RAMBUTAN PEEL EXTRACT

(CAS #93165-68-5)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: July 8, 2024

Expiration Date: July 8, 2029

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GreenScreen® Executive Summary for Rambutan Peel Extract (CAS #93165-68-5)

Rambutan peel extract is an extract of the peel of the fruit Rambutan, also known by its scientific name *Nephelium lappaceum L*. The peel of the fruit rambutan is considered an agriculture waste and contains cellulose (24.28%), lignin (35.34%), hemicellulose (11.6%), and phenolic compounds. Only hemicellulose and phenolic compounds are extractable from the peel, with available data indicating a high content level of polyphenols in rambutan fruit peel extracts. Based on this, rambutan peel extract is expected to be a complex mixture, composed primarily of polyphenolic substances with geraniin identified as the predominant component. The exact composition of rambutan peel extract is dependent on the extraction method, type of solvent, extraction time, and temperature.

Due to the high level of phenolic compounds in rambutan peel extract, it has several bioactivities and is used as anti-inflammatory, antioxidant, antimicrobial, and antibacterial agent. It is also used as a skin conditioning agent in cosmetic formulations.

Based on data for the predominant component geraniin, rambutan peel extract is a solid that is moderately soluble in water. It is neither flammable nor reactive.

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

- Benchmark 2c
    - Very High Persistence - P + Moderate Group II Human Toxicity (eye irritation-IrE)
    - Very High Persistence - P + Moderate Group II* Human Toxicity (skin sensitization – SnS* and respiratory sensitization – SnR*)
    - Very High Persistence - P + High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity, skin and eye irritation, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation. 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 rambutan peel extract's NAMs include the invalidity of the *in vitro* SOS chromotest by OECD, the absence of experimental data for skin sensitization, respiratory sensitization, chronic aquatic toxicity, and environmental partitioning, and lack of established test methods for respiratory sensitization. Rambutan peel extract's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, the limitation of the *in vitro* skin corrosion test **(**OECD Guideline 439) to identify substances classified as mild skin irritant (GHS Category 3), the limitation of the *in vitro* eye irritation test (OECD Guideline 437) to identify substances classified as eye irritant (GHS Category 2), lack of defined

applicability domains for OECD Toolbox and Toxtree and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries in combination with *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

GreenScreen® Hazard Summary Table for Rambutan Peel Extract

Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	**M**	**R**	**D**	**E**	**AT**	**ST**		**N**		**SnS**	**SnR**	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
						s	r*	s	r*	*	*								
L	*L*	*L*	*L*	DG	**L**	*L*	**L**	*L*	DG	*M*	*M*	*L*	*H*	*H*	*H*	*vH*	*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 Rambutan Peel Extract (CAS #93165-68-5)

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

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Organization: ToxServices LLC
Date: July 8, 2024

Expiration Date: July 8, 2029[2]

Chemical Name: Rambutan peel extract

CAS Number: 93165-68-5

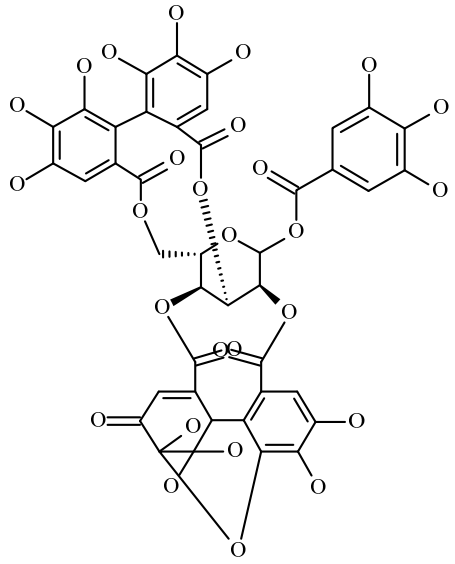
Chemical Structure(s): Rambutan peel extract is considered to be of unknown or variable composition, complex reaction products or biological materials (UVCB). It is the extract of the peel of the fruit rambutan, also known by its scientific name *Nephelium lappaceum L*. The peel of the fruit contains cellulose (24.28%), lignin (35.34%), hemicellulose (11.6%), and phenolic compounds. Only hemicellulose and phenolic compounds are extractable from the peel (Torgbo et al. 2024), with available data indicating a high level of polyphenols in rambutan peel extracts. Therefore, rambutan peel extract is expected to be a complex mixture, composed primarily of polyphenolic substances (ellagitannins) with geraniin (CAS #60976-49-0), identified as the predominant component. The exact composition of rambutan peel extract is dependent on the extraction method, type of solvent, extraction time, and temperature (Tingting et al. 2022).

Also called: Nephelium lappaceum peel extract (EC 2024, Pharos 2024).

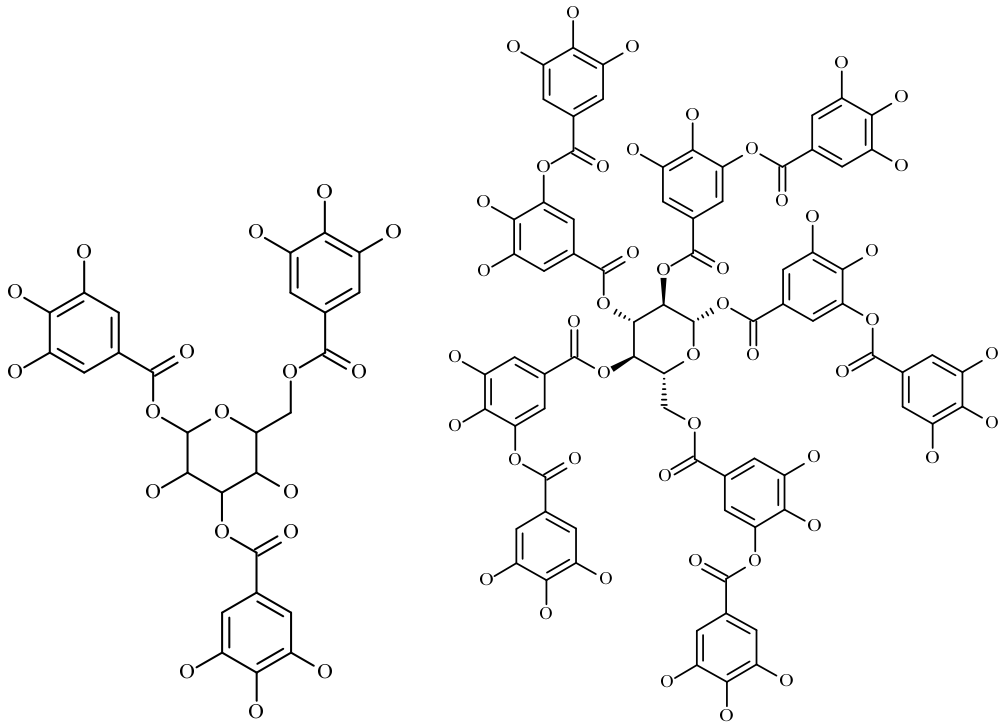
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Rambutan peel extract has very limited toxicological data. As mentioned previously, chemical analysis of rambutan fruit peel extracts obtained from different methods and using different solvents (ether, methanol, ethanol, and water) showed that they contain high levels of phenolic compounds (ellagitannins), which are the major responsible functional elements for the antioxidant activity of the extract (Tingting et al. 2022). Ellagitannins, also called hydrolysable tannin, are derivatives of gallic acid, hexahydroxydiphenic acid, and glucose, with a wide range of structures from simple monomers

[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).

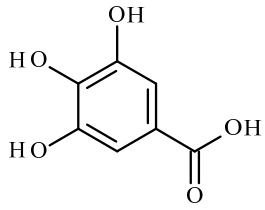
(i.e., ellagic acid glycosides), to complex polymers. The main ellagitannin compound identified in rambutan peel extract was geraniin (CAS #60976-49-0) (Tingting et al. 2022). Therefore, ToxServices considered data on this constituent in to fill the data gaps. However, geraniin has also limited toxicological data. ToxServices identified tannic acid (CAS #1401-55-4), a hydrolysable tannin, as a surrogate with sufficient toxicological data. It is also a water-soluble polyphenolic compound with similar carbon number and moieties (gallic acid derivative with hexahydroxydiphenic acid and glucose) as geraniin. Therefore, tannic acid is expected to have a similar toxicological profile to geraniin. In addition, ToxServices considered data on gallic acid (CAS #149-91-7) as supporting evidence, since it is also present in rambutan peel extract and is a metabolite of geraniin (Tingting et al. 2022, Elendran et al. 2015).



Surrogate: Geraniin (CAS #60976-49-0) (PubChem 2024)



Surrogate: Tannic acid (CAS #1401-55-4) (ECHA 2024a, Sigmal-Aldrich 2024)



Surrogate: Gallic acid (CAS #149-91-7) (ECHA 2024b)

Identify Applications/Functional Uses: (EC 2024)
Skin conditioning agent in cosmetic formulations.

Known Impurities[3]**:**
No relevant information. The screen is performed on the theoretical pure substance (mixture).

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

GreenScreen® Summary Rating for Rambutan Peel Extract [4,5 6,7]**:** Rambutan peel extract 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 combination:

- Benchmark 2c
  - Very High Persistence - P + Moderate Group II Human Toxicity (eye irritation-IrE)
  - Very High Persistence - P + Moderate Group II* Human Toxicity (skin sensitization – SnS* and respiratory sensitization – SnR*)
  - Very High Persistence - P + High Ecotoxicity (acute aquatic toxicity-AA and chronic aquatic toxicity-CA)

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

Figure 1: GreenScreen® Hazard Summary Table for Rambutan Peel Extract

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

No data were identified rambutan peel extract. The predominant constituent geraniin is predicted not to be readily biodegradable. It is a hydrolysable tannin that undergoes hydrolysis in the presence of hot water, weak acids and weak bases to yield ellagic acid, gallic acid, and glucose (Cheng et al. 2017). As none of the transformation products are categorized as an LT-1 or BM 1 chemical, the Benchmark Score for rambutan peel extract is not modified by the transformation products.

[4] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

[5] See Appendix A for a glossary of hazard endpoint acronyms.

[6] For inorganic chemicals only, see GreenScreen® Guidance v1.4 Section 12 (Inorganic Chemical Assessment Procedure).

[7] For Systemic Toxicity and Neurotoxicity, repeated exposure data are preferred. Lack of single exposure data is not a Data Gap when repeated exposure data are available. In that case, lack of single exposure data may be represented as NA instead of DG. See GreenScreen® Guidance v1.4 Annex 2.

Table 1: Environmental Transformation Product Summary						
Life Cycle Stage	**Transformation Pathway**	**Environmental Transformation Product**	**CAS #**	**Feasible (Yes or No)**	**Relevant (Yes or No)**	**GreenScreen® List Translator Score or GreenScreen Benchmark™ Score[8,9]**
N/A	Hydrolysis	Gallic acid	149-91-7	Yes	Yes	LT-UNK
N/A	Hydrolysis	Ellagic acid	476-66-4	Yes	Yes	LT-UNK
N/A	Hydrolysis	Glucose	50-99-7	Yes	Yes	BM-3

Introduction

Rambutan peel extract is an extract of the peel of the fruit rambutan, also called, *Nephelium lappaceum L*. The fruit rambutan belongs to the family of Sapindaceae, and is a native plant to Southeast Asia, Australia, South America, and African countries. The peel of the fruit rambutan is considered an agriculture waste and contains cellulose (24.28%), lignin (35.34%), hemicellulose (11.6%), and phenolic compounds. Only the latter compounds are extractable from the peel, while the cellulose and insoluble polysaccharides remains. Due to the high level of phenolic compounds in rambutan peel extract, it has several bioactivities and is used as an anti-inflammatory, antioxidant, antimicrobial, and antibacterial agent (Tingting et al. 2022).

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

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

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

Rambutan peel extract 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),[10] 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 rambutan peel extract can be found in Appendix C.

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2024) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

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

- Rambutan peel extract is an LT-UNK chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Rambutan peel extract is not listed on the U.S. DOT.
- Rambutan peel extract is not listed on any lists for multiple endpoints or single endpoints.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for rambutan peel extract, as indicated in Table 2. No general personal protective equipment (PPE) recommendations or occupational exposure limits (OELs) were identified.

Table 2: GHS H Statements for Rambutan Peel Extract (CAS #93165-68-5) (ECHA 2024c)	
H Statement	**H Statement Details**
No harmonized GHS H statements are reported by the European Chemicals Agency (ECHA). According to the notifications provided by companies to ECHA in REACH registrations, no hazards have been classified.	

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Rambutan Peel Extract (CAS #93165-68-5)			
Personal Protective Equipment (PPE)	**Reference**	**Occupational Exposure Limits (OEL)**	**Reference**
None identified		None identified	

Physicochemical Properties of Rambutan Peel Extract

No physicochemical properties were identified for rambutan peel extract. The predominant component, geraniin is a solid that is moderately soluble in water. Its measured partition coefficient of -0.73 indicates that geraniin is not likely to bioaccumulate.

Table 4: Physical and Chemical Properties of Rambutan Peel Extract (CAS #93165-68-5)		
Property	**Value**	**Reference**
Molecular formula	Unspecified (UVCB)	
SMILES Notation	Unspecified (UVCB	
Molecular weight	Not identified 952.6 g/mol (predominant component geraniin)	
Physical state	Solid (predominant component geraniin)	
Appearance	Not identified	
Melting point	Not identified	
Boiling point	Not identified	
Vapor pressure	Not identified	
Water solubility	80 mg/L at 20°C (predominant component geraniin)	Elendran et al. 2015
Dissociation constant	Not identified	
Density/specific gravity	Not identified	
Partition coefficient	log K_{ow} = -0.73 at 25°C (predominant component geraniin)	Elendran et al. 2015

Toxicokinetics

No specific toxicokinetic data are available for rambutan peel extract. The predominant component, geraniin is poorly absorbed in the digestive tract. However, it may be metabolized in the gut by bacteria or enzymes, and its metabolites are absorbed. These metabolites are excreted into urine as free or conjugated derivatives of gallic acid (Tingting et al. 2022, EFSA 2014).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Rambutan peel extract was assigned a score of Low for carcinogenicity based on negative findings in a 2-year oral carcinogenicity study with the surrogate tannic acid. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2014
  - *Surrogate: Tannic acid (CAS #1401-55-4):* In a two-year carcinogenicity study, male and female F344 rats (50/sex/dose) were provided a mixture of 85.69 % tannic acid, 8.84 % gallic acid, and 7.5 % moisture in drinking water at concentrations of 0.25 and 0.5%, equivalent to 131 and 243 mg/kg/day of tannic acid in males, and 159 and 291 mg/kg/day in females, respectively, as calculated by the study authors. No statistically significant increases in tumors were reported for treated animals. The study authors concluded that under the conditions of the bioassay, the test item was non-carcinogenic in rats after oral administration even at the high dose level 243 mg/kg/day in males and 291 mg/kg/day in females as calculated by the study authors).

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

Rambutan peel extract was assigned a score of Low for mutagenicity/genotoxicity based on the weight of evidence from *in vitro and in vivo* genotoxicity and clastogenicity assays with surrogates. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both gene mutation and clastogenicity and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2009
  - *Surrogate: Surrogate: Gallic acid (CAS #149-91-7): In vitro*: Negative results for mutagenicity were obtained in four non-guideline bacterial mutagenicity assays in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 tested at concentrations up to 5,000 µg/plate.

  - *Surrogate: Surrogate: Gallic acid (CAS #149-91-7): In vitro*: Equivocal results were measured in two bacterial mutagenicity assays conducted according to OECD Guideline 471 using *S. typhimurium* TA98, TA100, TA1535, TA1537 and two solvents (dimethyl sulfoxide (DMSO) and acetone). Negative results were observed with strains TA98, TA1535, TA1537 using both solvents and with TA100 using DMSO. Positive results were measured with strain TA100 using acetone in the absence and in the presence of metabolic activation. The effect was reproducible in a second but not in a third experiment.
  - *Surrogate: Surrogate: Gallic acid (CAS #149-91-7): In vitro*: Both positive and negative results were reported in various i*n vitro* assays for mutagenicity and clastogenicity including chromosomal aberration, sister chromatid exchange (SCE), and mitotic gene conversion assays. However, the panel of the European Food Safety Authority (EFSA) noted that reliability of these studies cannot be assessed, as they were reported in primary literature.
  - *Surrogate: Surrogate: Gallic acid (CAS #149-91-7): In vivo:* The test substance was negative for clastogenicity in a non-GLP medium term rat liver bioassay. The EFSA panel noted that reliability of this study cannot be assessed due to the limited details.
- The EFSA panel concluded that there is no safety concern with respect to genotoxicity of gallic acid based on the weight of evidence from results with chemicals in the same family class as well as negative results in the *in vivo* study
- EFSA 2014
  - *Surrogate: Tannic acid (CAS #1401-55-4): In vitro:* Negative results for mutagenicity were obtained in five bacterial mutagenicity assays and one SOS chromotest assay using *Escherichia coli.* However tannic acid was positive for mutagenicity and clastogenicity in the comet assay, chromosomal aberration assay, and micronucleus test.
  - *Surrogate: Tannic acid (CAS #1401-55-4): In vivo:* In an *in vivo* bone marrow micronucleus test, BALB/c mice were administered tannic acid at single doses of 250, 500, or 750 mg/kg by gavage and at 500 mg/kg given intraperitoneally (i.p.). Treatment did not increase the frequency of micronucleated polychromatic erythrocytes in any treatment group.
  - The EFSA panel concluded that although the results from the *in vitro* assays indicated a potential for tannic acid to be mutagenic, it was negative in an *in vivo* bone marrow micronucleus test indicating that the mutagenicity was not expressed.

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

Rambutan peel extract was assigned a score of Low for reproductive toxicity based on lack of reproductive effects in three-generation reproduction study conducted with the surrogate tannic acid. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2006
  - *Surrogate: Tannic acid (CAS #1401-55-4):* In a three-generation reproduction study, male and female rats were fed tannin (extracted from fruit Peruvian tara) in feed at doses of 0.0, 0.058%, 0.117%, or 0.234%, equivalent to 0, 29, 60, or 117 mg/kg/day, respectively, as calculated by the study authors. There were no treatment related effects on fertility, gestation, viability, or lactation indices at any dose level. Treatment caused a significant

decrease in pups' body weight in the 0.234% dose group at weaning. Based on this, authors assigned a NOAEL of 0.117% for this study, equivalent to 60 mg/kg/day.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Rambutan peel extract was assigned a score of Low for developmental toxicity based on the lack of developmental effects in prenatal developmental toxicity studies conducted with the surrogate tannic acid. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and negative, and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2006
  - *Surrogate: Tannic acid (CAS #1401-55-4):* In the previously described three-generation reproduction study, male and female rats were fed tannic acid (extracted from fruit Peruvian tara) in feed at doses of 0.0, 0.058%, 0.117%, or 0.234%, equivalent to 0, 29, 60, or 117 mg/kg/day, respectively, as calculated by the study authors. Treatment caused a significant decrease in pups' body weight in the 0.234% dose group at weaning. Based on this, authors assigned a NOAEL of 0.117% for this study, equivalent to 60 mg/kg/day.
  - *Surrogate: Tannic acid (CAS #1401-55-4):* In a prenatal developmetnal toxicity study, pregnaant female mice were administered tannic acid at doses of 1.35, 6.27, 29.1, or 135 mg/kg/day on days 6-15 of gestation via gavage. There were no treatment related effects on nidation or on maternal or fetal survival and no skeletal abnormalities. No further details were provided.
  - *Surrogate: Tannic acid (CAS #1401-55-4):* In a prenatal developmetnal toxicity study, female rats were administered tannic acid at doses of 1.8, 8.4, 38.8, or 180 mg/kg/day on days 6-15 of gestation via gavage. There were no treatment related effects on nidation or on maternal or fetal survival and no skeletal abnormalities. No further details were provided.

Endocrine Activity (E) Score (H, M, or L): DG
Rambutan peel extract was assigned a score of Data Gap for endocrine activity based on insufficient 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.
- No data were identified for this endpoint.

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

Acute Mammalian Toxicity (AT) (Group II) Score (vH, H, M, or L): L
Rambutan peel extract was assigned a score of Low for acute toxicity based on measured oral LD_{50} > 2,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when the oral and dermal LD_{50} values are greater than 2,000 mg/kg and when inhalation LC_{50} values are greater than 5 mg/L/4-hour (dust/mist/fume) and 20 mg/L/4-hour (vapor/gas) and when they are not GHS classified

(CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Subramaniam et al. 2012
  - *Oral:* LD_{50} (female Sprague Dawley rats) > 2,000 mg/kg (acceptable OECD Guideline). Test substance is ethanolic extract of rambutan peel.
- Mahirotun et al. 2023
  - *Oral:* LD_{50} (male and female Wistar rats) > 17,000 mg/kg (acceptable OECD Guideline).
- Moorthy et al. 2019
  - *Oral:* LD_{50} (female Sprague Dawley rats) > 2,000 mg/kg (OECD Guideline 423). Test substance is ethanolic extract of rambutan peel.

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

Rambutan peel extract was assigned a score of Low for systemic toxicity (single dose) based on a lack of effects on clinical signs, body weight, and gross pathology in acute oral toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and negative and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of inhalation data to assess respiratory irritation. The eye irritation data on surrogates suggest a potential for mucous membrane irritation (the conjunctiva is a mucous membrane), and the respiratory tract is lined with mucous membrane as well.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Subramaniam et al. 2012
  - *Oral:* In an acute oral toxicity study conducted according to an unspecified OECD Guideline, Sprague-Dawley rats (6/dose, sex not specified) were administered ethanolic extract of Rambutan peel in saline at single doses of 50, 200, 1,000, or 2,000 mg/kg and were monitored for 14 days (oral administration method was not specified). Treatment caused no deaths or adverse clinical signs.
- Moorthy et al. 2019
  - *Oral:* In an acute oral toxicity study conducted according to OECD Guideline 423, female Sprague-Dawley rats (5/dose) were administered undiluted ethanolic extract of Rambutan peel (contains geraniin at 45%) at a single dose of 2,000 mg/kg via gavage and were monitored for 14 days. No adverse clinical signs were reported. Treatment caused no deaths, changes to body weight, or gross abnormalities of the major organs.
- Mahirotun et al. 2023
  - *Oral:* In an acute oral toxicity study conducted according to an unspecified OECD Guideline, male and female Wistar rats (4/sex/dose) were administered Rambutan peel extract (extraction method, solvent used, and composition/purity not provided) at single doses of 400, 1,400, 4,900, and 17,150 mg/kg and were monitored for 14 days (oral administration method was not specified). No adverse clinical signs were reported. Some animals at 4,900 mg/kg and above exhibited slightly glazed eyes. Treatment caused no deaths or changes to body weight. Authors identified an oral LD_{50} > 17,000 mg/kg.

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

Rambutan peel extract was assigned a score of Low for systemic toxicity (repeated dose) based on lack of systemic toxicity at oral doses up to 6,400 mg/kg/day in a subchronic repeated dose toxicity study. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate and negative data are available and they are not GHS classified (oral NOAELs are greater than 100 mg/kg/day, established in 90-day studies) (CPA 2018b). The confidence in the score is high as it is based on measured data of high quality for the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Subramaniam et al. 2012
  - *Oral:* In a 28-day repeated dose toxicity study conducted according to OECD Guideline 407, Sprague-Dawley rats (6/dose, sex not specified) were administered ethanolic extract of Rambutan peel in saline daily at doses of 500 or 2,000 mg/kg/day. Animals were evaluated for clinical signs of toxicity, body weight, water and food consumption, hematology, organ weights, and histopathology (liver and kidney). Treatment did not adversely affect these parameters up to the highest dose tested. Authors assigned a NOAEL of 2,000 mg/kg/day for systemic toxicity, the highest dose tested in this study.
- Mahirotun et al 2023
  - *Oral:* In a 90-day repeated dose toxicity study conducted according to an unspecified OECD Guideline, Wistar rats (10/sex/dose) were orally (specific oral route unspecified) administered rambutan peel extract (purity/composition not specified) daily at doses of 3,500 or 6,400 mg/kg/day. Animals were evaluated for clinical signs of toxicity, body weight, water and food consumption, hematology, clinical chemistry, and histopathology (liver and kidney). Treatment did not adversely affect these parameters up to the highest dose tested. *ToxServices assigned a NOAEL of 6,400 mg/kg/day for systemic toxicity, the highest dose tested in this study.*

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

Rambutan peel extract was assigned a score of Low for neurotoxicity (single dose) based on the lack of clinical signs of neurotoxicity in acute oral toxicity studies. 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 it is based on studies with limited neurotoxicity examinations.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Subramaniam et al. 2012
  - *Oral:* In the previously described acute oral toxicity study conducted according to an unspecified OECD Guideline, Sprague-Dawley rats (6/dose, sex not specified) were administered ethanolic extract of rambutan peel in saline at single doses of 50, 200, 1,000, or 2,000 mg/kg and were monitored for 14 days (oral administration method was not specified). Treatment caused no deaths or clinical signs of neurotoxicity. *Clinical signs of neurotoxicity often evaluated in animal studies include: drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness, lethargy, and ataxia. If these effects are not transient in nature, they shall be considered to support classification for*

Category 1 or 2 specific target organ toxicity single exposure. Therefore, ToxServices concluded that Rambutan peel extract was not neurotoxic in this study.

- Moorthy et al. 2019
  - *Oral:* In the previously described acute oral toxicity study conducted according to OECD Guideline 423, female Sprague-Dawley (5/dose) were administered undiluted ethanolic extract of rambutan peel (contains geraniin at 45%) at a single dose of 2,000 mg/kg via gavage and were monitored for 14 days. No adverse clinical signs of neurotoxicity were reported. Treatment caused no deaths, changes to body weight, or gross abnormalities of the major organs.
- Mahirotun et al. 2023
  - *Oral:* In the previously described acute oral toxicity study conducted according to an unspecified OECD Guideline, male and female Wistar rats (4/sex/dose) were administered Rambutan peel extract (extraction method, solvent used, and composition/purity not provided) at single doses of 400, 1,400, 4,900, and 17,150 mg/kg and were monitored for 14 days (oral administration method was not specified). No adverse clinical signs were reported. Some animals at 4,900 mg/kg and above exhibited slightly glazed eyes. Treatment caused no deaths or changes to body weight. Authors identified an oral LD_{50} > 17,000 mg/kg.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
Rambutan peel extract was assigned a score of Data Gap for neurotoxicity (repeated dose) based on the lack of 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.
- No data were identified for this endpoint.

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): *M*
Rambutan peel extract was assigned a score of Moderate for skin sensitization based on the presence of structural and mechanistic alerts, and positive predictions by Toxtree and OECD QSAR Toolbox for its predominant component. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when they are classified to GHS Category 1B (low to moderate frequency of occurrence) (CPA 2018b). The confidence in the score is low due to lack of measured data on the neat target chemical or a surrogate, as well as lack of chemical composition data for rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- South Korea Patent 2004
  - A 10% ethanolic extract of Rambutan fruit in propylene glycol was not sensitizing to the skin of male and female guinea pigs when tested according to Magnusson's and Kligman's test methods.
  - A 10% ethanolic extract of Rambutan fruit was not sensitizing to the skin of human volunteers when tested in a human repeated insult patch test (HRIPT) conducted according to an acceptable guideline.
- OECD 2023
  - *Surrogate: Geraniin (CAS #60976-49-0):* Geraniin contains one protein binding alert for skin sensitization by OASIS (Michael addition) as identified by the OECD QSAR toolbox.

It also contains one protein binding alert (alpha, beta-carbonyl compounds with polarized double bond) for skin sensitization according to GHS and a classification of GHS Category 1A is predicted (Appendix D).
    - ToxServices attempted to predict the skin sensitization potential of geraniin using the read-across methodology with the OECD Toolbox model, but no surrogates were identified for read-across evaluation (OECD Toolbox).
- Payne and Walsh 1994
    - *Surrogate: Geraniin (CAS #60976-49-0):* Geraniin is predicted to be a skin sensitizer based on the presence of a structural alert (hydroquinone) identified by Payne and Walsh (1994). See Appendix E for complete list of structural alerts.
- Toxtree 2018
    - *Surrogate: Geraniin (CAS #60976-49-0):* Toxtree identified Schiff base formation and Michael acceptor as skin sensitization reactivity domain alerts for geraniin (Appendix F).
- Based on the weight of evidence a score of Moderate was assigned. An ethanolic extract of rambutan fruit was not sensitizing to the skin when tested at concentration of 10% in an *in vivo* test and HRIPT. However, the main component of rambutan peel extract, geraniin, was predicted to be a skin sensitizer by OECD toolbox and contains alerts for skin sensitization according to Payne and Walsh and Toxtree. Although the OECD QSAR Toolbox predicts a GHS Category 1A classification for the main component, ToxServices attempted read-across using OECD QSAR Toolbox and there were no surrogates identified for the read-across evaluation. As there are no data available to support a Category 1A classification and the HRIPT on rambutan fruit was negative, ToxServices considered geraniin to be at most a weak skin sensitizer corresponding to Category 1B, which corresponds to a Moderate. The confidence is low as the available evidence is based on modeling data.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *M*
Rambutan peel extract was assigned a score of Moderate for respiratory sensitization based on positive predication for skin sensitization for the surrogate, the presence of a structural alert for respiratory sensitization for the surrogate, and according to ECHA's recommended strategy on evaluation of respiratory sensitization. GreenScreen® criteria classify chemicals as a Moderate hazard for respiratory sensitization when they are classified to GHS Category 1B (low to moderate frequency of occurrence) (CPA 2018b). . The confidence in the score is low due to lack of measured data on the target chemical or surrogate as well as lack of chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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
    - *Surrogate: Geraniin (CAS # 60976-49-0):* Geraniin contains a structural alert for respiratory sensitization (Pro-Michael addition) as identified by the OECD QSAR toolbox (Appendix D).
- Based on the weight of evidence, a score of Moderate was assigned. No data were identified for rambutan peel extract. Its predominant component, geraniin is a potential dermal sensitizer based on the presence of structural and mechanistic alerts (see skin sensitization section above). In addition, it contains a structural alert for respiratory sensitization. According to the ECHA guidance (ECHA 2017), the positive skin sensitization results and the presence of a structural alert for respiratory sensitization indicate that there is sufficient positive data for the chemical to be classified as a respiratory sensitizer. Therefore, rambutan peel extract is classifiable as a respiratory sensitizer. No

information is available to subcategorize it to GHS Category 1A/1B. However, as the evidence for both skin and respiratory sensitization is based on modeling data, ToxServices classified rambutan peel extract as a weak respiratory sensitizer (1B).

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
Rambutan peel extract was assigned a score of Low for skin irritation/corrosivity based on expert judgment as it is used as a skin conditioning agent in cosmetic formulations, negative results in human studies at concentrations up to 3%, and the lack of irritation to the skin in a GLP-compliant *in vitro* reconstructed human epidermis test conducted according to OECD Guideline 439 with the surrogate. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and negative, and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of measured data on the neat target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2024b
  - *Surrogate: Gallic acid (CAS #149-91-7):* In a GLP-compliant *in vitro* reconstructed human epidermis test conducted according to OECD Guideline 439, 25 mg test substance was applied to non-transformed keratinocytes in triplicate from human donors for 60 minutes (35 minutes at 37°C and 25 minutes at room temperature) and incubated for 45 hours. There was no reduction of cell viability found. The mean relative tissue viability for gallic acid was above 70% and therefore, the study authors concluded that gallic acid was not a skin irritant under the test conditions. Negative and positive controls were reported as valid (Klimisch 1, reliable without restriction). *According to GHS Guidance, this test method does not differentiate GHS Category 3 and GHS Not Classified.*
- EC 2024
  - Based on its reported use as a skin conditioning agent, rambutan peel extract is unlikely to be irritating to the skin.
- Sekar et al. 2017
  - A cosmetic formulation (cream) containing 3% rambutan peel extract was not irritating to the skin of 10 human volunteers when tested in a human repeat insult patch test (HRIPT). The cream did not cause any redness, edema, or inflammation in treated volunteers.

Eye Irritation/Corrosivity (IrE) (Group II) Score (vH, H, M, or L): *H*
Rambutan peel extract was assigned a score of High for eye irritation/corrosivity based on a surrogate tannic acid being associated with a GHS Category 2A classification (corresponds to H319). GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS Category 2A (H319) (CPA 2018b). The confidence in the score is low due to lack of measured data on the surrogate tannic acid as well as lack of chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2024a
  - *Surrogate: Tannic acid (CAS #1401-55-4):* The authors of its REACH dossier classified tannic acid to GHS Category 2A for eye irritation with a hazard statement of H319: Causes serious eye irritation. The basis of the classification was not provided.
- ECHA 2024b

- *Surrogate: Gallic acid (CAS #149-91-7):* The test substance produced equivocal results when tested in a GLP-compliant *in vitro* bovine corneal opacity and permeability (BCOP) assay conducted according to OECD Guideline 437. A volume of 750 µL of 20% gallic acid in water was applied to three bovine eyes for 4 hours. Control and treated corneas were then subjected to opacity and permeability measurements. The *in vitro* irritancy score (IVIS) was 20.3, which falls between the threshold values of 3 and 55 (Klimisch 2, reliable with restrictions).

Ecotoxicity (Ecotox)

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

Rambutan peel extract was assigned a score of High for acute aquatic toxicity based on a measured IC_{50} value of 2.19 mg/L in algae for a component (gallic acid). GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when the most conservative acute aquatic toxicity value is between 1 and 10 mg/L and they are classified to GHS Category 2 (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%). In addition, gallic acid may be present in the target substance at a very low level, and it is unclear how significantly it will impact the aquatic toxicity of the mixture.

- 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 2006
  - *Surrogate: Tannic acid (CAS #1401-55-4):*
    - Tannic acid is considered moderately toxic to practically nontoxic to most aquatic organisms based on measured and predicted LC_{50}/EC_{50} values that were as low as 26 mg/L in *Daphnia*.
- ECHA 2024a
  - *Surrogate: Tannic acid (CAS #1401-55-4):*
    - 96-hour LC_{50} (*Gambusia affinis*, fish) = 37 mg/L. No further details were reported.
    - 48-hour EC_{50} (*Dreissena polymorpha,* Zebra mussels, *aquatic mollusc* / invertebrate) = 29 mg/L. No further details were reported.
- ECHA 2024b
  - *Surrogate: Gallic acid (CAS #149-91-7):*
    - 96-hour LC_{50} (*Danio rerio*, fish) > 100 mg/L nominal (OECD Guideline 203) (Klimisch 2, reliable with restrictions).
    - 48-hour EC_{50} (*Daphnia magna*, invertebrate) = 19 mg/L for mobility (OECD Guideline 202) (Klimisch 2, reliable with restrictions).
    - 72-hour IC_{50} (*Raphidocelis subcapitata*, green algae) for growth rate = 2.19 mg/L (U.S. EPA Guideline) (Klimisch 2, reliable with restrictions).
    - 48-hour EC_{50} (*R. subcapitata*, green algae) for growth rate = 15.9 mg/L (Non-Guideline study) (Klimisch 2, reliable with restrictions).

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

Rambutan peel extract was assigned a score of High for chronic aquatic toxicity based on estimated chronic aquatic toxicity values as low as 0.55 mg/L in algae for a surrogate constituent (gallic acid). GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are > 0.1 to 1.0 mg/L (CPA 2018b). The confidence in the score is low as it is

based on predicted data and due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2006
  Surrogate: Tannic acid (CAS #1401-55-4): Predicted chronic aquatic toxicity values for tannic acid were approximately 70 mg/L in algae based on the ester SAR class and 330 mg/L in fish based on the phenol SAR class.
- U.S. EPA 2023
  - *Surrogate: Geraniin (CAS # 60976-49-0):* Geraniin belongs to several ECOSAR chemical classes (esters, neutral organics, vinyl/allyl/propargyl ketone, ketone alcohols, and phenols, poly). The most conservative predicted chronic values (ChVs) are 230 mg/L in fish, 140 mg/L in daphnia, and 14.9 mg/L in green algae (Appendix G).
- U.S. EPA 2023
  - *Surrogate: Gallic acid (CAS #149-91-7):* ToxServices performed modeling using ECOSAR, but because the predicted values for acute toxicity differ greatly (i.e., > 10X) from the available measured data described above, ToxServices did not consider the model to be reliable for this compound. Therefore, ECOSAR modeling on gallic acid is not considered in the weight of evidence.
- U.S. EPA 2013
  - *Surrogate: Gallic acid (CAS #149-91-7):* Using the lowest acute L/EC_{50} values described above and the acute to chronic ratios of 10, 10, and 4 for fish, daphnia, and algae, respectively, for neutral organics and classes with excess toxicity, ToxServices calculated ChVs of > 10 mg/L for fish, 1.9 mg/L for daphnia, and 0.55 mg/L for algae.

Environmental Fate (Fate)

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

Rambutan peel extract was assigned a score of Very High for persistence based on its predominant component being predicted not biodegradable with a half-life of 541 days in soil. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when they have half-lives of >180 days in sediment and soil (CPA 2018b). The confidence in the score is low as it is based on predicted data and due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- 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 2006
  - *Surrogate: Tannic acid (CAS #1401-55-4):* Tannic acid is expected to biodegrade in the environment with ultimate aerobic degradation estimated to be weeks and primary degradation estimated to be days.
- U.S. EPA 2017
  - *Surrogate: Geraniin (CAS # 60976-49-0):* The BIOWIN modeling Ready Biodegradable Predictor indicates that geraniin is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 59.4% will partition to sediment with a half-life of 541.6 days (1.3e+004 hours / 24 hours), 39.5% will partition to soil with a half-life of 116 days

(2,880 hours / 24 hours), 1.11 % will partition to water with a half-life of 60 days, and less than 1% will partition to air (Appendix H).

Bioaccumulation (B) Score (vH, H, M, L, or vL): *vL*
Rambutan peel extract was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} value of -0.73 and predicted BCFs of 0.90-3.16 for its predominant component geraniin. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the measured log K_{ow} values are ≤ 4 and/or BCF values are ≤ 100 (CPA 2018b). The confidence in the score is low due to lack of data on the chemical composition of rambutan peel extract, which may contain components other than polyphenols at a significant level (> 0.1%).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Elendran et al. 2015
  - *Surrogate: Geraniin (CAS # 60976-49-0):* Geraniin has a measured log K_{ow} of -0.73 ± 0.17 at 25°C obtained from a shake-flask method.
- U.S. EPA 2017
  - *Surrogate: Geraniin (CAS # 60976-49-0):* BCFBAF predicts a BCF of 3.162 using the regression based model based on a measured log K_{ow} of -0.73, and a BCF of 0.8966 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix I).
- U.S. EPA 2006
  - *Surrogate: Tannic acid (CAS #1401-55-4):* Tannin is not expected to bioaccumulate in the environment.

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Rambutan peel extract was assigned a score of Low for reactivity based on NFPA and HMIS instability rating of 0 for its main component (geraniin) supported by lack of functional groups associated with explosive or oxidizing properties. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when they are not GHS classified for any of the reactivity sub-endpoints (CPA 2018b). The confidence in the score is low due to 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.
- Cayman Chemicals 2023
  - *Surrogate: Geraniin (CAS # 60976-49-0):* A safety data sheet for geraniin states that it has a physical/reactivity hazard of 0 from HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives (e.g., helium)") [11] and NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") [12].
- Screening procedures for explosivity were used here to estimate the reactivity property of Rambutan peel extract. These procedures are listed in the GHS (UN 2023).

[11] https://www.bgsu.edu/content/dam/BGSU/envhs/documents/Hazard-Communication/HMIS-Labeling-Information.pdf
[12] https://www.nfpa.org/News-and-Research/Publications-and-media/Blogs-Landing-Page/NFPA-Today/Blog-Posts/2021/11/05/Hazardous-Materials-Identification

- Based on the structure of its components or moieties (phenolic compounds), rambutan peel extract is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (Appendix H).
- Based on the structure of its components or moieties (phenolic compounds), rambutan peel extract is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials.

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

Rambutan peel extract was assigned a score of Low for flammability based on NFPA and HMIS flammability rating of 0 for its main component (geraniin). GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low due to lack of measured data on the surrogates or the target chemical.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- Cayman Chemicals 2023
  - *Surrogate: Geraniin (CAS #60976-49-0):* A safety data sheet for geraniin states that it is not flammable and it has a flammability rating of 0 from HMIS and NFPA; which correspond to "Materials that will not burn and are not considered flammable or combustible under OSHA's Hazard Communication Standard.

Use of New Approach Methodologies (NAMs)[13] in the Assessment, Including Uncertainty Analyses of Input and Output

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* tests for genotoxicity, skin and eye irritation, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, persistence, and bioaccumulation. 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 (2018b), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

As shown in Table 5, Type I (input data) uncertainties in rambutan peel extract's NAMs include the invalidity of the *in vitro* SOS chromotest by OECD, the absence of experimental data for skin sensitization, respiratory sensitization, chronic aquatic toxicity, and environmental partitioning, and lack of established test methods for respiratory sensitization. Rambutan peel extract's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays to mimic *in vivo* metabolic conditions, the limitation of the *in vitro* skin corrosion test **(**OECD Guideline 439) to identify substances classified as mild skin irritant (GHS Category 3), the limitation of the *in vitro* eye irritation test (OECD Guideline 437) to identify substances classified as eye irritant (GHS Category 2), lack of defined applicability domains for OECD Toolbox and Toxtree and lack of consideration of non-immunological mechanisms of respiratory sensitization. Some of the type I and type II errors can be alleviated by the use of genotoxicity test batteries in combination with *in vivo* data, and ECHA's decision framework to evaluate respiratory sensitization.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Genotoxicity:** The *in vitro* SOS chromotest has not been validated by OECD. **Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Chronic aquatic toxicity:** No experimental data are available. **Persistence:** No environmental partitioning data were identified.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[14]. 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).[15] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[16]. **Skin sensitization**: Both the OECD QSAR Toolbox and Toxtree only identify structural alerts, and do not define applicability domains. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts, and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization. **Skin irritation:** The OECD 439 test is only used to identify irritating substances (GHS Category 2) and non-irritating substances (no category) (UN 2023). **Eye irritation:** The BCOP (OECD 437) is only used to identify corrosive substances (GHS Category 1) and non-irritating substances (no category) (UN 2023). There is no single *in vitro* method that can replace an *in vivo* eye irritation test	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay/ *in vitro* SOS chromotest
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: OECD Toolbox structural alerts, and
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts/
Skin irritation	Y	*In vitro* data: reconstructed human epidermis test (OECD 439)
Eye irritation	Y	*In vitro* data: The BCOP assay (OECD 437).
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Persistence	Y	*In silico* modeling: EPI Suite™
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

References

Cayman Chemicals. 2023. Safety Data Sheet (SDS) for Geraniin (CAS #60976-49-0). Revision date 05/22/2023. Available: https://cdn.caymanchem.com/cdn/msds/29924m.pdf

Cheng, H. S., S. Ton, and K. Kadir. 2017. Ellagitannin geraniin: a review of the natural sources, biosynthesis, pharmacokinetics and biological effects. *Phytochemistry Reviews*. 16. 10.1007/s11101-016-9464-2. Available: https://www.researchgate.net/publication/300002809_Ellagitannin_geraniin_a_review_of_the_natural_sources_biosynthesis_pharmacokinetics_and_biological_effects

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

Clean Production Action (CPA). 2018b. The GreenScreen® for Safer Chemicals Guidance. Version 1.4 Guidance. Dated January, 2018. Available: https://www.greenscreenchemicals.org/static/ee_images/uploads/resources/GreenScreen_Guidance_v1_4_2018_01_Final.pdf

Elendran, S., L. Wang Wang, R. Prankerd, and U. D. Palanisamy. 2015. The physicochemical properties of geraniin, a potential antihyperglycemic agent. *Pharmaceutical Biology*. 53:12, 1719-1726. Available: https://www.tandfonline.com/doi/full/10.3109/13880209.2014.1003356

European Chemicals Agency (ECHA). 2024a. REACH registration dossier for tannic acid (CAS #1401-55-4). Available: https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/20748/1/1

European Chemicals Agency (ECHA). 2024b. REACH registration dossier for gallic acid (CAS #149-91-7). Available: https://echa.europa.eu/ro/registration-dossier/-/registered-dossier/25188/1/1

European Food Safety Authority (EFSA). 2009. Flavouring Group Evaluation 20, Revision 1 (FGE.20Rev1) 1: Benzyl alcohols, benzaldehydes, a related acetal, benzoic acids and related esters from chemical group 23 Scientific Opinion of the Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC). *EFSA Journal*. ON- 976, 1-125. Available: https://www.efsa.europa.eu/en/efsajournal/pub/976

European Food Safety Authority (EFSA). 2014. Scientific Opinion on the safety and efficacy of tannic acid when used as feed flavouring for all animal species1 EFSA Panel on Additives and Products or Substances used in Animal Feed (FEEDAP). *EFSA Journal*. 12(10):3828. Available: https://www.efsa.europa.eu/pt/efsajournal/pub/3828

European Food Safety Authority (EFSA). 2018. Guidance on uncertainty analysis in scientific assessments. *EFSA Journal.* 16(1): e05123. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7009727/

European Commission. 2024. CosIng - Cosmetics Ingredients. Available: https://ec.europa.eu/growth/tools-databases/cosing/

Madden, J.C., S.J. Enoch, A. Paini, and M.T.D. Cronin. 2020. A review of *in silico* tools as alternatives to animal testing: principles, resources, and applications. *Alternatives to Laboratory Animals.* 48(4): 146-172. Available: https://journals.sagepub.com/doi/pdf/10.1177/0261192920965977

Mahirotun, A., M, H, and A. Suhendi, A. .2023. Acute and sub-chronic toxicity studies of rambutan (Nephelium lappaceum l.) Fruit peel extract in rats. *KnE Social Sciences*. 8(4), 746–754. Available: https://doi.org/10.18502/kss.v8i4.12969

Moorthy, M., J. J. Khoo, and U. D. Palanisamy. 2019. Acute oral toxicity of the ellagitannin geraniin and a geraniin-enriched extract from *Nephelium lappaceum* L rind in Sprague Dawley rats. *Heliyon*. 5(8):e02333. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6726880/pdf/main.pdf

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

Organisation for Economic Co-operation and Development (OECD). 2023. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 4.6. Available: http://toolbox.oasis-lmc.org/?section=download&version=latest.

Payne, M.P and P.T. Walsh. 1994. Structure-activity relationships for skin sensitization potential: development of structural alerts for use in knowledge-based toxicity prediction systems. *Journal of Chemical Information and Computer Sciences*. 34:154-161.

Pharos. 2024. Pharos Chemical and Material Library Entry for Rambutan peel extract (CAS #93165-68-5). Available: http://www.pharosproject.net/material/.

PubChem. 2023. Entry for Geraniin (CAS #60976-49-0). Available: https://pubchem.ncbi.nlm.nih.gov/compound/3001497#section=InChIKey

Sekar, M., P. Sivalinggam and A. Mahmad. 2017. Formulation And Evaluation Of Novel Antiaging Cream Containing Rambutan Fruits Extract. *IJPSR*. 8(3): 1056-1065. Available: https://www.researchgate.net/profile/Mahendran-Sekar2/publication/315707989_FORMULATION_AND_EVALUATION_OF_NOVEL_ANTIAGING_CREAM_CONTAINING_RAMBUTAN_FRUITS_EXTRACT/links/5e738f9f299bf134dafd2103/FORMULATION-AND-EVALUATION-OF-NOVEL-ANTIAGING-CREAM-CONTAINING-RAMBUTAN-FRUITS-EXTRACT.pdf

Sigma-Aldrich. 2024. Tannic acid (CAS #1401-55-4). Available: https://www.sigmaaldrich.com/US/en/search/1401-55-4?focus=products&page=1&perpage=30&sort=relevance&term=1401-55-4&type=product

South Korea Patent. 2004. Skin-whitening cosmetic composition containing extract of rambutan and method for extracting rambutan. Available: https://patents.google.com/patent/KR20060007083A/en

Subramania, S., S. Chakravarthi, U. D. Palanisamy, A. Radhakrishnan, and N. Haleagrahara, Nagaraja. 2012. Acute and sub chronic oral toxicity assessment of the ethanolic extract from the rind of

Nephelium lappaceum in Rats. *Journal of Pharmacology and Toxicology*. 7:378-385. Available: https://www.researchgate.net/publication/273718133_Acute_and_Sub_Chronic_Oral_Toxicity_Assessment_of_the_Ethanolic_Extract_from_the_Rind_of_Nephelium_lappaceum_in_Rats

Tingting, Z., Z. Xiuli, W. Kun, S. Liping, and Z. Yongliang. 2022. A review: extraction, phytochemicals, and biological activities of rambutan (Nephelium lappaceum L) peel extract. *Heliyon.* 8:e11314. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9647437/pdf/main.pdf

Torgbo, S., P. Sukyai, U. Sukatta, S. Böhmdorfer, M. Beaumont, and T. Rosenau. 2024. Cellulose fibers and ellagitannin-rich extractives from rambutan (Nephelium Lappaceum L.) peel by an eco-friendly approach. *International Journal of Biological Macromolecules.* 259 (2): 128857. Available: https://www.sciencedirect.com/science/article/abs/pii/S0141813023057562

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

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

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

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

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

United States Environmental Protection Agency (U.S. EPA). 2006. Inert Reassessment - Tannin (CAS Reg. No. 1401-55-4). Dated: February 27, 2006. Available: https://www.epa.gov/sites/default/files/2015-04/documents/tannin.pdf

United States Environmental Protection Agency (U.S. EPA). 2013. Interpretive assistance document for assessment of discrete organic chemicals. Available: https://www.epa.gov/sites/default/files/2015-05/documents/05-iad_discretes_june2013.pdf

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

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

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

United States Environmental Protection Agency (U.S. EPA). 2023. ECOSAR 2.2. Washington, DC, USA. Available: http://www.epa.gov/oppt/newchems/tools/21ecosar.htm/

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

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 Rambutan Peel Extract (CAS #93165-68-5)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

			Group I Human					Group II and II* Human								Ecotox		Fate		Physical	
			Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details									S	R *	S	R *	*	*								
Inorganic Chemical?	**Chemical Name**	**CAS#**	**C**	**M**	**R**	**D**	**E**	**AT**	**STs**	**STr**	**Ns**	**Nr**	**SNS***	**SNR***	**IrS**	**IrE**	**AA**	**CA**	**P**	**B**	**Rx**	**F**
No	**Rambutan Peel Extract**	**93165-68-5**	*L*	*L*	*L*	*L*	DG	**L**	*L*	**L**	*L*	DG	*M*	*M*	*L*	*H*	*H*	*H*	*vH*	***vL***	*L*	*L*

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Rambutan Peel Extract	2

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

Table 6

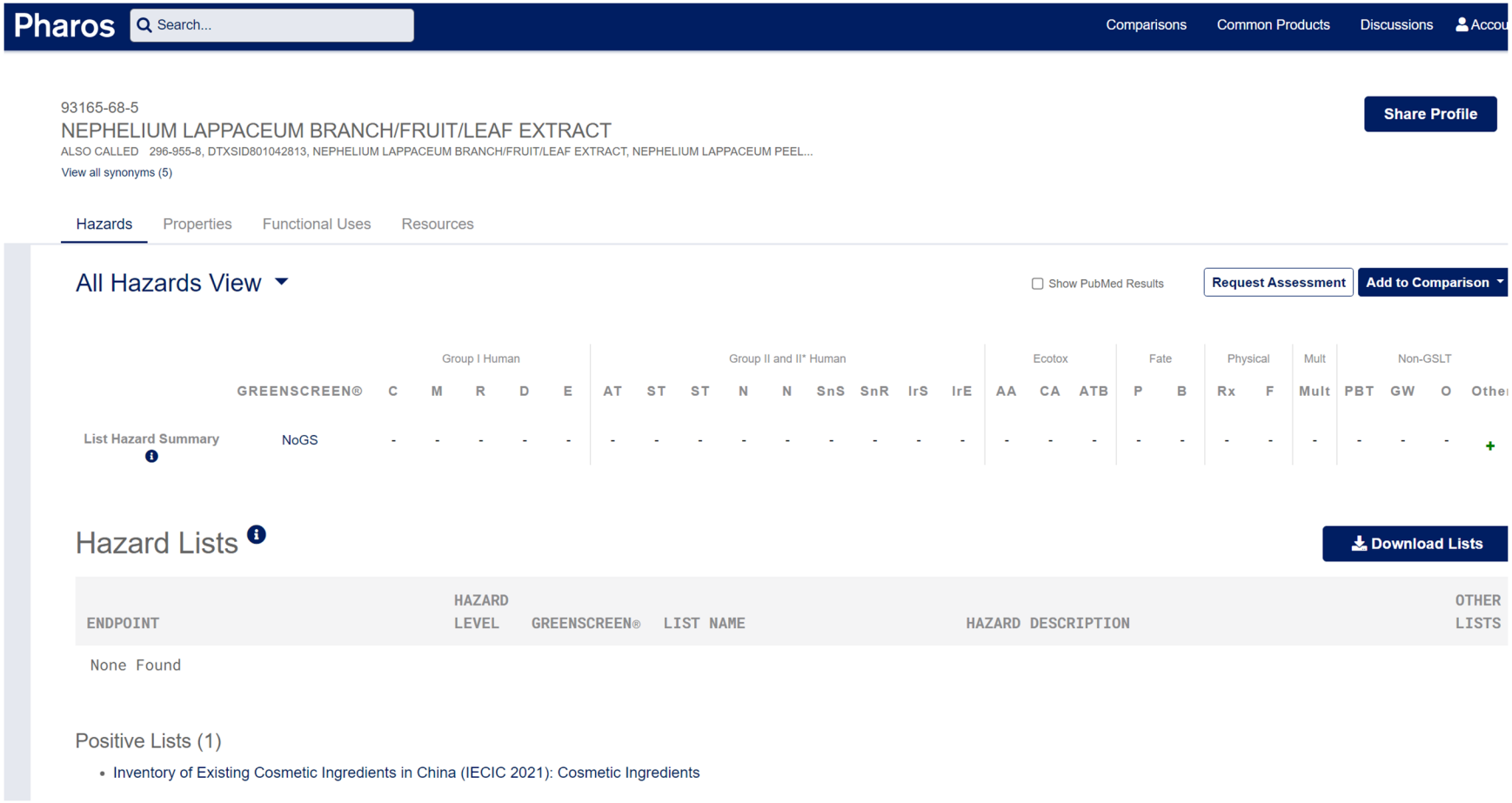
Chemical Name	Final GreenScreen® Benchmark Score
Rambutan Peel Extract	2

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

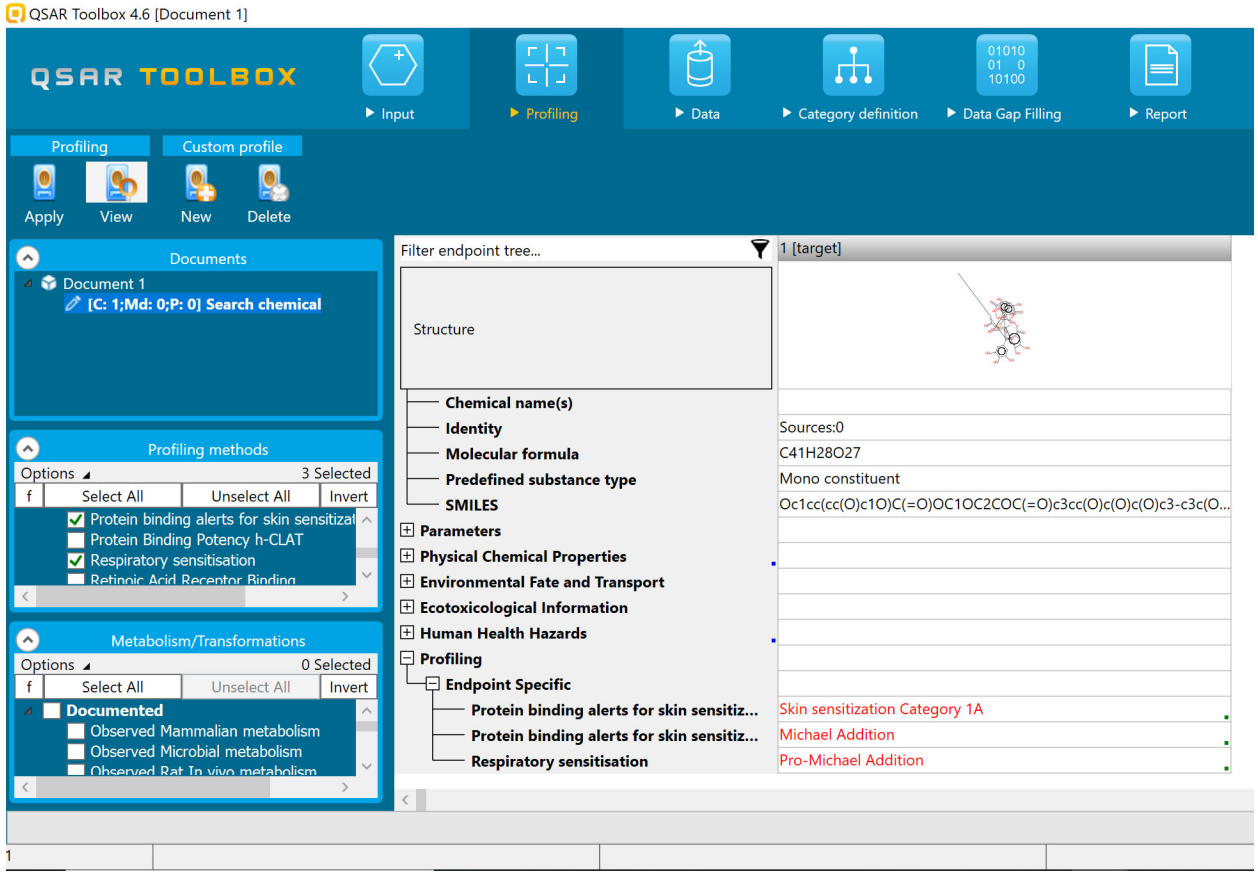
Table 5: Data Gap Assessment Table

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 Rambutan Peel Extract (CAS #93165-68-5)

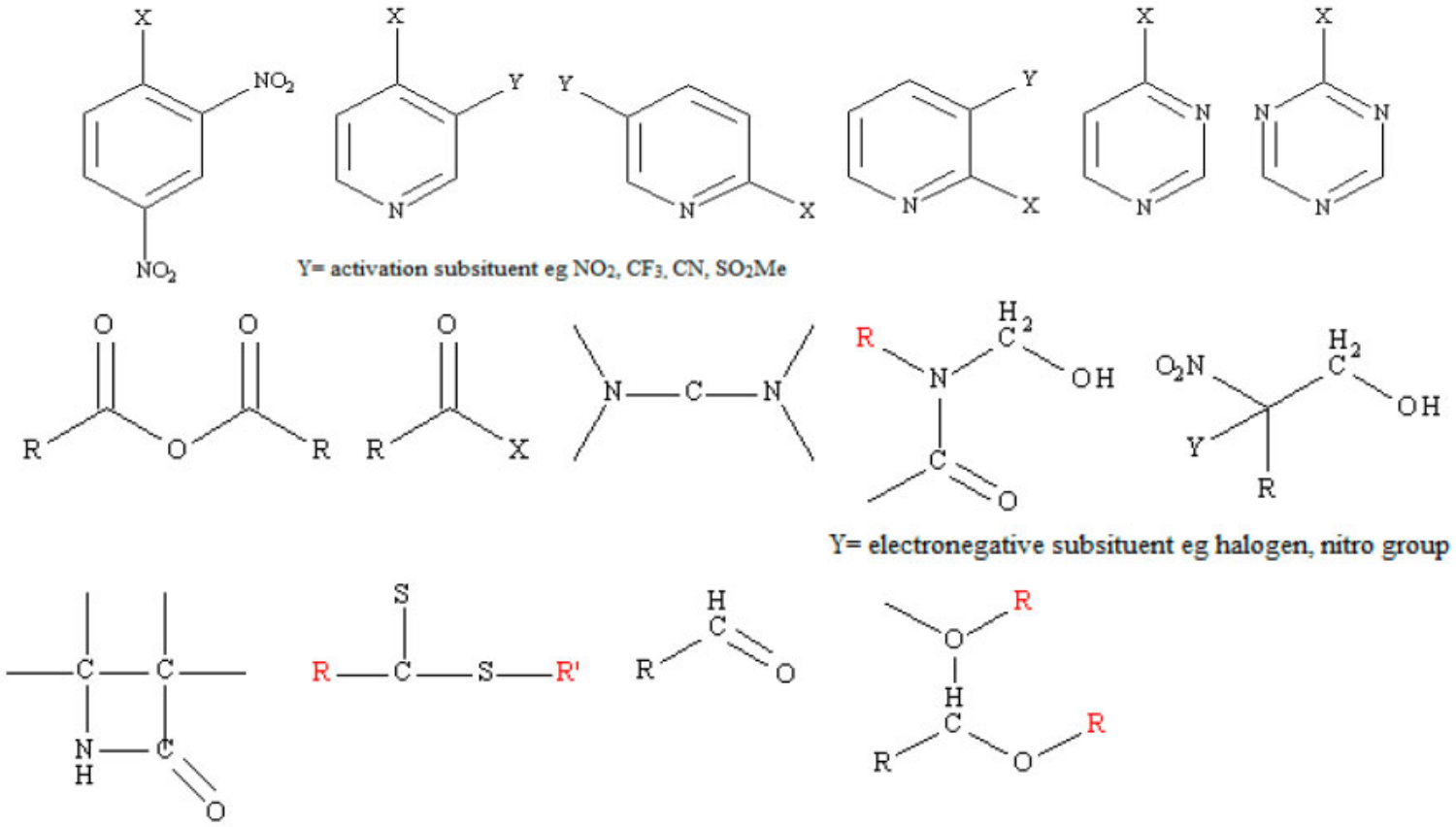


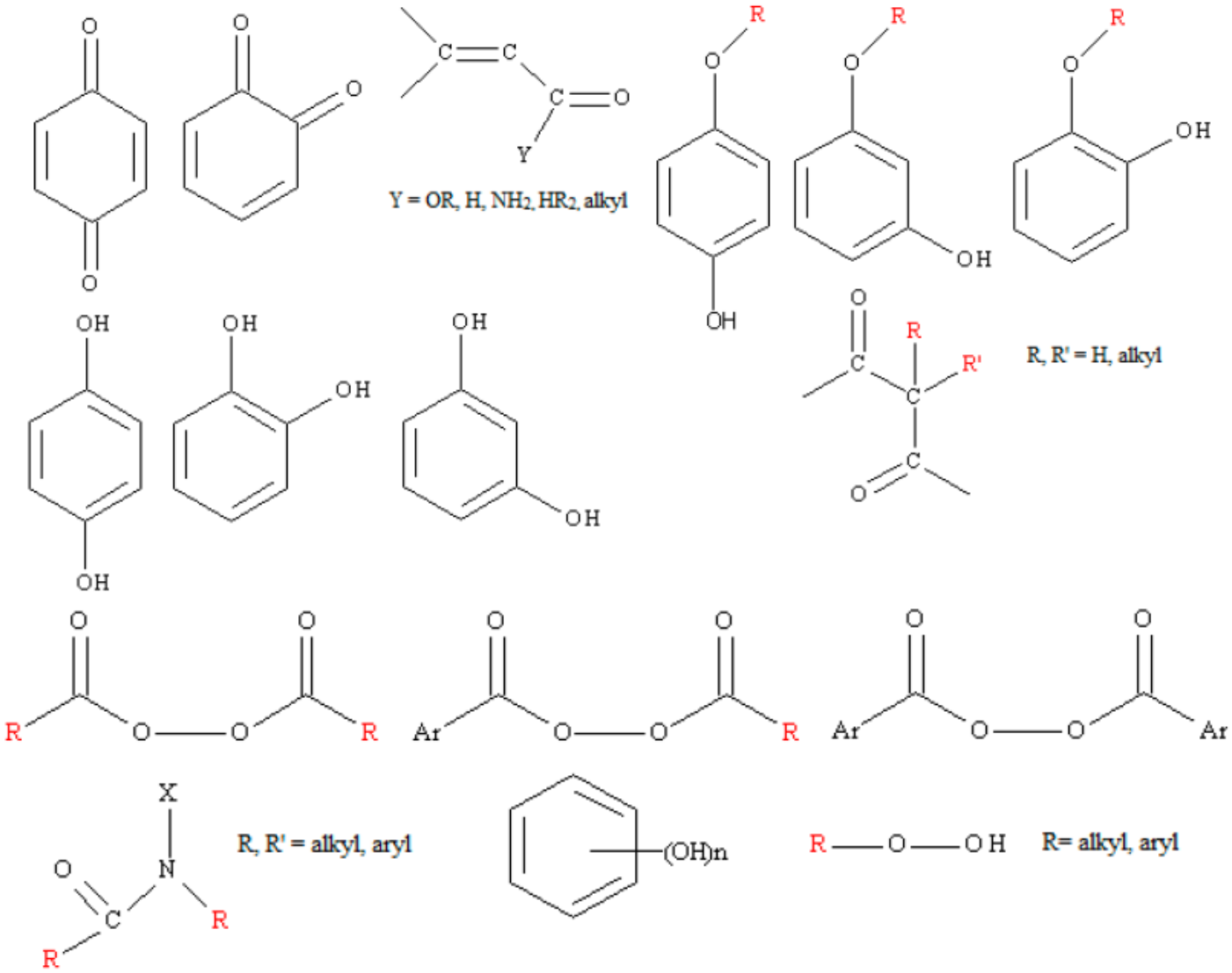
APPENDIX D: OECD Toolbox Profile for Geraniin (CAS # 60976-49-0), the Predominant Component in Rambutan Peel Extract

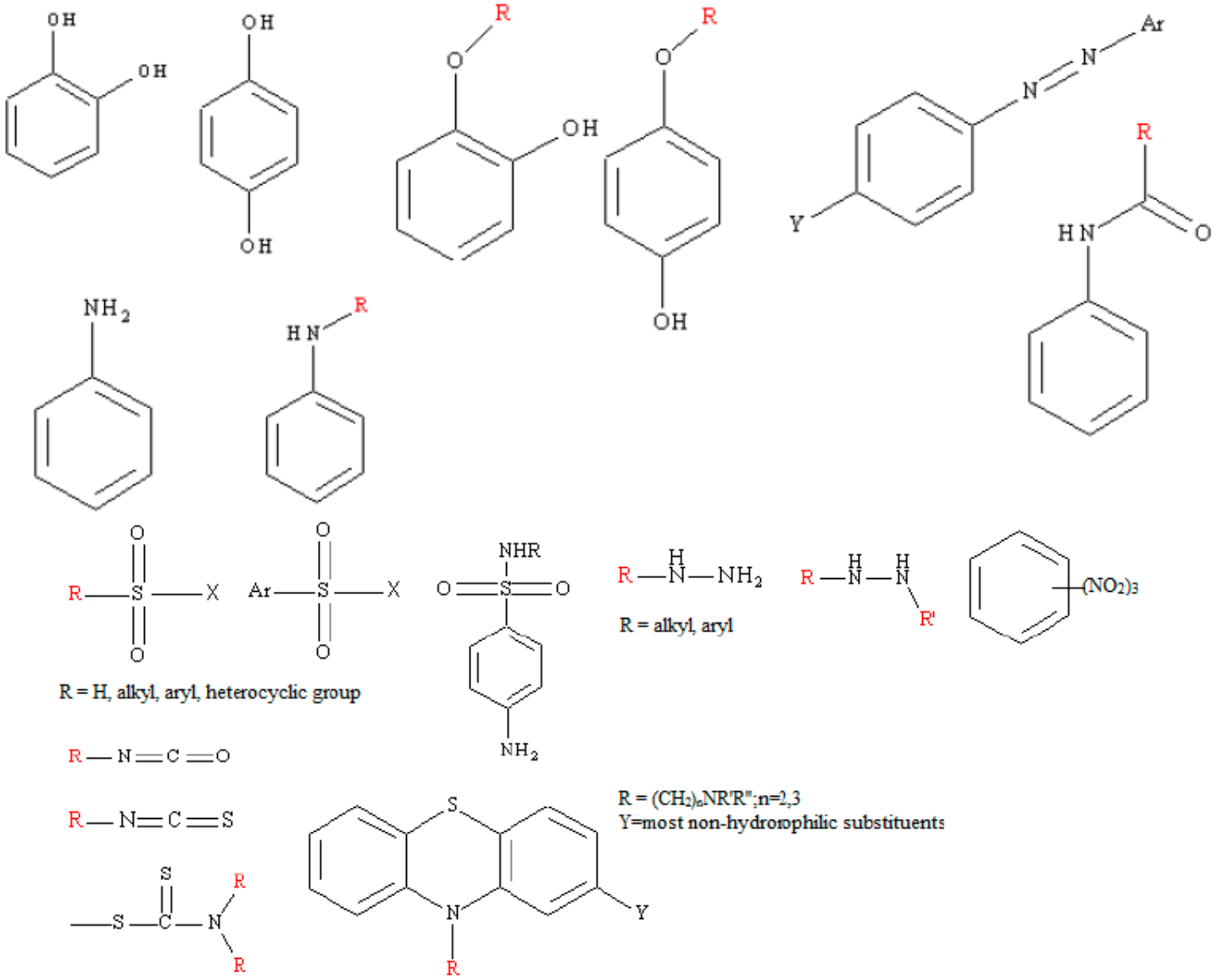


APPENDIX E: Known Structural Alerts for Skin Sensitization

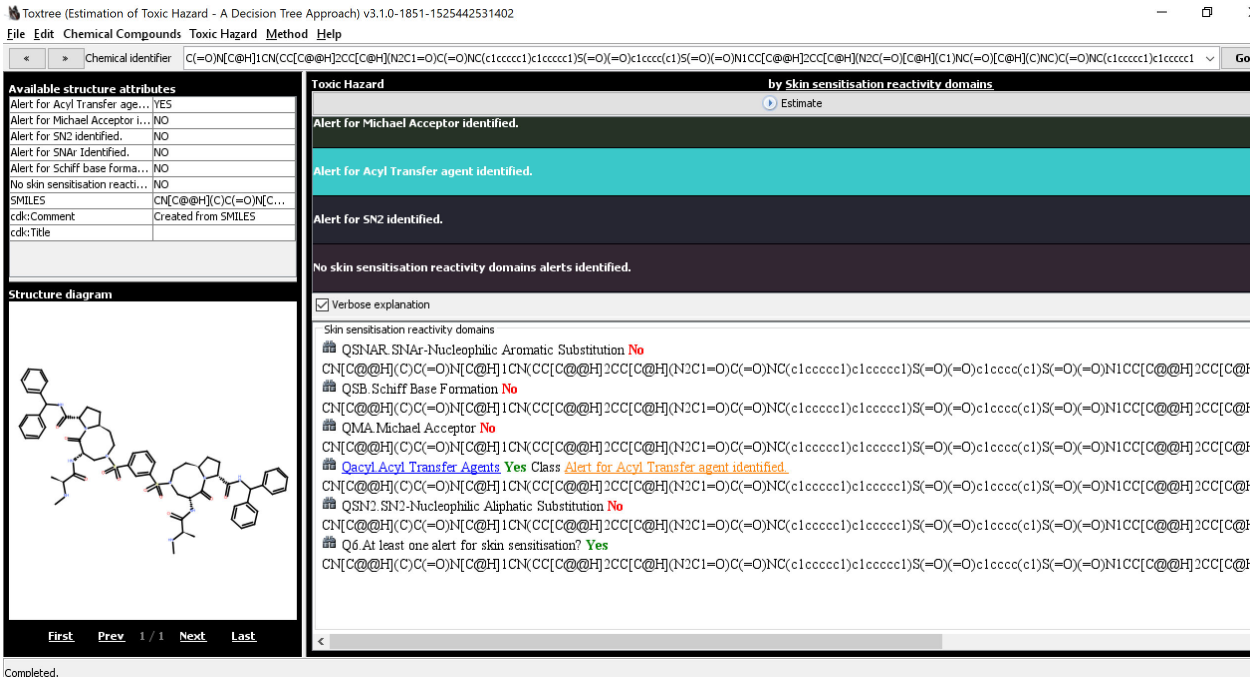
Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). The surrogate geraniin possesses hydroquinone structural alert.







APPENDIX F: Toxtree Skin Sensitization Results for Geraniin (CAS # 60976-49-0), the Predominant Component in Rambutan Peel Extract



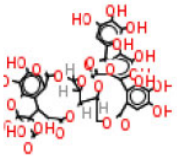
APPENDIX G: ECOSAR Modeling Results for Geraniin (CAS # 60976-49-0), the Predominant Component in Rambutan Peel Extract

Created on Mar 23, 2024 4:03:21 PM

Organic Module Report

Results of Organic Module Evaluation

CAS	Name	SMILES
		Oc1cc(cc(O)c1O)C(=O)OC2O[C@H]3COC(=O)c4cc(O)c(O)c(O)c4c5c(O)c(O)c(O)cc5C(=O)O[C@@H]6[C@H]3OC(=O)C7=CC(=O)C8(O)Oc9c(O)c(O)cc(C(=O)O[C@H]26)c9C7C8(O)O

Structure


Details	
Mol Wt	952.66
Selected LogKow	-0.73
Selected Water Solubility (mg/L)	
Selected Melting Point (°C)	
Estimated LogKow	0.23
Estimated Water Solubility (mg/L)	0.86
Measured LogKow	
Measured Water Solubility (mg/L)	
Measured Melting Point (°C)	

Class Results:	

Esters

1/ 10

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	5.11E03	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	1.46E04	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	1.22E04	6.4	• 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		ChV	2.39E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid		ChV	1.26E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae		ChV	2.91E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)	96h	LC50	1.01E04	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	1.16E04	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	8.57E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Mysid (SW)		ChV	2.49E08	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Fish	14d	LC50	3.29E07	6	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Earthworm	14d	LC50	9.43E04	6	• 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

Neutral Organics

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	2.21E05	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	9.77E04	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	2.57E04	6.4	• 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		ChV	1.61E04	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid		ChV	4.73E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae		ChV	3.84E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish (SW)	96h	LC50	2.74E05	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	1.30E06	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	5.62E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Mysid (SW)		ChV	2.52E05	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Earthworm	14d	LC50	3.18E03	6	• 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

Vinyl/Allyl/Propargyl Ketones

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

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	1.15E04	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	8.02E03	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	4.62E04	6.4	• 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		ChV	1.25E05	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid		ChV	9.96E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported , • The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Green Algae		ChV	6.44E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Fish (SW)	96h	LC50	1.23E07	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 (SW)	96h	LC50	4.64E05	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	5.52E05	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Mysid (SW)		ChV	5.81E04	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported , • The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document

Ketone Alcohols

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	3.57E03	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	1.53E03	5	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae	96h	EC50	3.07E02	6.4	• 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		ChV	3.30E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported • The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document

Class Results:	

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Daphnid		ChV	1.40E02	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported , • The toxicity value was estimated through application of acute-to-chronic ratios per methods outlined in the ECOSAR Methodology Document
Green Algae		ChV	1.27E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

Phenols, Poly

Organism	Duration	End Point	Concentration (mg/L)	Max Log Kow	Flags
Fish	96h	LC50	2.16E03	7	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid	48h	LC50	5.00E04	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
Green Algae	96h	EC50	1.67E02	6.4	• 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		ChV	1.80E03	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Daphnid		ChV	2.21E04	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported
Green Algae		ChV	1.49E01	8	• Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported

APPENDIX H: EPI Suite™ Modeling Results for Geraniin (CAS # 60976-49-0), the Predominant Component in Rambutan Peel Extract

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

CAS Number: 60976-49-0
SMILES : C1C2C3C(C(C(O2)OC(=O)c4cc(c(c(c4)O)O)O)OC(=O)c5cc(c(c6c5C7C(=CC(=O)C(
C7(O)O)(O6)O)C(=O)O3)O)O)OC(=O)c8cc(c(c(c8c9c(c(c(cc9C(=O)O1)O)O)O)O)O)
O)O
CHEM :
MOL FOR: C41 H28 O27
MOL WT : 952.66
Vapor Pressure (mm Hg) : ------
Henry LC (atm-m3/mole) : ------
Log Kow (octanol-water): -0.73
Physical Property Inputs:
---------- EPI SUMMARY (v3.20) ----------
Water Solubility (mg/L): ------
Boiling Point (deg C) : ------
Melting Point (deg C) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 0.57

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 1495.85 (Adapted Stein & Brown method)
Melting Pt (deg C): 349.84 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 0 (Modified Grain method)
VP (Pa, 25 deg C) : 0 (Modified Grain method)
Subcooled liquid VP: 0 mm Hg (25 deg C, Mod-Grain method)
: 0 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 0.857
log Kow used: -0.73 (user entered)
no-melting pt equation used

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 9.5266e-007 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters
Vinyl/Allyl Ketones
Ketone alcohols
Phenols, Poly

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

Group Method: Incomplete
For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
not available

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

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.9170
Biowin2 (Non-Linear Model) : 1.0000
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 1.8268 (months)
Biowin4 (Primary Survey Model) : 3.7244 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.4332
Biowin6 (MITI Non-Linear Model): 0.0018
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.8889
Ready Biodegradability Prediction: NO

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Insufficient Data Available.

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 293.8247 E-12 cm3/molecule-sec
Half-Life = 0.036 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 26.210 Min
Ozone Reaction:
OVERALL Ozone Rate Constant = 1.137500 E-17 cm3/molecule-sec
Half-Life = 1.007 Days (at 7E11 mol/cm3)
Half-Life = 24.179 Hrs
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.0192 (Junge-Pankow, Mackay avg)
0.0218 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 1.741E+008 L/kg (MCI method)
Log Koc: 8.241 (MCI method)
Koc : 36.6 L/kg (Kow method)
Log Koc: 1.563 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 2.460E-001 L/mol-sec
Kb Half-Life at pH 8: 32.612 days
Kb Half-Life at pH 7: 326.124 days
(Total Kb applies only to esters, carbmates, alkyl halides)

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) = -13.4224 days (HL = 3.781e-014 days)
Log BCF Arnot-Gobas method (upper trophic) = -0.047 (BCF = 0.8966)
Log BAF Arnot-Gobas method (upper trophic) = -0.047 (BAF = 0.8966)
log Kow used: -0.73 (user entered)

Volatilization from Water:
Henry LC: 1.46E-015 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 1.235E+012 hours (5.148E+010 days)
Half-Life from Model Lake : 1.348E+013 hours (5.616E+011 days)

Removal In Wastewater Treatment:
Total removal: 1.85 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.76 percent
Total to Air: 0.00 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**0.00143**	**0.843**	**1000**
Water	**1.11**	**1.44e+003**	**1000**
Soil	**39.5**	**2.88e+003**	**1000**
Sediment	**59.4**	**1.3e+004**	**0**

Persistence Time: 5.98e+003 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.00143	0.843	1000
Water	1.11	1.44e+003	1000
water	(0.00425)		
biota	(3.96e-011)		
suspended sediment	(1.11)		
Soil	39.5	2.88e+003	1000
Sediment	59.4	1.3e+004	0

Persistence Time: 5.98e+003 hr

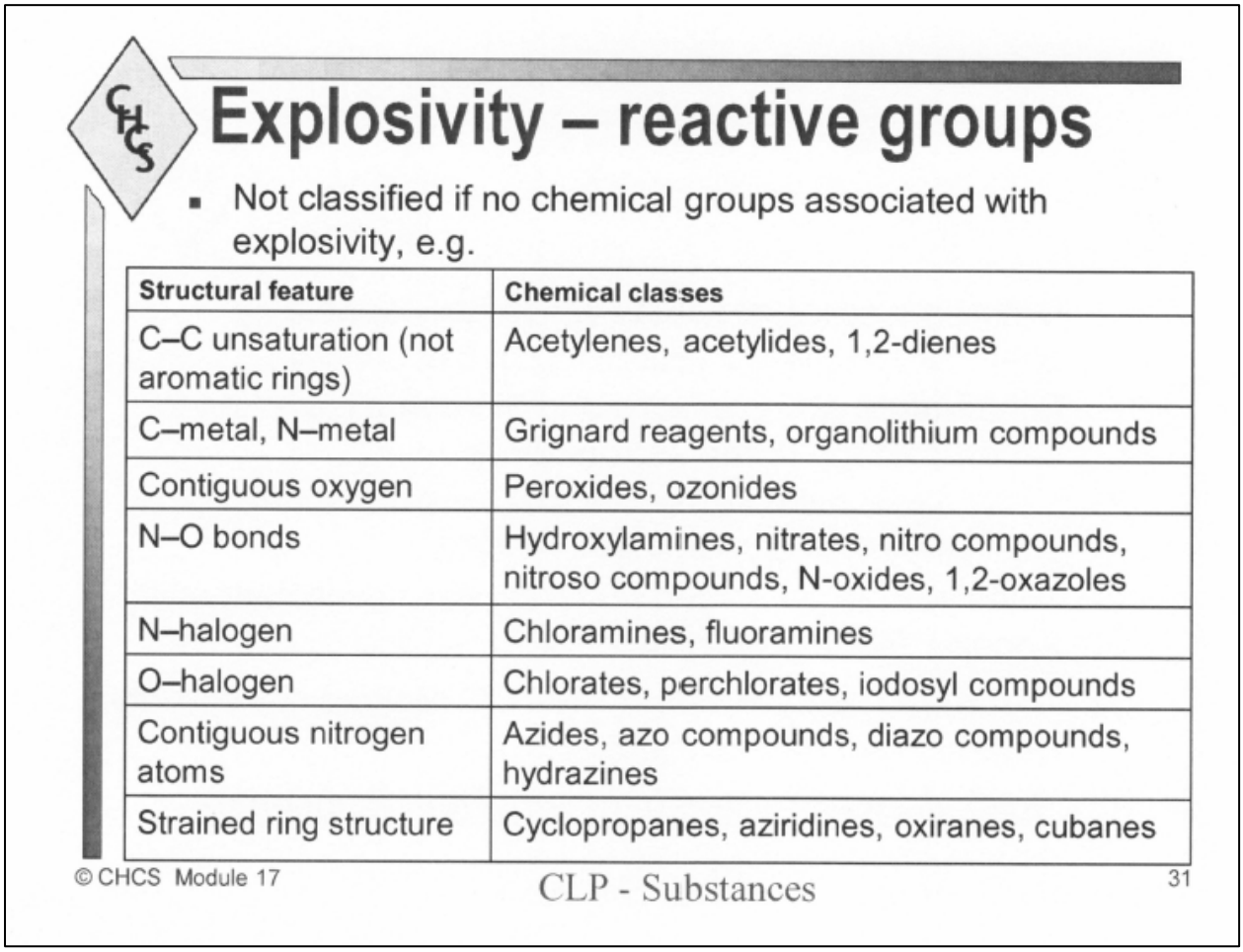
Level III Fugacity Model: (EQC Default)

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

Air	0.00798	0.843	1000
Water	50.3	1.44e+003	1000
water	(50.3)		
biota	(4.68e-007)		
suspended sediment	(5.76e-006)		
Soil	49.6	2.88e+003	1000
Sediment	0.0979	1.3e+004	0
Persistence Time:	1.07e+003 hr		

APPENDIX I: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



Explosivity – reactive groups

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

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

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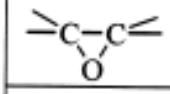
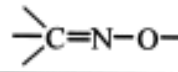
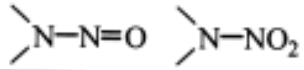
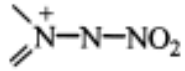
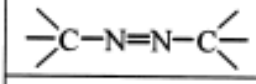
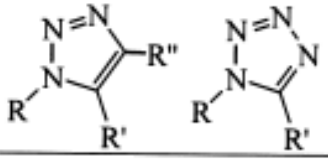
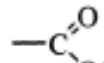
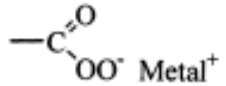
Explosivity – Full List

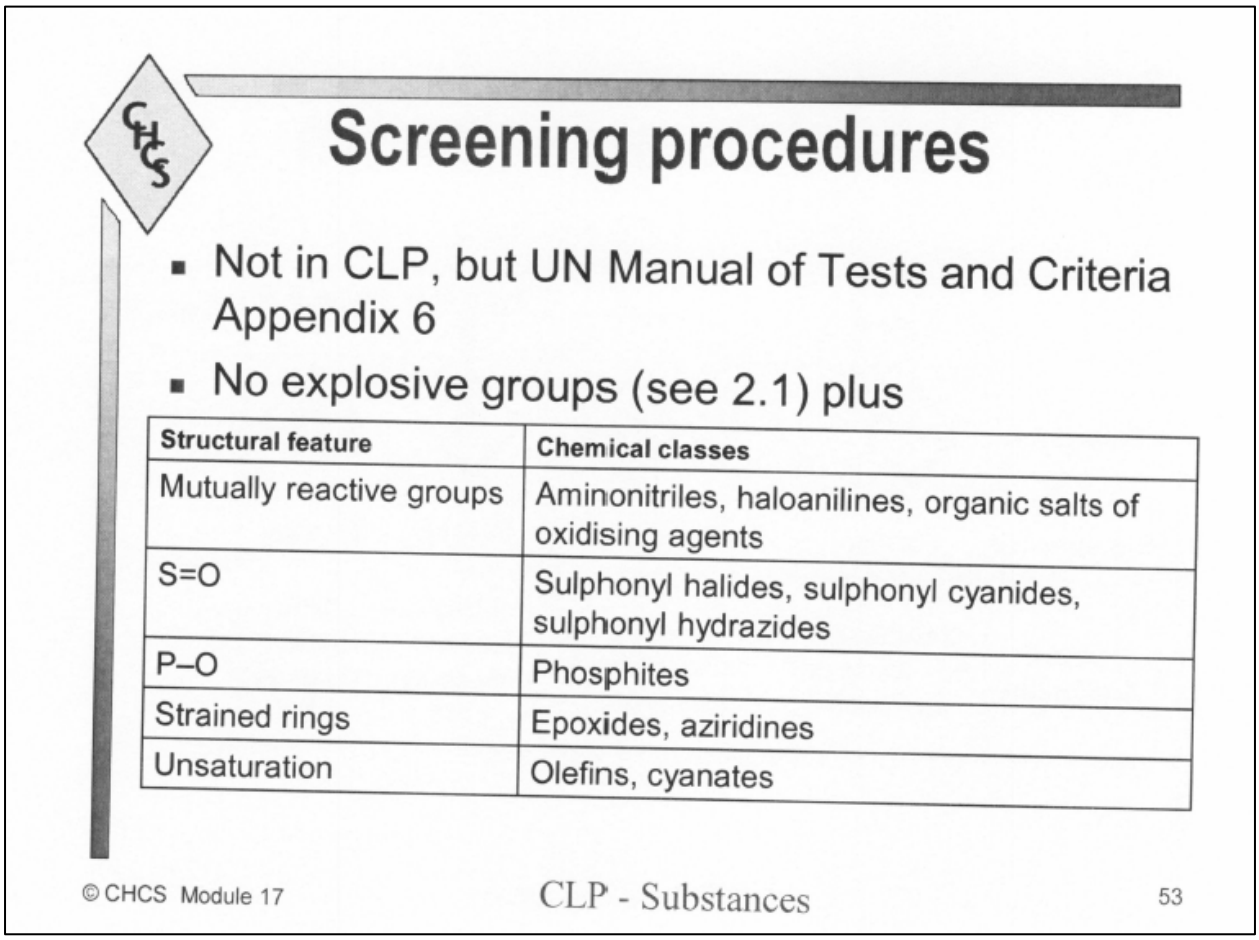
Table R.7.1-28 Chemical groups associated with explosive properties

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

Chemical group	Chemical Class
[1] ROOR',  [2]	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal,  [2]	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
$^{-}O-C-N_2^{+}$	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

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

Self-Reactive Substances



APPENDIX J: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for rambutan peel extract. The GreenScreen® for rambutan peel extract is a new assessment.

Table 6: Change in GreenScreen® Benchmark™ for Rambutan Peel Extract

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
June 24, 2024	BM-2	v. 1.4	New GreenScreen® assessment.
July 5, 2024	BM-2	v. 1.4	No change in Benchmark score. Addressed WA Ecology's clarifying questions and comments.

Licensed GreenScreen® Profilers

Rambutan Peel Extract GreenScreen® (v 1.4) Prepared by:

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