcinogen
No. alerts for carcinogenicity: 1
Structural Alerts: Carcinogenity alert no. 17
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

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



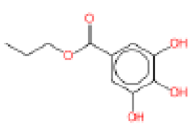
Compound #1

CAS: 331-39-5
Dataset id:121 (Test Set)
SMILES: O=C(O)C=Cc1ccc(O)c(O)c1
Similarity: 0.908
Experimental value : Carcinogen
Predicted value : Possible NON-Carcinogen



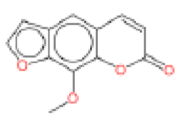
Compound #2

CAS: 71835-85-3
Dataset id:649 (Training Set)
SMILES: O=C(OCCc1ccccc1)C=Cc2ccc(O)c(OC)c2
Similarity: 0.839
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #3

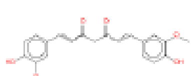
CAS: 121-79-9
Dataset id:673 (Training Set)
SMILES: O=C(OCCC)c1cc(O)c(O)c(O)c1
Similarity: 0.821
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #4

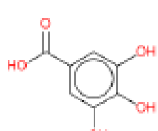
CAS: 298-81-7
Dataset id:441 (Training Set)
SMILES: O=C1Oc2c(OC)c3occc3(cc2(C=C1))
Similarity: 0.819
Experimental value : Carcinogen
Predicted value : Carcinogen

Alerts (not found also in the target): Carcinogenity alert no. 117



Compound #5

CAS: 458-37-7
Dataset id:788 (Training Set)
SMILES: O=C(C=Cc1ccc(O)c(OC)c1)CC(=O)C=Cc2ccc(O)c(OC)c2
Similarity: 0.812
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen



Compound #6

CAS: 149-91-7
Dataset id:344 (Training Set)
SMILES: O=C(O)c1cc(O)c(O)c(O)c1
Similarity: 0.806
Experimental value : NON-Carcinogen
Predicted value : Possible NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index AD index = 0.638 Explanation: The predicted compound could be out of the Applicability Domain of the model.
Similar molecules with known experimental value Similarity index = 0.85 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
Accuracy of prediction for similar molecules Accuracy index = 0.643 Explanation: Accuracy of prediction for similar molecules found in the training set is not optimal..
Concordance for similar molecules Concordance index = 0.357 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

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

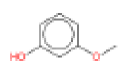
The feature has a bad assessment, model is not reliable regarding this aspect.

4.1 Reasoning:

Relevant Chemical Fragments and Moieties

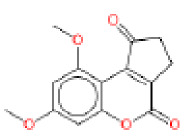
(Molecule 0) Reasoning on fragments/structural alerts :.

Fragment found: Carcinogenity alert no. 17



Structural alert for carcinogenity defined by the SMARTS: COc1cccc(O)c1

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

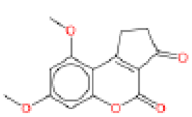


CAS: 1150-37-4
Dataset id:258 (Training Set)
SMILES: O=C2Oc1cc(OC)cc(OC)c1C=3C(=O)CCC2=3
Similarity: 0.803

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 17

Alerts (not found also in the target): Carcinogenity alert no. 18; Carcinogenity alert no. 76; Carcinogenity alert no. 77

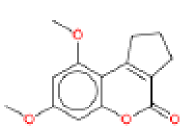


CAS: 1150-42-1
Dataset id:259 (Training Set)
SMILES: O=C2Oc1cc(OC)cc(OC)c1C3=C2C(=O)CC3
Similarity: 0.803

Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 17

Alerts (not found also in the target): Carcinogenity alert no. 18; Carcinogenity alert no. 76; Carcinogenity alert no. 77



CAS: 1146-71-0
Dataset id:257 (Training Set)
SMILES: O=C2Oc1cc(OC)cc(OC)c1C3=C2CCC3
Similarity: 0.795

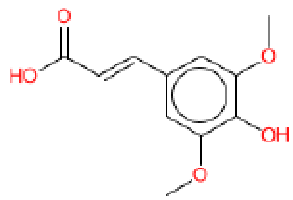
Experimental value : NON-Carcinogen
Predicted value : Carcinogen

Alerts (found also in the target): Carcinogenity alert no. 17

Alerts (not found also in the target): Carcinogenity alert no. 18; Carcinogenity alert no. 76; Carcinogenity alert no. 77

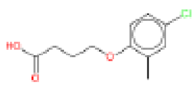
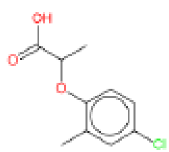
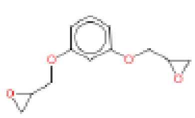
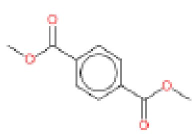
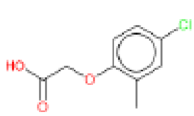
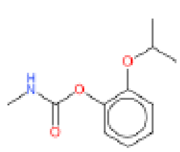
1. Prediction Summary

Prediction for compound Molecule 0 -

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

Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Oral Carcinogenic class: NON-Carcinogen
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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

	Compound #1 CAS: 94-81-5 Dataset id:559 (Test Set) SMILES: O=C(O)CCCOc1ccc(cc1C)Cl Similarity: 0.776 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #2 CAS: 93-65-2 Dataset id:560 (Training Set) SMILES: O=C(O)C(Oc1ccc(cc1C)Cl)C Similarity: 0.77 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #3 CAS: 101-90-6 Dataset id:118 (Training Set) SMILES: O(c2cccc(OCC1OC1)c2)CC3OC3 Similarity: 0.769 Experimental value : Carcinogen Predicted value : Carcinogen
	Compound #4 CAS: 120-61-6 Dataset id:468 (Training Set) SMILES: O=C(OC)c1ccc(cc1)C(=O)OC Similarity: 0.767 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #5 CAS: 94-74-6 Dataset id:558 (Training Set) SMILES: O=C(O)COc1ccc(cc1C)Cl Similarity: 0.767 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #6 CAS: 114-26-1 Dataset id:633 (Training Set) SMILES: O=C(Oc1ccccc1(OC(C)C))NC Similarity: 0.764 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index AD index = 0.879 Explanation: The predicted compound is into the Applicability Domain of the model.
Similar molecules with known experimental value Similarity index = 0.773 Explanation: Only moderately similar compounds with known experimental value in the training set have been found..
Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

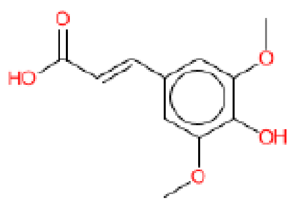
The feature has a good assessment, model is reliable regarding this aspect.

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

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

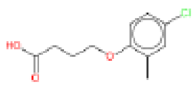
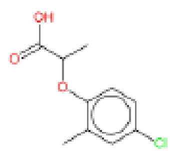
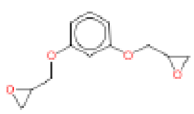
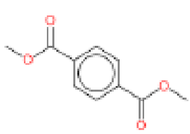
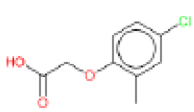
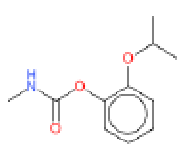
1. Prediction Summary

Prediction for compound Molecule 0 -

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

Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted Inhalation Carcinogenic class: Carcinogen
Reliability: The predicted compound is outside the Applicability Domain of the model
Remarks:
none

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

	Compound #1 CAS: 94-81-5 Dataset id:538 (Training Set) SMILES: O=C(O)CCCOc1ccc(cc1C)Cl Similarity: 0.776 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #2 CAS: 93-65-2 Dataset id:539 (Training Set) SMILES: O=C(O)C(Oc1ccc(cc1C)Cl)C Similarity: 0.77 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #3 CAS: 101-90-6 Dataset id:98 (Training Set) SMILES: O(c2cccc(OCC1OC1)c2)CC3OC3 Similarity: 0.769 Experimental value : Carcinogen Predicted value : Carcinogen
	Compound #4 CAS: 120-61-6 Dataset id:439 (Training Set) SMILES: O=C(OC)c1ccc(cc1)C(=O)OC Similarity: 0.767 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #5 CAS: 94-74-6 Dataset id:537 (Training Set) SMILES: O=C(O)COc1ccc(cc1C)Cl Similarity: 0.767 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen
	Compound #6 CAS: 114-26-1 Dataset id:619 (Training Set) SMILES: O=C(Oc1ccccc1(OC(C)C))NC Similarity: 0.764 Experimental value : NON-Carcinogen Predicted value : NON-Carcinogen

3.2 Applicability Domain:

Measured Applicability Domain Scores

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

Similar molecules with known experimental value
Similarity index = 0.773
Explanation: Only moderately similar compounds with known experimental value in the training set have been found..

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

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

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

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

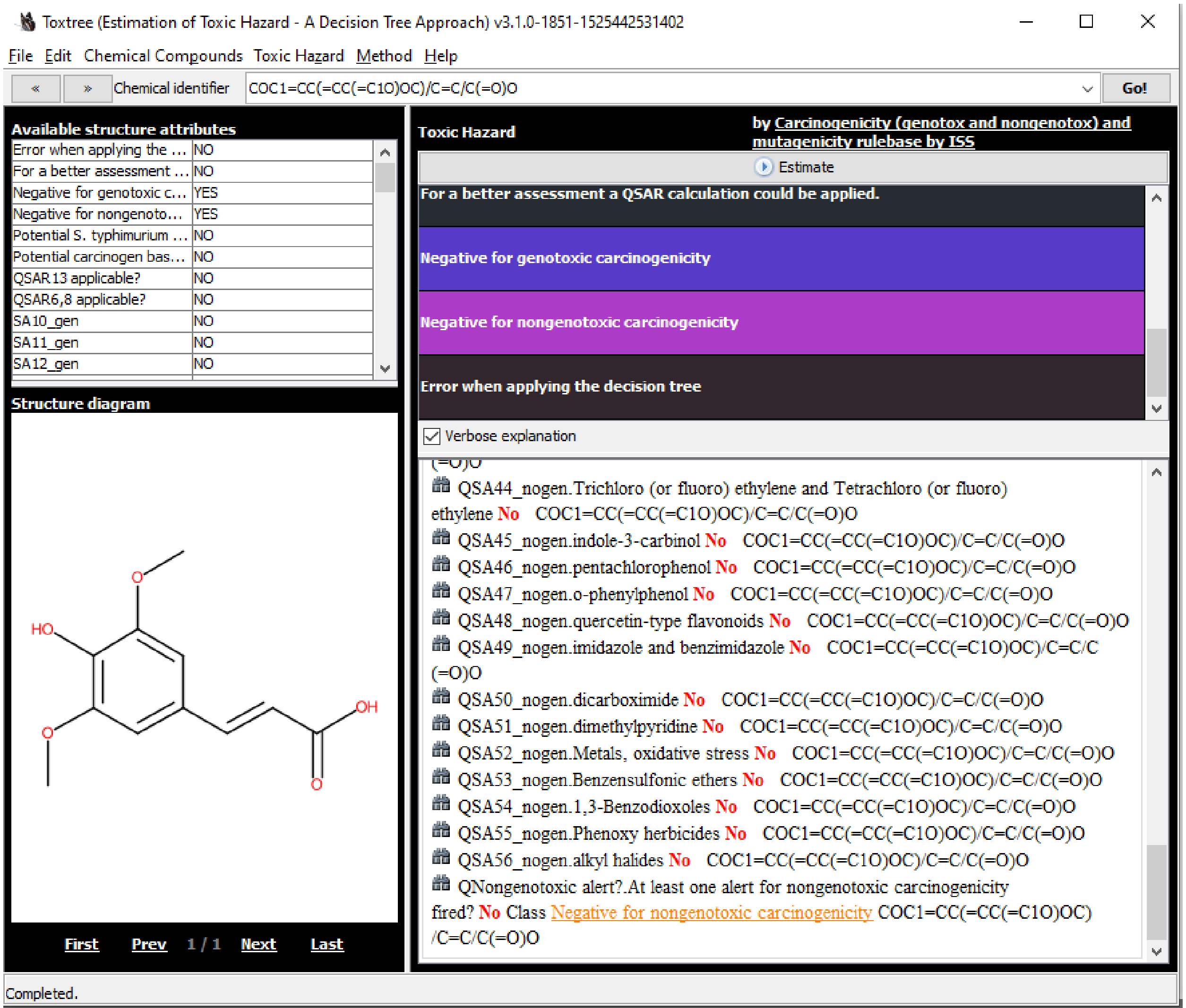
Symbols explanation:

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

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

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

APPENDIX F: Toxtree Carcinogenicity Results for Sinapic Acid (CAS #530-59-6)



APPENDIX G: Danish QSAR Carcinogenicity Results for Sinapic Acid (CAS #530-59-6)

Carcinogenicity

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

Commercial models from CASE Ultra and Leadscope

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

Carcinogenicity (genotox and nongenotox) alerts by ISS, alerts in:	
- parent only	No alert found
Oncologic Primary Classification, alerts in:	
- parent only	Phenol Type Compounds

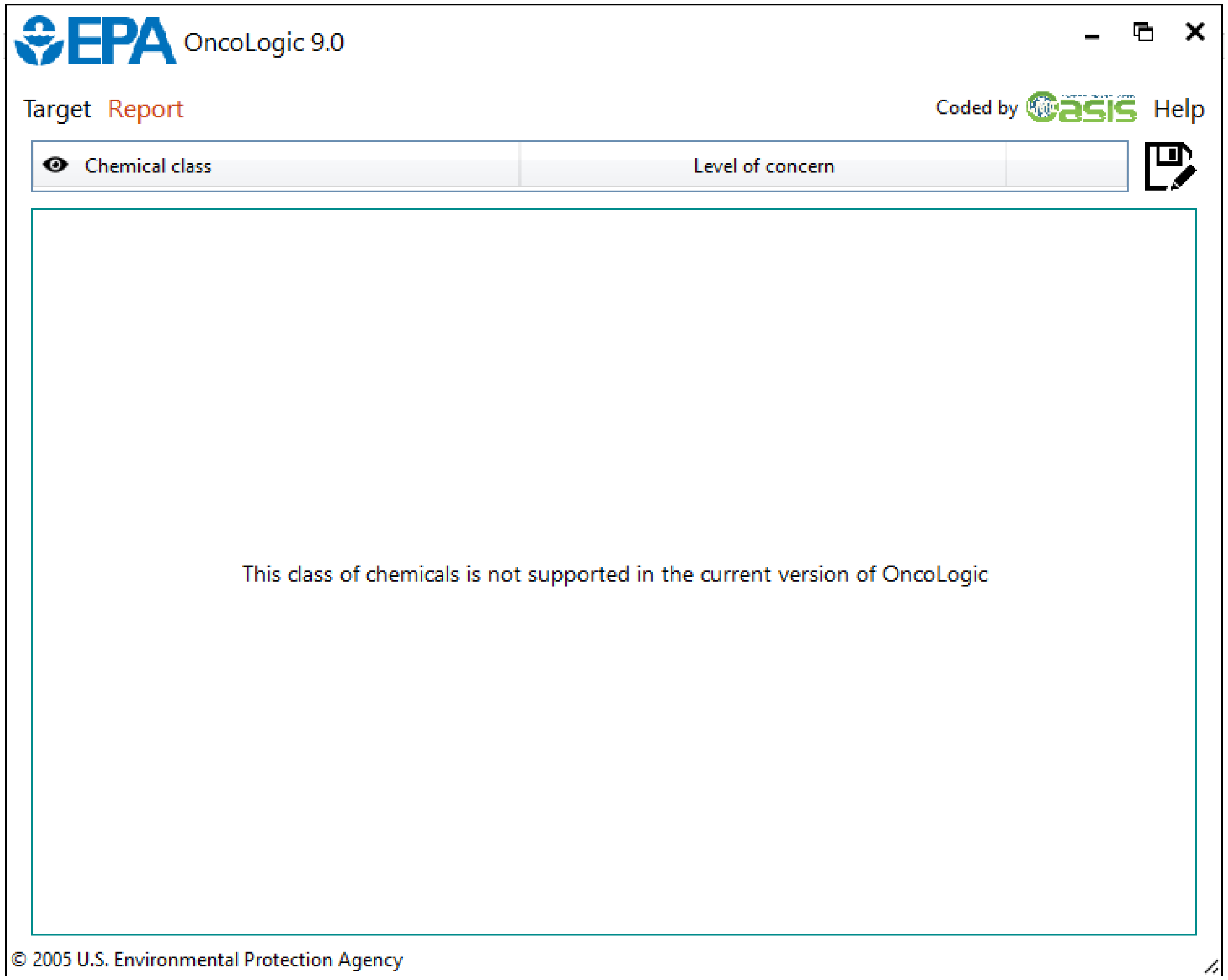
OECD QSAR Toolbox v.4.2 profilers

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

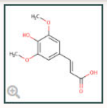
	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Liver Specific Cancer in Rat or Mouse		INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT

DTU-developed models

APPENDIX H: OncoLogic Carcinogenicity Results for Sinapic Acid (CAS #530-59-6)



APPENDIX I: CompTox ToxCast Models Prediction Results for Sinapic Acid (CAS #530-59-6)



3-(4-Hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid

530-59-6 | DTXSID40862129

Searched by CASRN

Bioactivity - ToxCast: Models

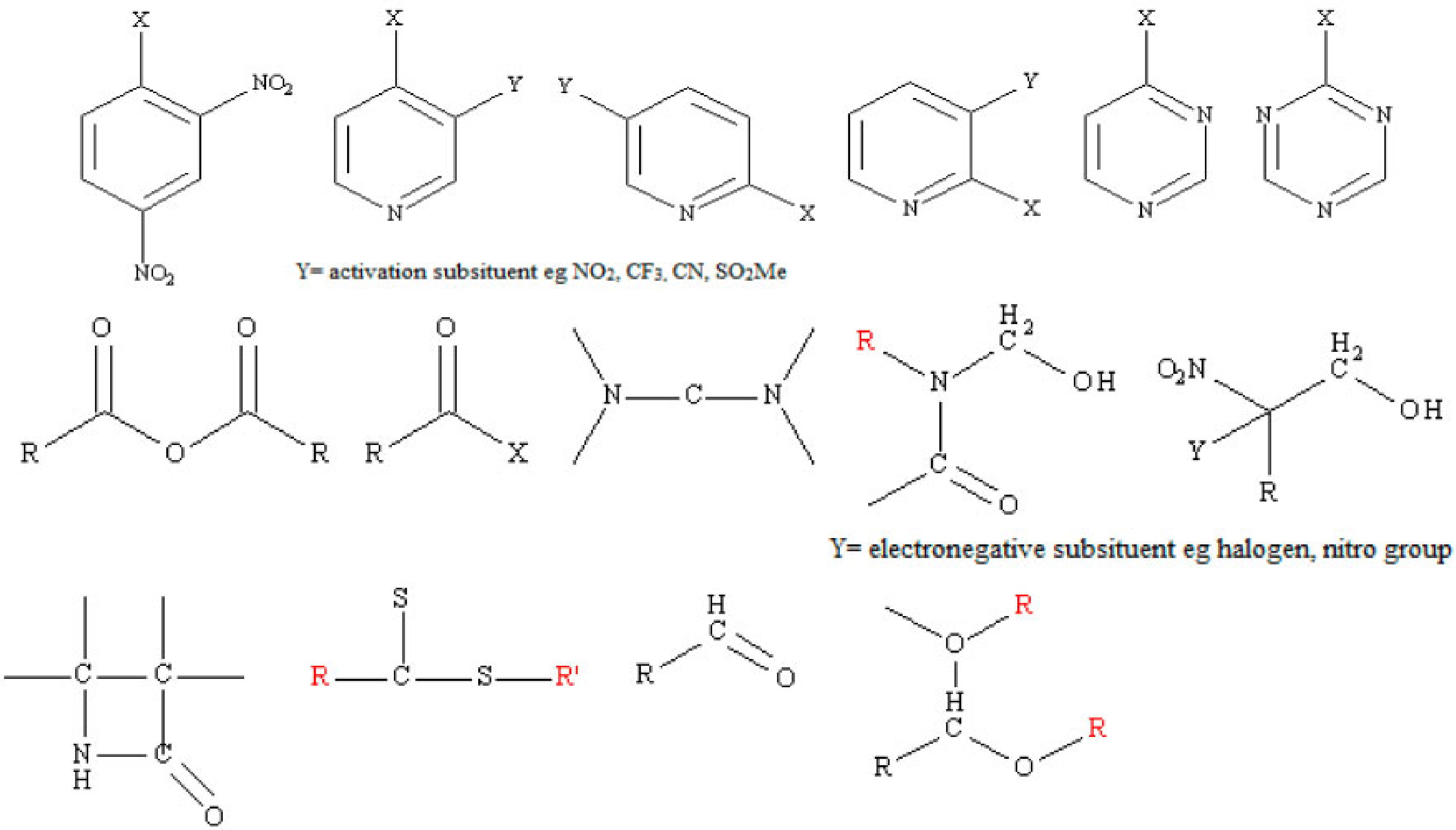
EXPORT

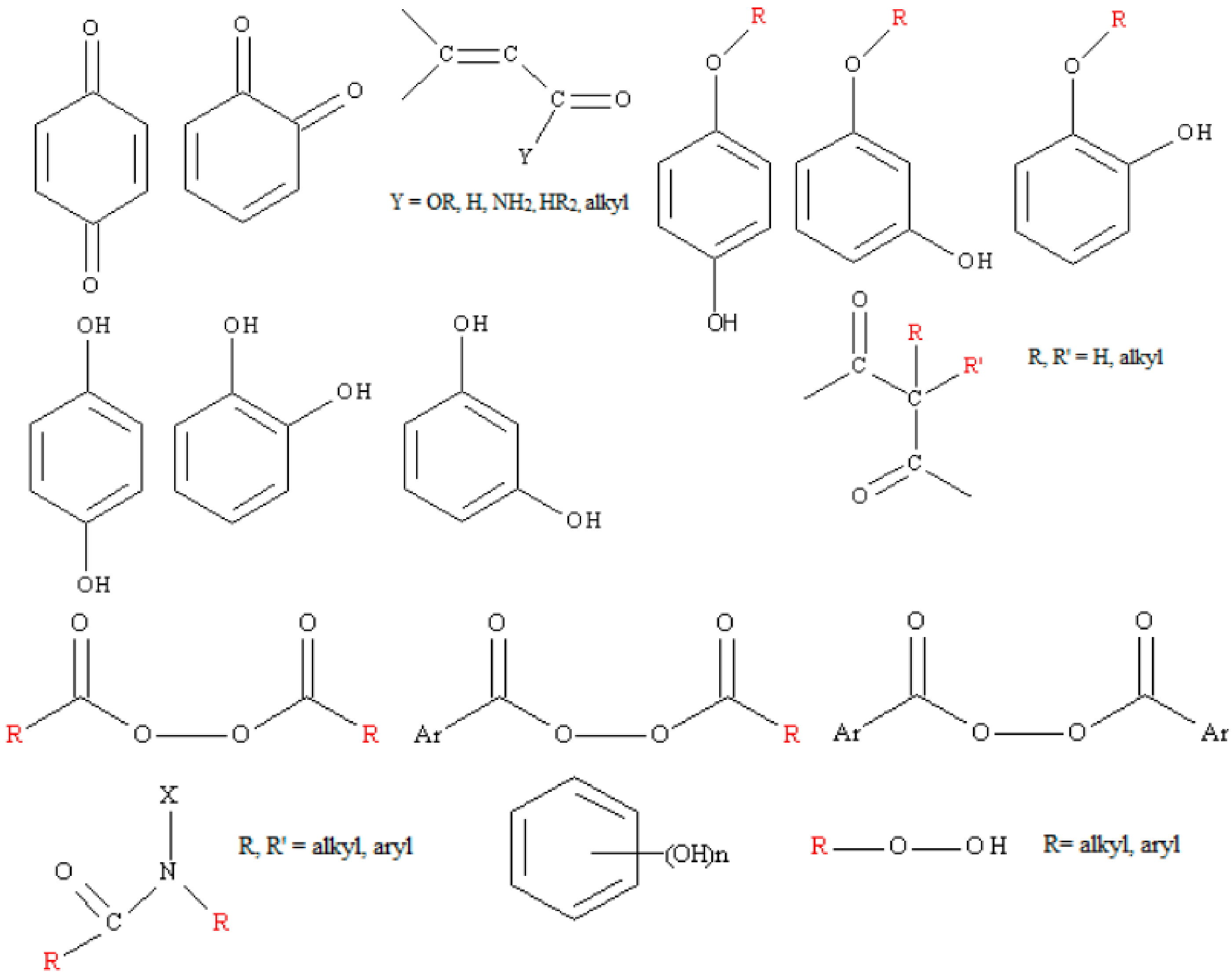
ToxCast Model Predictions

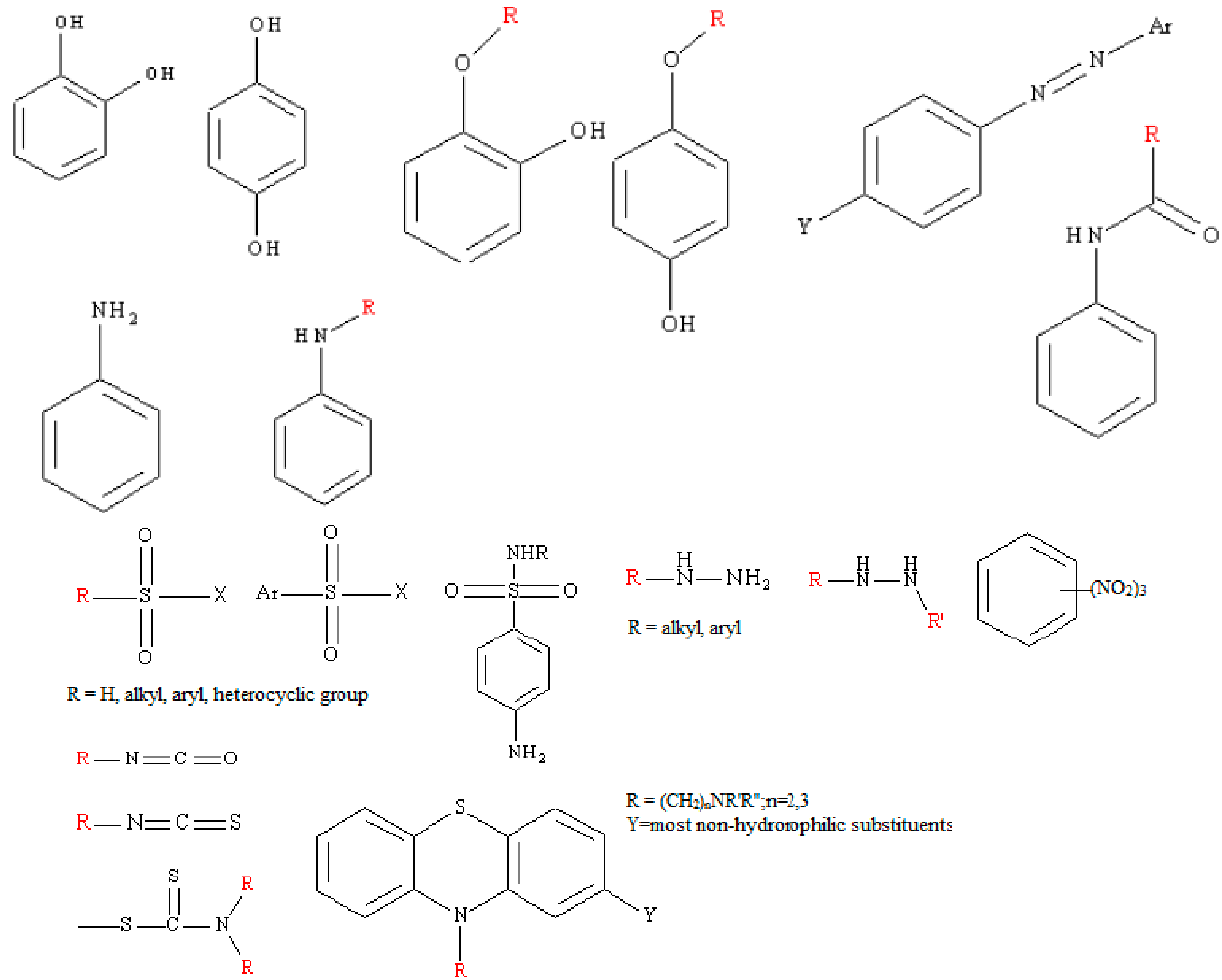
Model	Receptor	Agonist	Antagonist	Binding
CERAPP Potency Level (From Literature)	Estrogen	VeryWeak	VeryWeak	VeryWeak
CERAPP Potency Level (Consensus)	Estrogen	1.00	1.00	1

APPENDIX J: Known Structural Alerts for Skin Sensitization

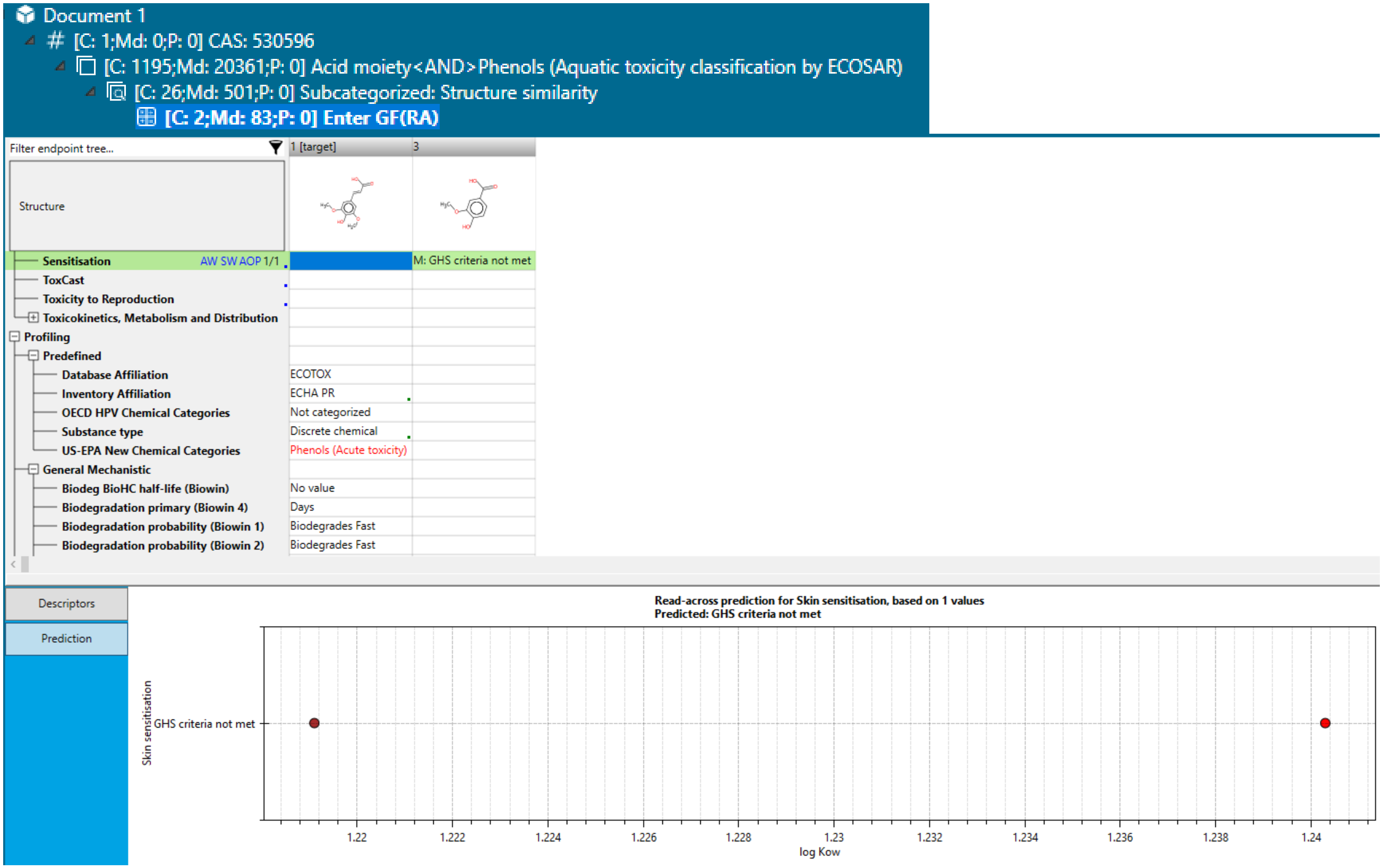
Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Sinapic acid possesses the alert of Michael addition electrophiles and precursors which is a known structural alert.



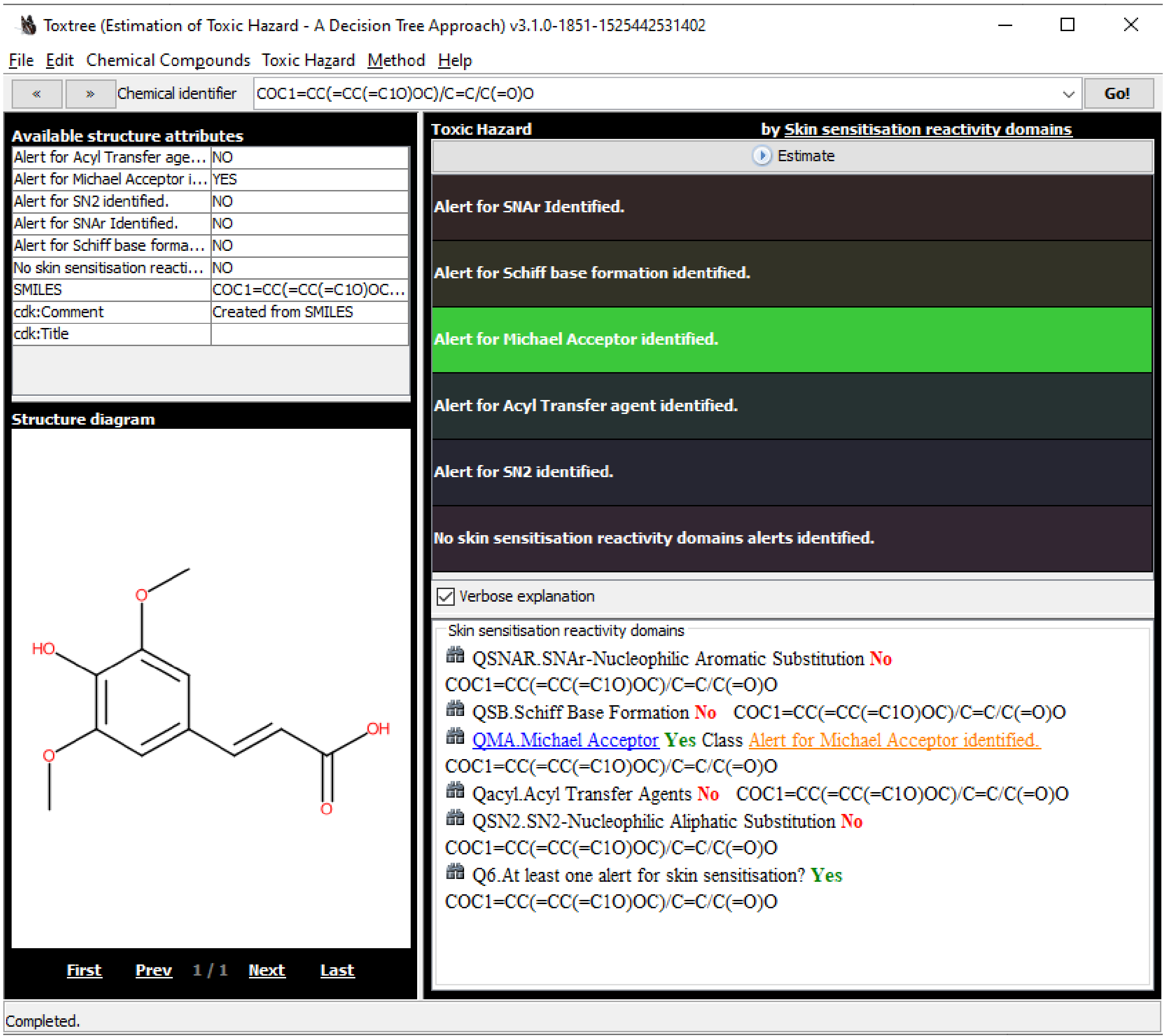

Y = OR, H, NH2, HR2, alkyl
R, R' = H, alkyl
R, R' = alkyl, aryl
(OH)n
R= alkyl, aryl

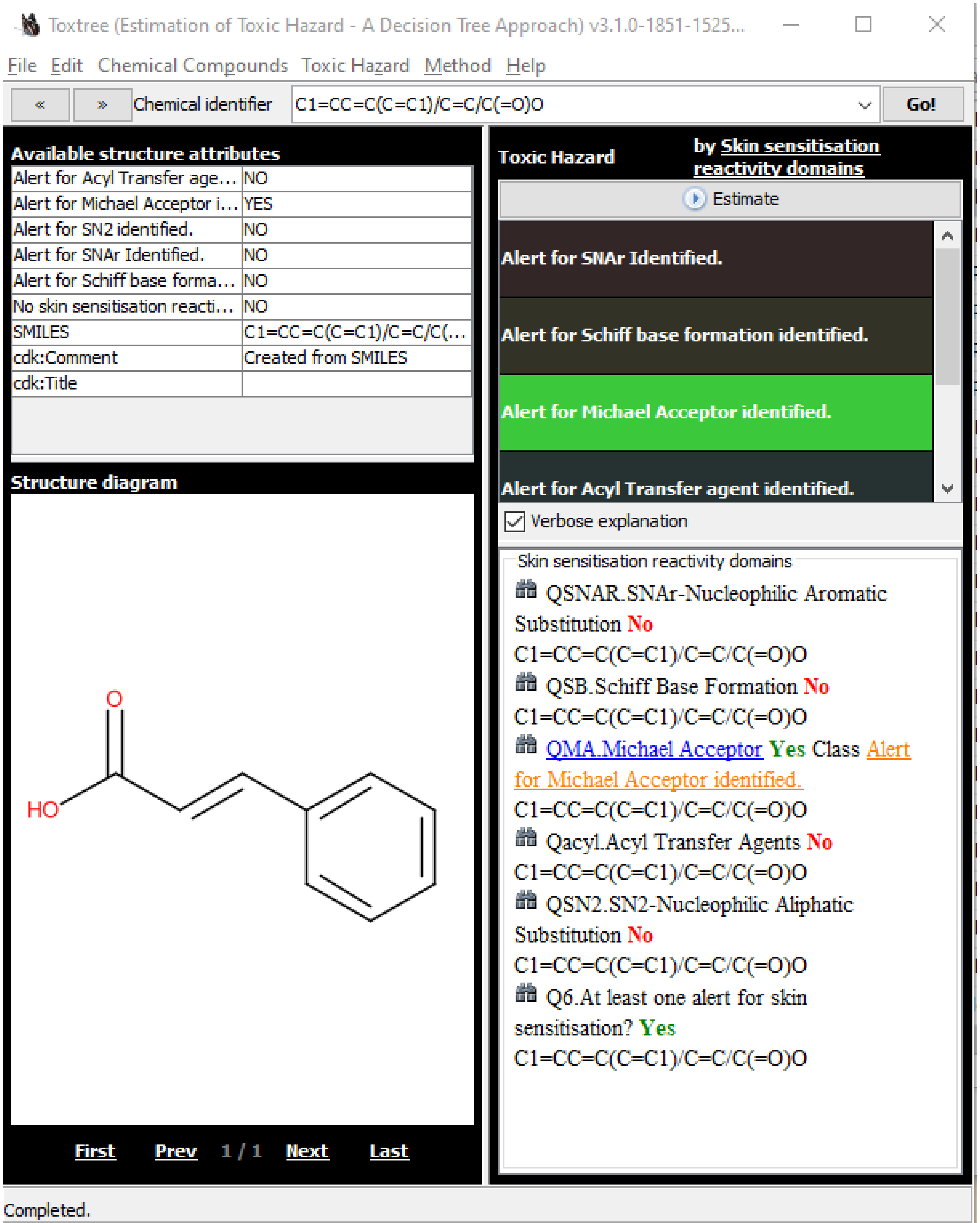

R = H, alkyl, aryl, heterocyclic group
R = alkyl, aryl
$(NO_2)_3$
R = $(CH_2)_nNR'R''$;n=2,3
Y=most non-hydrophilic substituents

APPENDIX K: OECD Toolbox Skin Sensitization Results for Sinapic Acid (CAS #530-59-6)



APPENDIX L: Toxtree Skin Sensitization Results for Sinapic Acid (CAS #530-59-6)

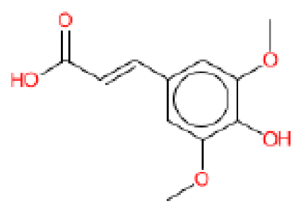



Toxtree (Estimation of Toxic Hazard - A Decision Tree Approach) v3.1.0-1851-1525...
File Edit Chemical Compounds Toxic Hazard Method Help
Chemical identifier
C1=CC=C(C=C1)/C=C/C(=O)O
Go!
Available structure attributes
Alert for Acyl Transfer age... NO
Alert for Michael Acceptor i... YES
Alert for SN2 identified. NO
Alert for SNAr Identified. NO
Alert for Schiff base forma... NO
No skin sensitisation reacti... NO
SMILES C1=CC=C(C=C1)/C=C/C(...
cdk:Comment Created from SMILES
cdk:Title
Structure diagram
O
HO
First Prev 1 / 1 Next Last
Toxic Hazard
by Skin sensitisation reactivity domains
Estimate
Alert for SNAr Identified.
Alert for Schiff base formation identified.
Alert for Michael Acceptor identified.
Alert for Acyl Transfer agent identified.
Verbose explanation
Skin sensitisation reactivity domains
QSNAR.SNAr-Nucleophilic Aromatic Substitution No
C1=CC=C(C=C1)/C=C/C(=O)O
QSB.Schiff Base Formation No
C1=CC=C(C=C1)/C=C/C(=O)O
QMA.Michael Acceptor Yes Class Alert for Michael Acceptor identified.
C1=CC=C(C=C1)/C=C/C(=O)O
Qacyl.Acyl Transfer Agents No
C1=CC=C(C=C1)/C=C/C(=O)O
QSN2.SN2-Nucleophilic Aliphatic Substitution No
C1=CC=C(C=C1)/C=C/C(=O)O
Q6.At least one alert for skin sensitisation? Yes
C1=CC=C(C=C1)/C=C/C(=O)O
Completed.

APPENDIX M: VEGA Skin Sensitization Results for Sinapic Acid (CAS #530-59-6)

1. Prediction Summary

Prediction for compound Molecule 0 -

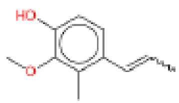


Prediction: Reliability:

Prediction is Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

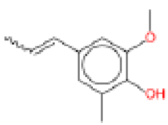
Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted skin sensitization activity: Sensitizer
O(Active): 1
O(Inactive): 0
Reliability: The predicted compound is into the Applicability Domain of the model
Remarks:
none

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



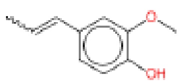
Compound #1

CAS: 186743-29-3
Dataset id:150 (Test Set)
SMILES: Oc1ccc(C=CC)c(c1(OC))C
Similarity: 0.843
Experimental value : Sensitizer
Predicted value : Sensitizer



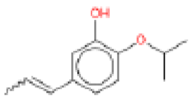
Compound #2

CAS: 13041-12-8
Dataset id:151 (Training Set)
SMILES: Oc1c(OC)cc(C=CC)cc1C
Similarity: 0.841
Experimental value : Sensitizer
Predicted value : Sensitizer



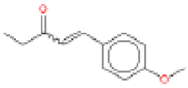
Compound #3

CAS: 97-54-1
Dataset id:120 (Training Set)
SMILES: Oc1ccc(C=CC)cc1(OC)
Similarity: 0.84
Experimental value : Sensitizer
Predicted value : Sensitizer



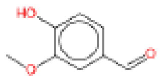
Compound #4

CAS: 2953-00-7
Dataset id:124 (Training Set)
SMILES: Oc1cc(ccc1(OC(C)C))C=CC
Similarity: 0.821
Experimental value : Sensitizer
Predicted value : Sensitizer



Compound #5

CAS: 104-27-8
Dataset id:134 (Training Set)
SMILES: O=C(C=Cc1ccc(OC)cc1)CC
Similarity: 0.815
Experimental value : Sensitizer
Predicted value : Sensitizer



Compound #6

CAS: 121-33-5
Dataset id:208 (Training Set)
SMILES: O=Cc1ccc(O)c(OC)c1
Similarity: 0.799
Experimental value : NON-Sensitizer
Predicted value : NON-Sensitizer

3.2 Applicability Domain:

Measured Applicability Domain Scores

✓	Global AD Index AD index = 0.918 Explanation: The predicted compound is into the Applicability Domain of the model.
✓	Similar molecules with known experimental value Similarity index = 0.842 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✓	Accuracy of prediction for similar molecules Accuracy index = 1 Explanation: Accuracy of prediction for similar molecules found in the training set is good..
✓	Concordance for similar molecules Concordance index = 1 Explanation: Similar molecules found in the training set have experimental values that agree with the predicted value..
✓	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✓	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

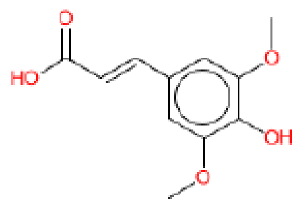
✓ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

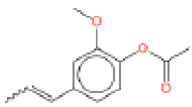
Prediction for compound Molecule 0 -

	Prediction: Reliability: Prediction is Sensitizer, but the result shows some critical aspects, which require to be checked: - Accuracy of prediction for similar molecules found in the training set is not adequate - similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted skin sensitization activity: Sensitizer
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

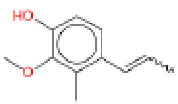
3.1 Applicability Domain:

Similar Compounds, with Predicted and Experimental Values



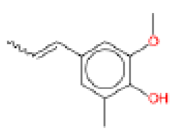
Compound #1

CAS: 93-29-8
Dataset id:248 (Training Set)
SMILES: O=C(Oc1ccc(C=CC)cc1(OC))C
Similarity: 0.855
Experimental value : NON-Sensitizer
Predicted value : NON-Sensitizer



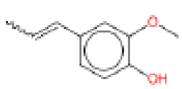
Compound #2

CAS: 186743-29-3
Dataset id:294 (Test Set)
SMILES: Oc1ccc(C=CC)c(c1(OC))C
Similarity: 0.843
Experimental value : Sensitizer
Predicted value : NON-Sensitizer



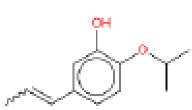
Compound #3

CAS: 13041-12-8
Dataset id:122 (Training Set)
SMILES: Oc1c(OC)cc(C=CC)cc1C
Similarity: 0.841
Experimental value : Sensitizer
Predicted value : NON-Sensitizer



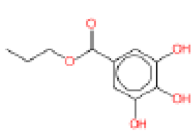
Compound #4

CAS: 97-54-1
Dataset id:48 (Training Set)
SMILES: Oc1ccc(C=CC)cc1(OC)
Similarity: 0.84
Experimental value : Sensitizer
Predicted value : Sensitizer



Compound #5

CAS: 2953-00-7
Dataset id:113 (Training Set)
SMILES: Oc1cc(ccc1(OC(C)C))C=CC
Similarity: 0.821
Experimental value : Sensitizer
Predicted value : NON-Sensitizer



Compound #6

CAS: 121-79-9
Dataset id:171 (Training Set)
SMILES: O=C(OCCC)c1cc(O)c(O)c(O)c1
Similarity: 0.821
Experimental value : Sensitizer
Predicted value : Sensitizer

3.2 Applicability Domain:
Measured Applicability Domain Scores

⚠	Global AD Index AD index = 0.651 Explanation: The predicted compound could be out of the Applicability Domain of the model.
✔	Similar molecules with known experimental value Similarity index = 0.849 Explanation: Strongly similar compounds with known experimental value in the training set have been ..
✘	Accuracy of prediction for similar molecules Accuracy index = 0.504 Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..
✘	Concordance for similar molecules Concordance index = 0.496 Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..
✔	Model's descriptors range check Descriptors range check = True Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..
✔	Atom Centered Fragments similarity check ACF index = 1 Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

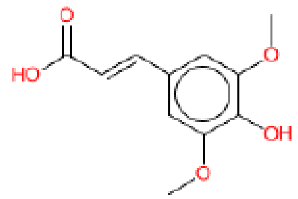
✔ The feature has a good assessment, model is reliable regarding this aspect.

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

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

1. Prediction Summary

Prediction for compound Molecule 0 -

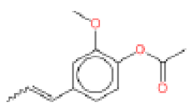


Prediction: Reliability:

Prediction is Sensitizer, but the result shows some critical aspects, which require to be checked:
- Accuracy of prediction for similar molecules found in the training set is not adequate
- similar molecules found in the training set have experimental values that disagree with the predicted value

Compound: Molecule 0
Compound SMILES: O=C(O)C=Cc1cc(OC)c(O)c(OC)c1
Experimental value: -
Predicted skin sensitization activity: Sensitizer
Predicted consensus reliability: Good reliability
Prediction from VEGA Caesar model: Sensitizer (GOOD reliability)
Prediction with ToxTree classes: Sensitizer (Michael Acceptor)
Prediction with fragment-based model: Sensitizer
Structural Alerts: -
Reliability: The predicted compound could be out of the Applicability Domain of the model
Remarks:
none

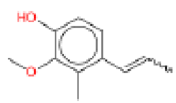
3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



Compound #1

CAS: 93-29-8
Dataset id:248 (Training Set)
SMILES: O=C(Oc1ccc(C=CC)cc1(OC))C
Similarity: 0.855
Experimental value : NON-Sensitizer
Predicted value : Sensitizer

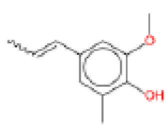
Alerts (not found also in the target): Skin sensitizer alert no. 11; Skin sensitizer alert no. 35



Compound #2

CAS: 186743-29-3
Dataset id:294 (Test Set)
SMILES: Oc1ccc(C=CC)c(c1(OC))C
Similarity: 0.843
Experimental value : Sensitizer
Predicted value : Sensitizer

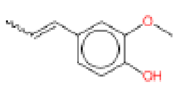
Alerts (not found also in the target): Skin sensitizer alert no. 17; Skin sensitizer alert no. 35



Compound #3

CAS: 13041-12-8
Dataset id:122 (Training Set)
SMILES: Oc1c(OC)cc(C=CC)cc1C
Similarity: 0.841
Experimental value : Sensitizer
Predicted value : Sensitizer

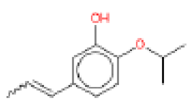
Alerts (not found also in the target): Skin sensitizer alert no. 17; Skin sensitizer alert no. 35



Compound #4

CAS: 97-54-1
Dataset id:48 (Training Set)
SMILES: Oc1ccc(C=CC)cc1(OC)
Similarity: 0.84
Experimental value : Sensitizer
Predicted value : Sensitizer

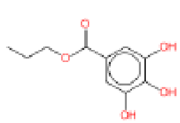
Alerts (not found also in the target): Skin sensitizer alert no. 35



Compound #5

CAS: 2953-00-7
Dataset id:113 (Training Set)
SMILES: Oc1cc(ccc1(OC(C)C))C=CC
Similarity: 0.821
Experimental value : Sensitizer
Predicted value : Sensitizer

Alerts (not found also in the target): Skin sensitizer alert no. 35



Compound #6

CAS: 121-79-9
Dataset id:171 (Training Set)
SMILES: O=C(OCCC)c1cc(O)c(O)c(O)c1
Similarity: 0.821
Experimental value : Sensitizer
Predicted value : Sensitizer

Alerts (not found also in the target): Skin sensitizer alert no. 23

3.2 Applicability Domain:
Measured Applicability Domain Scores

Global AD Index
AD index = 0.649
Explanation: The predicted compound could be out of the Applicability Domain of the model.

Similar molecules with known experimental value
Similarity index = 0.849
Explanation: Strongly similar compounds with known experimental value in the training set have been ..

Accuracy of prediction for similar molecules
Accuracy index = 0.496
Explanation: Accuracy of prediction for similar molecules found in the training set is not adequate..

Concordance for similar molecules
Concordance index = 0.496
Explanation: similar molecules found in the training set have experimental values that disagree with the predicted value..

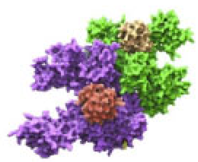
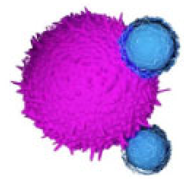
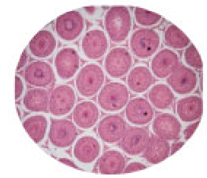
Model's descriptors range check
Descriptors range check = True
Explanation: descriptors for this compound have values inside the descriptor range of the compounds of the training set..

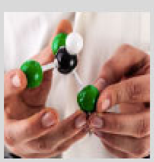
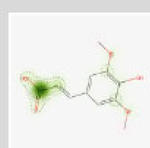
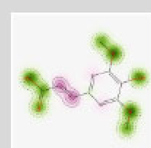
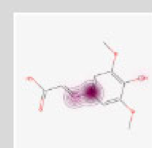
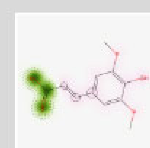
Atom Centered Fragments similarity check
ACF index = 1
Explanation: all atom centered fragment of the compound have been found in the compounds of the training set..

Symbols explanation:

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

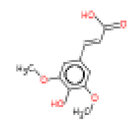
APPENDIX N: LabMol Skin Sensitization Results for Sinapic Acid (CAS #530-59-6)

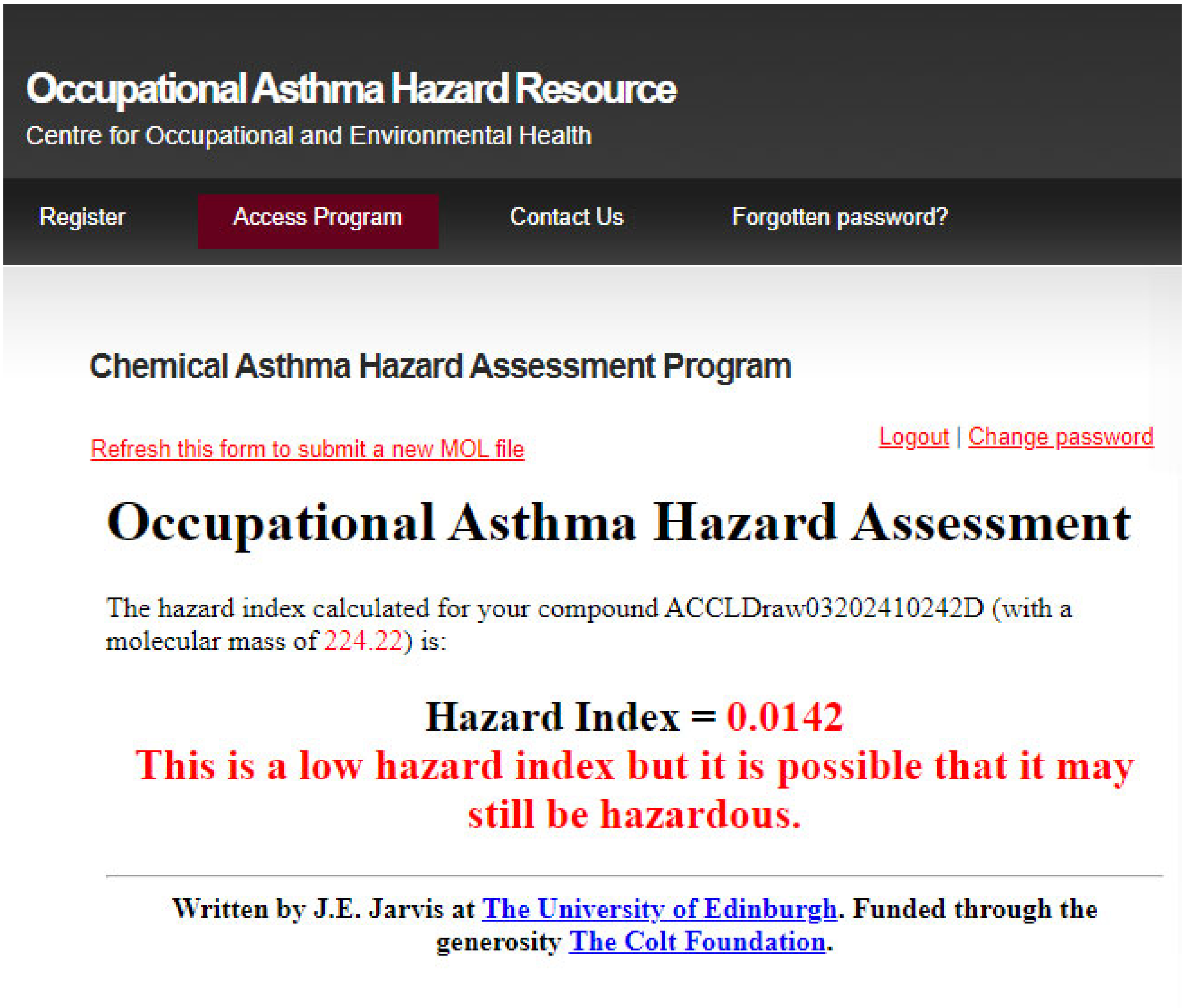
Chemical Exposure	Molecular initiating event *in chemico*	Cellular response *in vitro*		Tissue / Organ response *in vivo*	Organism response *in vivo*	Pred-Skin 3.0 Outcome *in silico*
•Skin Penetration •Electrophilic substance: directly or via auto-oxidation or metabolism	Covalent interaction with proteins in the skin (OECD442C) Haptenation: covalent modification of epidermal proteins	Keratinocyte responses (OECD442D) • Activation of inflammatory cytokines •Induce cytoprotective genes	Dendritic cells (DCs) (OECD442E) • Induction of inflammatory cytokines •Mobilization of DCs	Proliferation of antigen-specific T cells (OECD429) •Histocompatibility complex representation by DCs •Activation of T cells •Proliferation of activated T cells	Inflammation upon challenge allergen To maximise the use of existing knowledge, we also incorporate historical HRIPT (human repeated insult patch test) and HMT (human maximization test)	The Bayesian model is a consensus model integrating predictions from all the other assays for an integrative qualitative risk assessment (QRA) of skin sensitization based on the weight of evidence (WoE).
•Exposure consideration ? •Physicochemical and Biopharmaceutical properties ? •Skin Penetration ? •Skin Metabolism ? 	**Prediction DPRA** Sensitizer (+) (AD, Confiability) (Inside , 90.4%) Probability map 	**Prediction KeratinoSens** Non-Sensitizer (-) (AD, Confiability) (Inside, 94.6%) Probability map 	**Prediction h-CLAT** Non-Sensitizer (-) (AD, Confiability) (Inside, 57.7%) Probability map 	**Prediction LLNA** Sensitizer (+) (AD, Confiability) (Outside, 99.9%) Probability map 	**Prediction HRIPT/HMT** Non-Sensitizer (-) (AD, Confiability) (Inside, 80.3%) Probability map 	**Bayesian Outcome** Non-sensitizer (-) (Confiability) (High)

Low (-) confidence prediction for the Bayesian model means two or more individual predictions are in disagreement with Bayesian Outcome.

APPENDIX O: OECD Toolbox Respiratory Sensitization Results for Sinapic Acid (CAS #530-59-6)

Filter endpoint tree...	1 [target]
Structure	
Structure info	
Additional Ids	EC Number:2084873
CAS Number	530-59-6
CAS-SMILES relation	High
Chemical name(s)	(2E)-3-(4-hydroxy-3,5-dimethoxyphenyl)prop-2-enoic acid
Identity	Sources:4
Molecular formula	C11H12O5
Predefined substance type	Mono constituent
SMILES	COc1cc(\C=C\C(O)=O)cc(OC)c1O
Parameters	
Physical Chemical Properties	
Environmental Fate and Transport	
Ecotoxicological Information	
Human Health Hazards	
Profiling	
Endpoint Specific	
Respiratory sensitisation	No alert found

APPENDIX P: COEH Occupational Asthma Hazard Assessment for Sinapic Acid (CAS #530-59-6)



Occupational Asthma Hazard Resource

Centre for Occupational and Environmental Health

Register | Access Program | Contact Us | Forgotten password?

Chemical Asthma Hazard Assessment Program

Refresh this form to submit a new MOL file

Logout | Change password

Occupational Asthma Hazard Assessment

The hazard index calculated for your compound ACCLDraw03202410242D (with a molecular mass of 224.22) is:

Hazard Index = 0.0142

This is a low hazard index but it is possible that it may still be hazardous.

Written by J.E. Jarvis at The University of Edinburgh. Funded through the generosity The Colt Foundation.

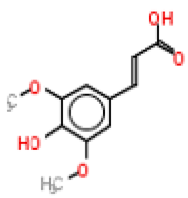
APPENDIX Q: ECOSAR Modeling Results for Sinapic Acid (CAS #530-59-6)

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
530596	SINAPIC ACID	OC(=O)C=Cc1cc(OC)c(O)c(OC)c1

Structure



Details	
Mol Wt	224.22
Selected LogKow	�
Selected Water Solubility (mg/L)	�
Selected Melting Point (°C)	�
Estimated LogKow	1.24
Estimated Water Solubility (mg/L)	7082.11
Measured LogKow	�
Measured Water Solubility (mg/L)	�
Measured Melting Point (°C)	�

Class Results:	

Neutral Organics

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	8.86E03	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Daphnid	48h	LC50	4.69E03	5	
Green Algae	96h	EC50	2.61E03	6.4	
Fish		ChV	7.97E02	8	
Daphnid		ChV	3.76E02	8	
Green Algae		ChV	5.86E02	8	
Fish (SW)	96h	LC50	1.11E04	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Mysid	96h	LC50	1.38E04	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Fish (SW)		ChV	7.58E02	8	
Mysid (SW)		ChV	1.50E03	8	
Earthworm	14d	LC50	4.67E03	6	

Phenols

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	1.02E03	7	
Daphnid	48h	LC50	3.13E02	7	
Green Algae	96h	EC50	1.25E03	6.4	
Fish		ChV	9.33E01	8	
Daphnid		ChV	3.00E01	8	
Green Algae		ChV	1.54E02	8	
Fish (SW)	96h	LC50	1.27E03	7	
Mysid (SW)	96h	LC50	2.87E02	7	
Green Algae (SW)	96h	LC50	5.54E03	6.4	
Lemna gibba	7d	EC50	1.27E03	6.4	

APPENDIX R: EPI Suite™ Modeling Results for Sinapic Acid (CAS #530-59-6)

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

```
CAS Number: 530-59-6
SMILES : OC(=O)C=Cc1cc(OC)c(O)c(OC)c1
CHEM   : SINAPIC ACID
MOL FOR: C11 H12 O5
MOL WT : 224.22
------------------------------ EPI SUMMARY (v4.11) --------------------------
 Physical Property Inputs:
    Log Kow (octanol-water):   ------
    Boiling Point (deg C)  :   ------
    Melting Point (deg C)  :   192.00
    Vapor Pressure (mm Hg) :   ------
    Water Solubility (mg/L):   ------
    Henry LC (atm-m3/mole) :   ------
```

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 1.24

```
Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
    Boiling Pt (deg C):  377.86  (Adapted Stein & Brown method)
    Melting Pt (deg C):  146.32  (Mean or Weighted MP)
```
VP(mm Hg,25 deg C): 1.18E-007 (Modified Grain method)
```
    VP (Pa, 25 deg C) :  1.58E-005  (Modified Grain method)
    Subcooled liquid VP: 6.68E-006 mm Hg (25 deg C, Mod-Grain method)
                       : 0.00089 Pa (25 deg C, Mod-Grain method)
```

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 1830
log Kow used: 1.24 (estimated)
melt pt used: 192.00 deg C

```
 Water Sol Estimate from Fragments:
    Wat Sol (v1.01 est) =  8221.9 mg/L

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

 Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
   Bond Method :   4.71E-015  atm-m3/mole  (4.77E-010 Pa-m3/mole)
   Group Method:   1.65E-013  atm-m3/mole  (1.68E-008 Pa-m3/mole)
 For Henry LC Comparison Purposes:
   User-Entered Henry LC:  not entered
   Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
      HLC:  1.902E-011 atm-m3/mole  (1.928E-006 Pa-m3/mole)
      VP:   1.18E-007 mm Hg (source: MPBPVP)
      WS:   1.83E+003 mg/L (source: WSKOWWIN)
```

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 1.24 (KowWin est)
Log Kaw used: -12.715 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 13.955
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.0931
Biowin2 (Non-Linear Model) : 0.9972
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.0084 (weeks)
Biowin4 (Primary Survey Model) : 4.1037 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.7859
Biowin6 (MITI Non-Linear Model): 0.8229
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.9626
Ready Biodegradability Prediction: YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.000891 Pa (6.68E-006 mm Hg)
Log Koa (Koawin est): 13.955
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 0.00337
Octanol/air (Koa) model: 22.1
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.108
Mackay model : 0.212
Octanol/air (Koa) model: 0.999

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 175.5562 E-12 cm3/molecule-sec [Cis-isomer]
OVERALL OH Rate Constant = 178.2162 E-12 cm3/molecule-sec [Trans-isomer]
Half-Life = 0.731 Hrs (12-hr day; 1.5E6 OH/cm3) [Cis-isomer]
Half-Life = 0.720 Hrs (12-hr day; 1.5E6 OH/cm3) [Trans-isomer]
Ozone Reaction:
OVERALL Ozone Rate Constant = 1.050000 E-17 cm3/molecule-sec [Cis-]
OVERALL Ozone Rate Constant = 2.100000 E-17 cm3/molecule-sec [Trans-]
Half-Life = 1.091 Days (at 7E11 mol/cm3) [Cis-isomer]
Half-Life = 13.097 Hrs (at 7E11 mol/cm3) [Trans-isomer]
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.16 (Junge-Pankow, Mackay avg)
0.999 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 29.58 L/kg (MCI method)
Log Koc: 1.471 (MCI method)
Koc : 13.19 L/kg (Kow method)
Log Koc: 1.120 (Kow method)

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

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.1691 days (HL = 0.06775 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.341 (BCF = 2.191)
Log BAF Arnot-Gobas method (upper trophic) = 0.341 (BAF = 2.191)
log Kow used: 1.24 (estimated)

Volatilization from Water:
Henry LC: 1.65E-013 atm-m3/mole (estimated by Group SAR Method)
Half-Life from Model River: 5.313E+009 hours (2.214E+008 days)
Half-Life from Model Lake : 5.796E+010 hours (2.415E+009 days)

Removal In Wastewater Treatment:
Total removal: 1.92 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.82 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	**Half-Life (hr)**	**Emissions (kg/hr)**
Air	**3.8e-006**	**1.38**	**1000**
Water	**24.5**	**360**	**1000**
Soil	**75.5**	**720**	**1000**
Sediment	**0.0749**	**3.24e+003**	**0**

Persistence Time: 693 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.8e-006	1.38	1000
Water	24.5	360	1000
water	(24.5)		
biota	(2.13e-005)		
suspended sediment	(0.00109)		
Soil	75.5	720	1000
Sediment	0.0749	3.24e+003	0

Persistence Time: 693 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	4.2e-006	1.38	1000
Water	32.3	360	1000
water	(32.3)		
biota	(2.8e-005)		
suspended sediment	(0.000345)		
Soil	67.7	720	1000
Sediment	0.0688	3.24e+003	0

Persistence Time: 627 hr

APPENDIX S: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for sinapic acid. The original GreenScreen® assessment was performed in 2024 under version 1.4 criteria and ToxServices assigned a Benchmark 2 (BM-2) score.

Table 5: Change in GreenScreen® Benchmark™ for Sinapic Acid			
Date	**GreenScreen® Benchmark™**	**GreenScreen® Version**	**Comment**
March 20, 2024	BM-2	v. 1.4	Original GreenScreen® assessment.

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