PROPYLPARABEN

(CAS #94-13-3)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: June 21, 2023

Expiration Date: June 21, 2028

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

TABLE OF CONTENTS

GreenScreen® Executive Summary for Propylparaben (CAS #94-13-3) 1
Chemical Name 2
GreenScreen® Summary Rating for Propylparaben 4
Environmental Transformation Products 5
Introduction 5
U.S. EPA Safer Choice Program's Safer Chemical Ingredients List 5
GreenScreen® List Translator Screening Results 6
Hazard Statement and Occupational Control 6
Physicochemical Properties of Propylparaben 7
Toxicokinetics 7
Hazard Classification Summary 8
Group I Human Health Effects (Group I Human) 8
Carcinogenicity (C) Score 8
Mutagenicity/Genotoxicity (M) Score 11
Reproductive Toxicity (R) Score 13
Developmental Toxicity incl. Developmental Neurotoxicity (D) Score 17
Endocrine Activity (E) Score 19
Group II and II* Human Health Effects (Group II and II* Human) 22
Acute Mammalian Toxicity (AT) (Group II) Score 22
Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-single) (Group II) Score 23
Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST-repeat) (Group II*) Score 23
Neurotoxicity (single dose, N-single) (Group II) Score 25
Neurotoxicity (repeated dose, N-repeated) (Group II*) Score 25
Skin Sensitization (SnS) (Group II*) Score 26
Respiratory Sensitization (SnR) (Group II*) Score 28
Skin Irritation/Corrosivity (IrS) (Group II) Score 28
Eye Irritation/Corrosivity (IrE) (Group II) Score 30
Ecotoxicity (Ecotox) 31
Acute Aquatic Toxicity (AA) Score 31
Chronic Aquatic Toxicity (CA) Score 32
Environmental Fate (Fate) 33
Persistence (P) Score 33
Bioaccumulation (B) Score 33
Physical Hazards (Physical) 34
Reactivity (Rx) Score 34
Flammability (F) Score 34

Use of New Approach Methodologies (NAMs) in the Assessment, Including Uncertainty Analyses of Input and Output 35
References 37
APPENDIX A: Hazard Classification Acronyms 41
APPENDIX B: Results of Automated GreenScreen® Score Calculation for Propylparaben (CAS #94-13-3) 42
APPENDIX C: Pharos Output for Propylparaben (CAS #94-13-3) 43
APPENDIX D: OECD Toolbox Profiling Results for Propylparaben (CAS #94-13-3) 45
APPENDIX E: ECOSAR Modeling Results for Propylparaben (CAS #94-13-3) 46
APPENDIX F: EPI Suite™ Modeling Results for Propylparaben (CAS #94-13-3) 47
APPENDIX G: Known Structural Alerts for Reactivity 51
APPENDIX H: Change in Benchmark Score 55
Licensed GreenScreen® Profilers 56

TABLE OF FIGURES

Figure 1: GreenScreen® Hazard Summary Table for Propylparaben 5

TABLE OF TABLES

Table 1: GHS H Statements for Propylparaben (CAS #94-13-3) (ECHA 2023a,b) 6
Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Propylparaben (CAS #94-13-3) 6
Table 3: Physical and Chemical Properties of Propylparaben (CAS #94-13-3) 7
Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses 35
Table 5: Change in GreenScreen® Benchmark™ for Propylparaben 55

GreenScreen® Executive Summary for Propylparaben (CAS #94-13-3)

Propylparaben is a commonly used preservative in food and cosmetics. It is a crystalline powder at room temperature, and is not explosive, oxidizing, or flammable. If released to the environment, propylparaben is expected to partition to soil and water. Propylparaben is soluble in water and has a very low vapor pressure; therefore, it is unlikely to volatilize and is not a volatile organic compound (VOC).

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (endocrine activity-E)

The GreenScreen® Benchmark Score for propylparaben has not changed over time. The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. Although the hazard ratings for some individual endpoints have changed, and all previous data gaps have been filled based on new data, the BM-2 score has been maintained with the version 1.3 update in 2016, and with the current update to version 1.4.

New Approach Methodologies (NAMs) used in this GreenScreen® include *in vitro* testing for mutagenicity, endocrine activity, skin irritation, and eye irritation, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, 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 propylparaben's NAMs dataset include lack of, or insufficient experimental data for respiratory sensitization and chronic aquatic toxicity, and lack of validated methods for assessing respiratory sensitization. Propylparaben's Type II (extrapolation output) uncertainties include reliance on *in vitro* data in which the exogenous metabolic activation does not entirely mimic *in vivo* conditions, the limitation of the OECD TG 437 method to detect GHS Category 2 eye irritants, and extrapolation of skin sensitization data to respiratory sensitization which is incomplete in that it does not account for non-immunologic mechanisms of respiratory sensitization. Some of propylparaben's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Propylparaben

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**	*M*	**L**	*M*	**L**	*L*	**L**	**L**	*L*	*L*	**L**	**H**	*H*	**vL**	**vL**	*L*	**L**

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

GreenScreen® Chemical Assessment for Propylparaben (CAS #94-13-3)

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

GreenScreen® Assessment (v.1.2) Prepared By:
Name: Sara M. Ciotti, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: April 24, 2015

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: May 1, 2015

GreenScreen® Assessment (v.1.3) Updated By:
Name: Mouna Zachary, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 07, 2016

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 12, 2016

GreenScreen® Assessment (v.1.4) Updated By:
Name: Nancy Linde, M.S.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: March 31, 2023; June 8, 2023

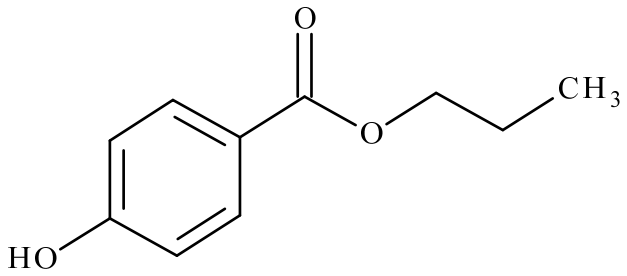
Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Senior Toxicologist
Organization: ToxServices LLC
Date: April 17, 2023; June 21, 2023

Expiration Date: June 21, 2028[2]

Chemical Name: Propylparaben

CAS Number: 94-13-3

Chemical Structure(s):

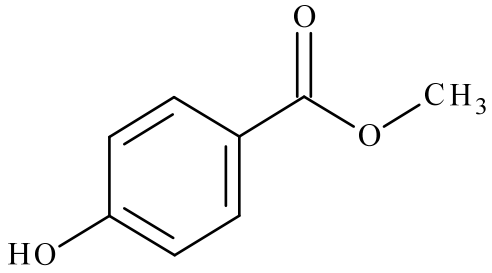


Also called: Propyl 4-hydroxybenzoate; 4-hydroxybenzoic acid propyl ester; propyl p-hydroxybenzoate; propyl parahydroxybenzoate; n-propyl 4-hydroxybenzoate; n-propyl p-hydroxybenzoate; p-hydroxypropyl benzoate; p-hydroxybenzoic acid propyl ester; n-propylparaben; p-

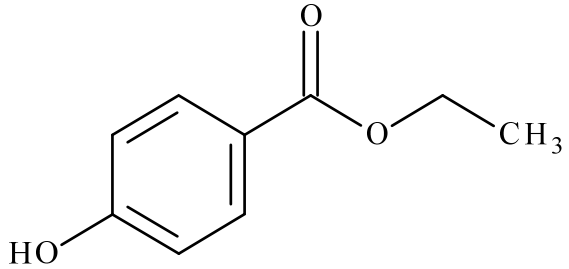
[1] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), or "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent).
[2] Assessments expire five years from the date of completion starting from January 1, 2019. An assessment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

hydroxybenzoic propyl ester; propyl-4-hydroxybenzoate; 4-hydroxybenzoic acid, propyl ester; propyl 4-oxidanylbenzoate (SCCS 2021).

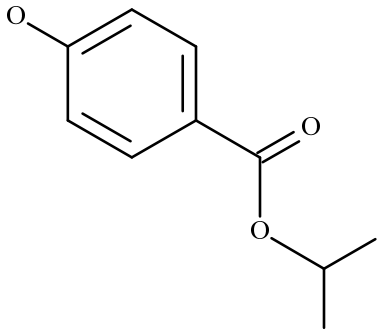
Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
Propylparaben has a relatively complete dataset. In its REACH registration dossier, as well as assessments by Health Canada (2020), Cosmetic Ingredient Review (CIR) (2020), and Scientific Committee on Consumer Safety (SCCS) (2021), methylparaben (CAS# 99-76-3), ethylparaben (CAS# 120-47-8), isopropylparaben (CAS #4191-73-5), butylparaben (CAS# 94-26-8), and isobutylparaben (CAS #4247-02-3) were used as surrogates to either fill data gaps or add supporting evidence. As some data suggest toxicity of parabens increases with increasing alkyl chain length, ToxServices considered ethylparaben and methylparaben weak surrogates, and isopropylparaben, butylparaben, and isobutylparaben strong surrogates.



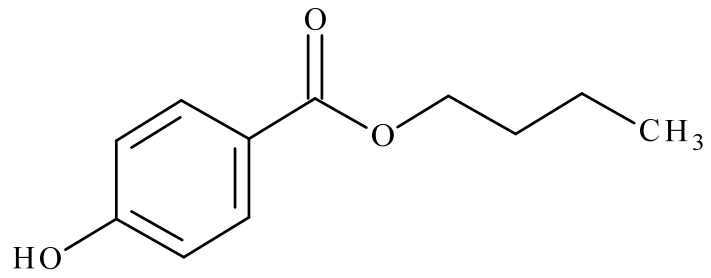
Methylparaben (CAS #99-76-3)



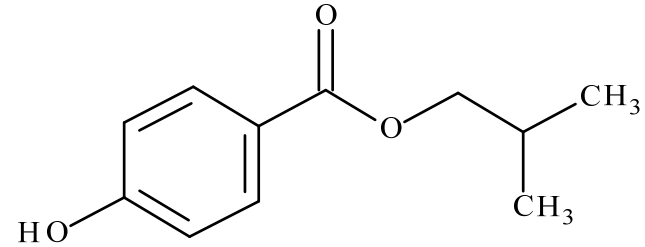
Ethylparaben (CAS #120-47-8)



Isopropylparaben (CAS #4191-73-5)



Butylparaben (CAS #94-26-8)



Isobutylparaben (CAS #4247-02-3)

Identify Applications/Functional Uses:
A preservative in food, cosmetics, and numerous consumer and industrial products. Reported maximum use levels in cosmetics include 0.3% in rinse-off products (e.g. shampoo), 0.7% in leave-on products, 0.7% in products used near the eye (e.g., mascara), 0.3% bath oils, tablets, and salts, 0.15% in baby lotions, oils, and creams (CIR 2020). In the United States, propylparaben is Generally Recognized as Safe (GRAS) as a direct food additive and it is acceptable for use as an antimicrobial agent (21 CFR § 184.1670), as an antimycotic in food-packaging materials (21 CFR § 181.23), and food flavoring agent (21 CFR § 172.515) (U.S. FDA 2022). Propylparaben is also approved for use as an excipient (inactive ingredient) in pharmaceuticals (e.g., up to 2.5 mg/5 mL in oral concentrate, up to 200 mg as elixir, up to 0.22 mg in extended release capsules) (U.S. FDA 2023).

Known Impurities[3]:
p-Hydroxybutanoic acid is a commonly specified impurity at ≤ 0.1% based on multiple studies summarized in the REACH dossier (ECHA 2023a). This impurity is a starting compound in the manufacturing process of propylparaben, as well as a functional group, and primary metabolite. This GreenScreen®, however, is performed on the theoretical pure substance.

GreenScreen® Summary Rating for Propylparaben[4,5 6,7]: Propylparaben 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:

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

- Benchmark 2e
    - Moderate Group I Human Toxicity (endocrine activity-E)

Figure 1: GreenScreen® Hazard Summary Table for Propylparaben

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**	*M*	**L**	*M*	**L**	*L*	**L**	**L**	*L*	*L*	**L**	**H**	*H*	**vL**	**vL**	*L*	**L**

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

Environmental Transformation Products

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

Introduction

Propylparaben is an ester of p-hydroxybenzoate that is used as an antimicrobial preservative in foods, drugs and cosmetics for over 50 years. It is produced by the *n*-propanol esterification of *p*-hydroxybenzoic acid in the presence of sulfuric acid followed by distillation (HSDB 2017).

Propylparaben is Generally Recognized as Safe (GRAS) as a food ingredient in the United States, and is acceptable for use as an antimicrobial agent (21 CFR §184.1670). It is also permitted as an antimycotic in food-packaging materials (21 CFR § 181.23) and a food flavoring agent (21 CFR § 172.515) (U.S. FDA 2022). In 2004, the European Food Safety Authority (EFSA) Scientific Panel on Food Additives, Flavorings, Processing Aids and Materials in Contact with Food evaluated the safety of parabens in food and concluded that the Acceptable Daily Intake (ADI) for methylparaben and ethylparaben should not extend to propylparaben due to concerns for reproductive toxicity and lack of a clear NOAEL (EFSA 2004). Although the EFSA opinion has not been updated, the SCCS who previously shared EFSA's opinion (SCCS 2013) recently concluded, based on new data, that propyl paraben is safe when used as a preservative in cosmetic products up to a maximum concentration of 0.14% (SCCS 2021).

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

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2023). 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).

Propylparaben is not currently present on the SCIL.

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2023) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[8] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for propylparaben can be found in Appendix C.

- Propylparaben is a BM-2 chemical when screened using Pharos, however, ToxServices' GreenScreen® on which this score is based has expired and is conducted under version 1.2 criteria, and therefore a full GreenScreen® update is required.
- Propylparaben is not listed on the U.S. DOT list.
- Propylparaben is on the following GreenScreen®-specified list for multiple endpoints:
  - GHS – New Zealand: Hazardous to the aquatic environment – chronic Category 2.
  - German FEA – Substances Hazardous to Waters: Class 1 – Low Hazard to Waters.
  - ChemSec – SIN List: Equivalent concern.
- GreenScreen®-specified lists for single endpoints are presented under their respective endpoints below.

Hazard Statement and Occupational Control

No Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements were identified for propylparaben, however, self-classifications by the majority of notifiers and by the authors of the REACH dossier are indicated in Table 1, below. General personal protective equipment (PPE) recommendations are presented in Table 2, below. Russia reports an occupational exposure limit (OEL) for acute inhalation exposure; no further OELs were identified.

Table 1: GHS H Statements for Propylparaben (CAS #94-13-3) (ECHA 2023a,b)

H Statement	H Statement Details
H315	Causes skin irritation (majority of notifiers)
H319	Causes serious eye irritation (majority of notifiers)
H335	May cause respiratory irritation (majority of notifiers)
H412	Harmful to aquatic life with long lasting effects (REACH dossier authors)

Table 2: Occupational Exposure Limits and Recommended Personal Protective Equipment for Propylparaben (CAS #94-13-3)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respiratory protection – short term (filter apparatus, Filter P2); wear chemical resistant gloves (according to category III of DIN EN374), safety goggles, and protective clothing	ECHA 2023a	STEL: 10 mg/m^3 (Russia)	RTECS 2015

STEL: Short-term Exposure Limit

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

Physicochemical Properties of Propylparaben

Propylparaben is a white or colorless crystalline powder under standard temperature and pressure. Its calculated water solubility indicates that it is moderately soluble in water. It has negligible vapor pressure and is therefore not a volatile organic compound (VOC). Inhalation exposure to dust or aerosol particles is possible, and at least 10% will be respirable (i.e., > 10 µm). It is expected to have a low potential for bioaccumulation based on its measured log K_{ow} of up to 3.04.

Table 3: Physical and Chemical Properties of Propylparaben (CAS #94-13-3)

Property	Value	Reference
Molecular formula	$C_{10}H_{12}O_3$	PubChem 2023
SMILES Notation	CCCOC(=O)C1=CC=C(C=C1)O	PubChem 2023
Molecular weight	180.2	PubChem 2023
Physical state	Solid	ECHA 2023a
Appearance	Colorless or white crystalline solid	ECHA 2023a
Melting point	97°C	ECHA 2023a
Boiling point	301°C	ECHA 2023a
Vapor pressure	0.00034 Pa at 20°C (OECD 104 C)	ECHA 2023a
Water solubility	424.53 mg/L at 25°C (estimated)	U.S. EPA 2017a
Dissociation constant	pKa = 8.46 at 20°C	ECHA 2023a
Density/specific gravity	1.287 g/cm^3 at 20°C	ECHA 2023a
Partition coefficient	Log K_{ow} = 2.34-3.04	ECHA 2023a
Particle size	D10: 2.6 µm D50: 16.2 µm D90: 113 µm	ECHA 2023a

Toxicokinetics

Propylparaben is highly absorbed and rapidly metabolized in animals and humans following oral and dermal exposure. Absorption is faster for the shorter alkyl chain parabens compared to longer chain parabens for both the dermal and oral routes of exposure (HC 2020).

Parabens applied to the skin are rapidly hydrolyzed to 4-hydroxybenzoic acid and the corresponding alcohol by carboxylesterases present in the keratinocytes. The rate of hydrolysis in the skin is faster for rodents than humans, and is faster for intact skin compared to dermatomed skin. Chemicals that disrupt the stratum corneum may increase the skin penetration of shorter parabens, such as methylparaben and ethylparaben, but do not affect the penetration of longer-chain parabens (CIR 2020). A single dermal radiolabeled dose of 100 mg/kg propylparaben administered to rats by oral and dermal routes resulted in maximum plasma concentrations in less than 1 hour and 8 hours, respectively. Both routes produced a single peak in the plasma corresponding to that of para-hydroxybutanoic acid (PHBA), the primary metabolite, whereas propylparaben was not detected. Over 70% of the oral dose was excreted in 24 hours, with < 4% detected in the feces, and < 1% in tissues. Approximately 60% of the dermally applied dose was not absorbed after 24 hours, 17-20% was excreted in the urine, <2% in the feces, and the remainder was purportedly in the external tissues (e.g., hair, nails) (Aubert et al. 2012 as cited in HC 2020). In dogs administered propylparaben at 1 g/kg orally, or 50 mg/kg intravenously, the parent compound was not detected in plasma at any time, PHBA was detected within 1 hour, 53% of the applied dose was excreted within 24 hours as PHBA and other metabolites, and the parent compound was excreted at 0.042%. Following oral exposed for 1 year at 1 g/kg/day in dogs, urinary excretion increased to 96% in 24 hours, and small amounts of propylparaben were detected in the brain (Jones et al. 1956 as cited in HC 2020).

In humans orally administered propylparaben at up to 20 mg/kg, the parent compound was not detected in the blood, but PHBA was detected within 60 minutes (Heim 1960 and Andersen 2008 as cited in HC 2020). In a single volunteer orally administered 2 g propylparaben for 5 days, 17.4% was excreted in the urine as PHBA, 55% as the sulfuric acid conjugate, and the parent compound was not detected and the majority of the administered dose was unaccounted for.

In human liver and skin subcellular fractions, propylparaben is metabolized up to an order of magnitude more slowly than methylparaben and ethylparaben. In human plasma, propylparaben was reduced to 47% after 6 hours, and in liver microsomes, the half-life was 67 minutes (Abbas et al. 2010 as cited in HC 2020). Whereas rat skin and rat liver cell fractions hydrolyze parabens at roughly the same rate in *in vitro* studies, the rates for rat skin and liver cells are about 3 and 10 orders of magnitude faster than those of human skin and liver cells, respectively (Harville et al. 2007 as cited in HC 2020).

Ingested parabens are quickly absorbed from the gastrointestinal tract, and similar to the dermal route of exposure, are hydrolyzed to PHBA, conjugated, and excreted in the urine.

Chronic exposure studies indicate that parabens do not accumulate in the body (CIR 2020), however, propylparaben has been detected at low levels in tumorous breast tissue, human adipose tissue, and in the brain (free or conjugated not specified) (Barr et al. 2012; Wang et al. 2015, and van der Meer 2017, as cited in HC 2020).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): *L*
Propylparaben was assigned a score of Low for carcinogenicity based on numerous chronic oral exposure studies in multiple species exposed to the target compound in which there were no indications of carcinogenicity. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is low as the dataset includes only non-guideline studies which had fewer test parameters, fewer doses, and fewer numbers of animals relative to current guidelines.

- 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 2023a[9]
  - *Oral:* Propylparaben was evaluated in a non-guideline study (GLP not specified) examining the induction of lesions of the forestomach, glandular stomach, and urinary bladder in hamsters. Fifteen male Syrian hamsters were administered the test substance (> 99.8% purity) in the feed (no vehicle) at 3% for 20 weeks (equivalent to 1,009.6 – 2,163.5 mg/kg/day, based on average body weight of 208 g and average daily food intake of 7-15 g). Animals were sacrificed at the end of the exposure period, and the liver and kidney weights were determined, and five sections from each animal were cut from the anterior and posterior walls of the forestomach, two from the glandular stomach, and four from the urinary bladder. Sections were stained for analysis of the labelling index. Counts were made on 4,000 cells of urinary bladder epithelium, 3,000 cells of pyloric gland epithelium

[9] Throughout this GreenScreen, only studies with sufficient details and reliability ratings (Klimisch 1, reliable without restriction, or Klimisch 2, reliable with restrictions) are included in this assessment, unless noted otherwise.

(1000 cells each of the fundic side, middle portion and pyloric side), and 2,000 basal cells of the forestomach epithelium (1,000 cells each from regions proximal to the fundic gland of the greater curvature and of the lesser curvature of the anterior wall). The labelling index was expressed as the number of labelled cells per 100 cells. There were no mortalities during the treatment period, and no significant effect on body or liver weights in treated animals compared to controls. There were no findings of papillomatous lesions. No significant inflammation, hyperplasia, or tumorous lesions were identified in the urinary bladder. Labelling indices of the forestomach and pyloric region in treated animals was comparable to controls. The labelling index was significantly ($p < 0.05$) increased in the urinary bladder to 0.52 ± 0.18 for the treated group, compared to 0.08 ± 0.14 in the control animals, however, there were no corresponding histopathological findings (Klimisch 2, reliable with restrictions) (Hirose et al. 1986).

- *Oral:* Propylparaben was evaluated in a pre-GLP, pre-guideline, chronic oral repeated dose toxicity study. Male and female Mongrel dogs (negative control = 2 animals; 0.5 g/kg/day = 1 animal; 1.0 g/kg/day = 3 animals (sex not reported)) received 0, 0.5, or 1.0 g/kg/day (0, 500, and 1,000 mg/kg/day) propylparaben (purity not reported) in gelatin capsules 6 days per week. Negative control animals were treated for 195 and 422 days; the low dose animal was treated for 394 days; and the high dose animals were treated for 313 – 394 days. Animals were examined for clinical signs, body weight, and changes in blood and urine parameters. Pathology and histopathology was performed at termination of the study. Histopathological analysis focused on the kidney, liver, heart, lung, spleen, and pancreas. One control animal died after 195 days of pneumonia. Treatment had no effect on clinical signs, body weight and weight gain, hematology, urine parameters, gross pathology, or histopathology. The study authors identified a NOAEL of 1 g/kg/day (1,000 mg/kg/day; equivalent to 857 mg/kg/day after adjustment for a 7 day treatment period[10]) the highest dose tested (Klimisch 2, reliable with restrictions) (Matthews et al. 1956).
- *Oral:* Propylparaben was evaluated in a non-guideline study (GLP not specified) examining the induction of lesions of the forestomach and glandular stomach in rats. Five male Fischer 344 rats were administered the test substance (> 99.8% purity) in the feed (no vehicle) at 3% for 8 weeks (equivalent to 1,883.96 – 4,150.38 mg/kg/day, based on average body weight of 133 and 293 g, and average daily food intake of 18.4 g/rat). At week 8, the rats were injected i.p. with 100 mg/kg of bromodeoxyuridine (BrdU), 1 hour prior to sacrifice. Histopathological examination was performed on five strips of forestomach tissue, and four strips of glandular stomach tissue. The numbers of cells incorporating BrdU into DNA per 2,000 basal cells of the forestomach (1,000 cells each from regions proximal to the fundic. gland of the greater curvature and of the lesser curvature wall) and 1,000 cells of pyloric gland epithelium (pyloric side) were counted. The heights of pyloric glands were determined and the average numbers of pyloric gland epithelial cells comprising one crypt were calculated for each group. There were no mortalities during the exposure period. There were no significant effects on body weights, food and water consumption, histopathology and labeling indices, and no proliferative lesions in treated animals compared to controls (Klimisch 2, reliable with restrictions) (Shibata et al. 1990).
- *Oral:* Propylparaben was evaluated in a pre-GLP, pre-guideline, chronic oral repeated dose toxicity study. Male and female Wistar rats (6/sex/dose) were exposed to 0, 2, or 8% propylparaben (equivalent to 0, 0.9-1.2, and 5.5-5.9 g/kg/day[11]) in their diet for 96 weeks. Animals were examined for clinical signs, body weight, and changes in blood and urine

[10] 1,000 mg/kg/day * 6 days/7 days = 857 mg/kg/day
[11] Values reported in the ECHA REACH Dossier.

parameters. Pathology and histopathology was performed at termination of the study. Histopathological analysis focused on the kidney, liver, heart, lung, spleen, and pancreas. Animals treated with 8% propylparaben had a slower rate of weight gain compared to control animals, which was more apparent in the early part of the study. By the end of the study, these effects were no longer apparent. Decreased weight gain was more apparent in male rats compared to females. No other treatment-related effects were reported. Histopathological examination found no abnormalities. The study authors identified a NOAEL of 8% propylparaben (equivalent to 5.5-5.9 g/kg/day or 5,500 – 5,900 mg/kg/day) (highest dose tested) (Klimisch 2, reliable with restrictions) (Matthews et al. 1956).

- *Transplacental:* Propylparaben was evaluated for carcinogenicity in a non-guideline transplacental assay, and a newborn assay (Odashima 1976).
  - In the transplacental assay, pregnant rodents (strain not reported) were administered the maximum dose which did not cause abortion or early death of neonates (dose not reported). Animals (number not reported) were treated every other day for 5 days during gestation days 15 through 19. Offspring were observed for 1 year after birth for tumor development. Authors concluded that propylparaben was not carcinogenic. No further details were provided.
  - In the newborn assay, rodent pups (strain not reported) were administered four subcutaneous injections of propylparaben (total dose = LD_{20}; dose not reported) on post-natal days (PND) 1, 8, 15, and 22. Animals (number not reported) were observed for 1 year after birth for tumor development. Authors concluded that propylparaben was not carcinogenic. No further details were provided.

- CIR 2020 – no new data were identified.
- CIR 2008
  - "Ethylparaben, propylparaben, and butylparaben in the diet produced cell proliferation in the forestomach of rats, with the activity directly related to chain length of the alkyl chain, but isobutylparaben and butylparaben were noncarcinogenic in a mouse chronic feeding study. Methylparaben was non-carcinogenic when injected subcutaneously in mice or rats, or when administered intravaginally in rats, and was not cocarcinogenic when injected subcutaneously in mice. Propylparaben was noncarcinogenic in a study of transplacental carcinogenesis."
- SCCP 2005a
  - Parabens are not carcinogenic or co-carcinogenic.
- Darbre and Harvey 2008
  - Discussion of the possible role of parabens in breast cancer was sparked in 2004 when methylparaben, ethylparaben, propylparaben, and isobutylparaben were measured in human breast cancer tissue (Darbre et al. 2004). The Scientific Committee on Consumer Products (SCCP) (2005b) reviewed the available data and concluded that there is no evidence that demonstrates a risk of developing breast cancer with the use of 'underarm' cosmetics.
- HSDB 2017
  - A population-based, case-control, epidemiological study was performed to assess the carcinogenicity of paraben-containing (specific paraben not specified) underarm deodorant. Patients aged 20-74 (n=813) who developed breast cancer, and control subjects also aged 20-74 (n=793), were randomly assigned to frequency-matched 5-year age groups. Product use information was obtained by in-person interviews. The risk for breast cancer was not increased with application of antiperspirant or deodorant, or among those who shaved with a blade razor, or among those who applied the products within 1 hour of shaving. Authors

concluded the results do not suggest that antiperspirant use increases the risk of breast cancer.

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

Propylparaben was assigned a score of Low for mutagenicity/genotoxicity based on lack of mutagenicity in two bacterial reverse mutation assays and a mammalian cell gene mutation assay, and lack of clastogenicity in an *in vitro* micronucleus assay with human lymphocytes. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high based on reliable data for the target compound.

- 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 2023a[9]
  - *In vitro:* Propylparaben was not mutagenic when tested in a GLP-compliant bacterial reverse mutation assay conducted according to OECD TG 471. *Salmonella typhimurium* tester strains TA98, TA100, TA102, TA1535, and TA1537 were exposed to propylparaben (99.7% purity) in DMSO at concentrations up to 1 mg/plate, with and without exogenous metabolic activation, using the both the plate incorporation and pre-incubation methods. The positive controls were 2-nitrofluorene, sodium azide and 9-aminoacridine, and mitomycin C for trials without activation, and 2-aminoanthracene for trials with activation. Controls performed as expected. The highest concentration was based on cytotoxicity determined in a preliminary test. There were no increases in the mutation frequency in any of the tested strains, at any concentration, in the presence or absence of metabolic activation (Klimisch 1, reliable without restriction) (Unnamed 2018 study).
  - *In vitro:* Propylparaben was not mutagenic when tested in non-GLP compliant bacterial reverse mutation assay conducted equivalent or similar to OECD TG 471. *S. typhimurium* tester strains TA1535, and TA1537 were exposed to propylparaben (purity not specified) in DMSO at concentrations up to 0.075%, with and without exogenous metabolic activation from mice, rats, and primates, using the both the plate incorporation and pre-incubation methods. The positive controls were dimethylnitrosamine 2-acetylaminofluorene with activation, and ethyl methanesulfonate, 2-nitrofluorene, and quinacrine mustard without activation. Controls performed as expected. The highest concentration was based on cytotoxicity determined in a preliminary test. There were no increases in the mutation frequency in any of the tested strains, at any concentration, in the presence or absence of metabolic activation from any of the three species (Klimisch 2, reliable with restrictions) (Unnamed 1975 study).
  - *In vitro:* Propylparaben was not clastogenic or aneugenic in a GLP-compliant *in vitro* mammalian cell micronucleus test performed according to OECD TG 487. Human lymphocytes were obtained from male and female donors, 21-33 years of age. The test substance (99.7% purity) was added to the cell cultures at 2 mg/mL, in DMSO, with and without activation. Cells were exposed short term (3 to 6 hours) with and without activation, and long term (20-24 hours) without activation. Cytochalasin B was used for the cytokinesis block, and cytotoxicity was determined based on the cytokinesis-block proliferation index (CBPI). Positive controls were cyclophosphamide, mitomycin C, and colchicine. There were no significant increases in the number of micronuclei in treated cells, in the presence or absence of metabolic activation, at any concentration, compared to vehicle controls.

Authors concluded the test substance was not clastogenic and/or aneugenic under the conditions of the test (Klimisch 1, reliable without restriction) (Unnamed 2018 study).

- *In vitro:* Propylparaben was evaluated in a GLP-compliant *in vitro* mammalian cell gene mutation test conducted according to OECD TG 476 and EU Method B.17. Chinese hamster lung fibroblasts (V79) were exposed to propylparaben (purity not reported) in dimethyl sulfoxide (DMSO) at concentrations up to 112.0 µg/L without activation, and up to 448.0 µg/mL with activation for 4 hours in Experiment 1. In Experiment II, cells were exposed up to 224.0 µg/mL without activation for 24 hours, and up to 448.0 µg/mL with activation for 4 hours. Ethylmethanesulfonate and 7,12-dimethylbenzanthracene were the positive control substances and each provided the expected results. The highest concentrations were based on cytotoxicity. There were no significant increases in mutations at the HPRT locus in treated cells compared to vehicle controls at any concentration, with or without activation, in either experiment. Authors concluded the test substance was not mutagenic under the conditions of the test (Klimisch 1, reliable without restriction) (Unnamed 2012 study).

- CIR 2008
  - Numerous genotoxicity studies, including Ames testing, dominant lethal assay, host-mediated assay, and cytogenic assays, suggest the parabens are generally non-mutagenic, although ethylparaben and methylparaben did increase chromosomal aberrations in an *in vitro* CHO cell assay.
- CIR 2020
  - *In vivo:* No new *in vivo* studies were identified for the parabens.
  - *In vitro:* Propylparaben was evaluated in a non-guideline *in vitro* study in Vero cells from the African green monkey kidney. The study summary suggests an effect on cell cycle arrest at the G0/G1 phase and a resulting statistically significant, dose-dependent decrease in percentage of mitotic cells (Perez et al. 2010). *ToxServices notes that as this study is non-guideline, there is no discussion of concurrent or historical control values, and there is no indication of method validation, the study is included for completeness but the significance of the findings is unknown and this study is not included in the weight of evidence.*
  - A mixture of methylparaben, ethylparaben, propylparaben, and butylparaben was evaluated in a non-guideline *in vitro* study in human spermatozoa (Samarasinghe et al. 2018).
    - A statistically significant decrease in spermatozoa motility was observed immediately after the treatment and was further exacerbated after 24 hours at concentrations of 1, 2, and 4 mM.
    - After 24 hours the spermatozoa treated with 0.2 and 1 mM of the paraben mixture exhibited increased mitochondrial ROS which then declined with decreased cell viability.
    - Acute total superoxide response was observed with dihydroethidium shortly after exposure to the parabens and was statistically significant at 2 and 4 mM.
    - Capsase activation was observed at ≥ 1 mM of the paraben mixture and increased further at 24 hours.

    ToxServices notes that as this study is non-guideline, there is no discussion of concurrent or historical control values, and there is no indication of method validation, the study is included for completeness but the significance of the findings is unknown and this study is not included in the weight of evidence.

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

Propylparaben was assigned a score of Low for reproductive toxicity based on lack of indications of reproductive toxicity in multiple GLP-compliant, guideline studies, including an extended one-generation reproductive toxicity study (OECD TG 443) in rats orally exposed at up to 1,000 mg/kg/day. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high based on reliable data for the target compound.

- 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 2023a[9]
  - *Oral:* Propylparaben was evaluated in a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD TG 422 and EPA OPPTS 870.3650. Wistar rats (11/sex/dose) were exposed to propylparaben (purity not specified) in the diet at 0, 1,500, 4,500, or 15,000 ppm (equivalent to 98.0, 305.1, and 980.0 mg/kg/day in males (pre-pairing); 59.3, 178.3, and 605.0 mg/kg/day in males (after pairing); 116.0, 341.9, and 1,076.4 mg/kg/day in females (pre-pairing); 121.6, 349.2, and 1,124.6 mg/kg/day in females (gestation); and 137.3, 431.8, and 1,380.0 mg/kg/day in females (lactation) (values were reported in the ECHA REACH Dossier)). Male rats were treated for 2 weeks prior to mating and throughout the mating period (a minimum of 28 days). Females were treated for 2 weeks prior to mating, through pregnancy, and then to postpartum day 4 (approximately 7 weeks). The parental animals were evaluated for clinical signs of toxicity, food consumption, body and organ weights, estrous cyclicity, sperm parameters, fertility indices, post-implantation losses, mean litter size, functional observational battery, gross pathology and histopathology. Hematology and blood serum chemistry were only evaluated in parental animals. There were no treatment-related effects on clinical signs, mortality, body weight, food consumption, organ weights, gross pathology, or histopathology. High-dose parental males had slightly reduced body weight gain which occasionally reached statistical significance. No body weight changes were found in females. No treatment-related changes in hematology were found. High-dose male rats had a statistically significant increase in triglycerides concentration compared to controls; no histopathological changes accompanied this increase. The increase was above the range of historical control values. As no histopathological changes accompanied the increase in triglycerides concentration, the study authors noted that the reason for this change was unknown. There were no changes in sperm parameters or estrous cycles. There were no treatment-related effects on any of the fertility or reproductive indices measured. The study authors identified the NOAEL for systemic and reproductive toxicity at 15,000 ppm (corresponding to 1,124.6 mg/kg/day), which was the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2012 study).
  - *Oral:* Propylparaben was evaluated in a GLP-compliant extended one-generation reproductive toxicity study with both developmental neuro- and immunotoxicity (Cohorts 1A, 1B without extension, 2A, 2B, and 3) performed according to OECD TG 443. Wistar rats were administered propylparaben (99.7% purity) by gavage in 1% hydroxyethylcellulose at 0, 100, 300, or 1,000 mg/kg (25/sex/dose, plus an additional 5/sex/dose for the control and high dose groups). Parental (P1) males were dosed from 14 days pre-mating, through mating, and until terminal sacrifice, for a total of 10 weeks. P1 females were dosed from 14 days pre-mating, through mating, and gestation, and until weaning on PND 21, for a total of 8-10 weeks. Pups were dosed from weaning on PND 22

until sacrifice of the respective cohort. There were no significant findings based on clinical observations, mortality, body weight and weight changes, food consumption, hematology, clinical chemistry, urinalysis, behavior (functional findings), organ weights, or histopathology for any generation. There were no significant findings based on reproductive function, including estrus cycles and sperm measures. The systemic toxicity and reproductive toxicity NOAELs are reported at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2021 study).

- *Oral:* Propylparaben was evaluated in a non-GLP compliant reproductive and developmental toxicity screening test performed in a manner equivalent or similar to OECD TG 421. Wistar rats were administered the test substance (purity not specified) by gavage (vehicle not specified) at 0, 500, or 1,000 mg/kg (5/sex/dose). Males were exposed for 21 days pre-mating, and a maximum of 14 days of mating, for a total of 35 days. Females were exposed for 21 days or pre-mating, and 14 days of mating. One dam per group was additionally exposed through gestation to gestational day (GD) 20, and the others were exposed through gestation and up through PND 21. Pups from 3 litters (one per group) were exposed from PND 13 to PND21, in accordance with the treatment group of the dam. The final administration for each animal was given 30 +/- 10 minutes prior to sacrifice and necropsy. There were no significant findings based on clinical signs, mortality, body weight and weight changes, food consumption, reproductive function and performance (including copulation, viability, and delivery indices), for any group compared to controls. The NOAEL for reproductive toxicity was reported at 1,000 mg/kg, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2018 study).
- *Oral:* Propylparaben was evaluated in a reproductive toxicity study (guideline and GLP compliance not specified). Male and female Sprague-Dawley pups were administered the test substance (99.7% purity) by gavage in 1% hydroxyethylcellulose at 0, 10, 100, or 1,000 mg/kg/day. Phase 1: rats were administered the test substance on PND 4 to 90 (25/sex/group with 10/sex/group necropsied at end of dosing, and 15/sex/group assessed for reproduction/recovery). Phase 2: rats were administered the test substance on PND 4 through 21 (5/sex for controls, and 15-30/sex for treatment groups). A separate uterotrophic assay was conducted in immature female rats to measure estrogenic activity *in vivo*. Propylparaben was administered to immature female pups by oral gavage at 0, 10, 100, or 1,000 mg/kg on PND 21 through 23 (6/dose). A positive control group (n=6 female pups) was administered 17α-ethinyl estradiol (E2) at 1 µg/kg subcutaneously. Rats were evaluated daily for survival, clinical observations, and body weight. On PND 24, rats were examined for vaginal patency and were euthanized, and uteri were excised without the ovaries. For the group in which treated males were paired with untreated females, there were no significant effects on estrus cycles, mating and fertility, gestation length, sex ratios, number of live births, or viability at PND 4. For the group in which treated females were paired with untreated males, there were no effects on the number of corpora lutea, implantation sites, number of live embryos, pre-implantation loss, post-implantation loss, or early resorptions. For the pups exposed on PND 4 to 90, there were no effects on estrus cycles or uterine weights in treated females at necropsy on PND 91. Authors concluded there was no evidence of estrogenic activity at any dose, and no effects on reproductive organs or function. The NOAEL was assigned at 1,000 mg/kg/day, the highest dose tested (Klimisch 2, reliable with restrictions) (Sivaramana et al. 2018).
- Note: the following studies have Klimisch ratings of 3 – not reliable, and 4 – not assignable – in the REACH dossier. However, as they are considered key studies by World Health Organization (WHO) 2007 and SCCS 2013, they are included in the weight of evidence:

- *Oral:* Propylparaben was evaluated in a reproductive toxicity study conducted by Oishi (2002), groups of eight male Wistar rats aged 3 weeks were given diets containing 0, 0.01, 0.1, or 1% propylparaben for 4 weeks. The study authors estimated approximate intakes of 10, 100, and 1,000 mg/kg/day propylparaben, respectively. Following the 4-week treatment, rats were sacrificed, blood was collected for hormone assays, testes, epididymides, prostate, seminal vesicles, and preputial glands were weighed, and sperm counts in testes and epididymis were determined. Treatment had no effect on the weight of the reproductive organs. The authors found a significant decrease in cauda epididymal sperm reserves and concentrations in rats treated with 100 and 1,000 mg/kg/day. Daily sperm production and its efficiency in the testes were also significantly decreased in all treatment groups compared to controls. Daily sperm production was approximately 70% of control values in all treated groups; however, there was no dose-response relationship (Klimisch 3 – not reliable) (Oishi 2002, as cited in ECHA 2023a, WHO 2007, and SCCS 2013). *ToxServices identified a LOAEL of 10 mg/kg/day (lowest dose tested) based on decreased daily sperm production and efficiency in the testes.*
- *Oral:* Propylparaben was evaluated in a GLP-compliant reproductive toxicity study (guideline not specified). Male Wistar rats (20/dose) received 0, 3, 10, 100, or 1,000 mg/kg/day propylparaben (purity = 100%) via gavage at a dose volume of 10 ml/kg. Each group was divided into two subgroups of 10 animals: subgroup 1 was necropsied at the end of an 8 week treatment period and subgroup 2 was necropsied after a 26-week washout period. Dosing began on PND21 continued through sexual maturation, and up to 11 weeks of age (8 week treatment period). The treatment period covers juvenile (PND 21-35), peri-pubertal (PND 35-55), pubertal (PND 55-70), and early adult stages of the male rats. Animals were examined for clinical signs and weighed twice weekly during the 8-week treatment period, and then weekly during the washout period. On PND38, animals were examined to determine the day of balano preputial separation. At the end of the treatment period, animals were euthanized and examined for gross lesions, testes and epididymides were weighed separately, and the seminal vesicles and prostate were weighed together. Histopathological examination was performed on the right testis and epididymis. The study authors performed a testicular spermatid count and epididymal sperm analysis. High-dose animals experienced hypersalivation through the end of the treatment period. No other treatment-related clinical signs were observed. Treatment had no effect on mean body weight gain or sexual maturation. At the end of the 8-week treatment period there were no significant differences in the weight of the reproductive organs (epididymis, prostate and seminal vesicle, and testis). At the end of the recovery period, no consistent histopathological changes were found. The study authors found no changes in the mean testicular spermatid counts, epididymal sperm counts, or mean motility parameters in any group at the end of the treatment or recovery phase. Study authors concluded that propylparaben was not a reproductive toxicant and identified a NOAEL of 1,000 mg/kg/day; which was the highest dose tested (Klimisch 4 – not assignable) (Gazin et al. 2013).

- SCCS 2013
  - The SCCS (2013) concluded the study by Gazin et al. (2013) was well conducted and provided sufficient information to refute the findings of Oishi (2002) who found effects of sperm parameters and plasma testosterone concentrations of juvenile male Wistar and at doses of 100 mg/kg/day and above.

- CIR 2020
    - *Oral*: Several parabens were assessed for reproductive and developmental effects in a non-guideline study in prepubertal rats (Vo et al. 2010). Methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, and isobutylparaben were administered to groups of prepubertal Sprague Dawley rats (8 weeks old) at 0, 62.5, 250, or 1,000 mg/kg bw by gavage in corn oil once per day (10/group) on PND 21 to 40. EE was used as a positive control administered at 1 mg/kg/day. All rats were sacrificed at 24 hours following the final exposure.
        - A statistically significant delay in vaginal opening was observed in rats exposed to methylparaben at 1,000 mg/kg, and to isopropylparaben at ⩾ 250 mg/kg, whereas there was a statistically significant accelerated date of vaginal opening for the positive control animals. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens based on lack of reproducibility with ethylparaben, propylparaben, and butylparaben.*
        - At 1,000 mg/kg, there was a statistically significant decrease in ovary weights for rats exposed to methylparaben and isopropylparaben; decreased kidney weights in rats exposed to ethylparaben and isopropylparaben; increases in adrenal gland weights in rats exposed to methylparaben, ethylparaben, and propylparaben, and increases in thyroid gland weights in rats exposed to methylparaben. Liver weights were increased for all doses of rats exposed to butylparaben. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there was no mention of corresponding pathological effects.*
        - Decreased number of corpora lutea with increased number of cystic follicles and thinning of the follicular epithelium was observed in the ovaries of rats (test substance(s) and dose(s) not specified). Myometrial hypertrophy in the uterus was identified in rats exposed to propylparaben and isopropylparaben at 1,000 mg/kg, and in rats exposed to butylparaben and isobutylparaben at ≥ 62.5 mg/kg. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens.*
        - Serum estradiol concentrations were significantly reduced in rats exposed to ethylparaben and isopropylparaben at 1,000 mg/kg, and prolactin concentrations were increased in rats exposed to methylparaben at 1,000 mg/kg. *ToxServices notes the severity and biological significance of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens.*
        - Serum concentrations of T4 were statistically significantly reduced in rats exposed to methylparaben at 1,000 mg/kg, propylparaben and isopropylparaben at ≥ 250 mg/kg, and isobutylparaben, propylparaben, and isopropylparaben at ≥ 62.5 mg/kg. The IC50 (the concentration causing 50% inhibition activity) values for affinity to ERα and ERβ range from 2.07E-6 to 5.55E-5 in the following order: isobutylparaben > butylparaben > isopropylparaben = propylparaben > ethylparaben (the value for methylparaben was not reported); comparatively, the IC50 for 17 β-estradiol was approximately 3E-9. *ToxServices suggests these effects indicate the parabens have very weak affinity for ERα and Erβ.*

      ToxServices notes the observations of myometrial hypertrophy in the uterus, and reduced concentrations of serum T4, are of questionable toxicological significance

particularly as the study was not guideline, has limited reporting (e.g. severities are not reported), and there do not appear to be any corresponding pathological effects. Furthermore, these effects have not been reproduced in the other more comprehensive guideline reproductive toxicity studies.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): L

Propylparaben was assigned a score of Low for developmental toxicity based on lack of indications of developmental toxicity in multiple guideline studies for the target compound. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high based on high quality data for the target compound.

- 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 2023a[9]
  - *Oral:* Propylparaben was evaluated in a GLP-compliant prenatal developmental toxicity study performed according to OECD TG 414. Pregnant Wistar rats were administered the test substance (99.7% purity) by gavage in 1% hydroxyethylcellulose at 0, 100, 300, or 1,000 mg/kg once daily on GD 5 through 19 (25 animals/group). Caesarean sections were performed on GD 20, the day prior to the expected day of delivery. There were no significant findings based on clinical observations, mortality, body weight and weight changes, food consumption, ovary and uterine content, gross pathology, number of abortions, pre- and post-implantation loss, number of total, early, or late resorptions, number of dead fetuses, duration of pregnancy, number of pregnant dams, fetal body weights, number of live offspring, litter size and weights, or external, skeletal, and visceral malformations. Authors assigned the NOAEL for developmental toxicity at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2018 study).
  - *Oral:* Propylparaben was evaluated in a previously described GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD TG 422 and EPA OPPTS 870.3650. Wistar rats (11/sex/dose) were exposed to propylparaben (purity not specified) in the diet at 0, 1,500, 4,500, or 15,000 ppm (equivalent to 98.0, 305.1, and 980.0 mg/kg/day in males (pre-pairing); 59.3, 178.3, and 605.0 mg/kg/day in males (after pairing); 116.0, 341.9, and 1,076.4 mg/kg/day in females (pre-pairing); 121.6, 349.2, and 1,124.6 mg/kg/day in females (gestation); and 137.3, 431.8, and 1,380.0 mg/kg/day in females (lactation) (values were reported in the ECHA REACH Dossier)). Male rats were treated for 2 weeks prior to mating and throughout the mating period (a minimum of 28 days). Females were treated for 2 weeks prior to mating, through pregnancy, and then to postpartum day 4 (approximately 7 weeks). The parental animals were evaluated for clinical signs of toxicity, food consumption, body and organ weights, estrous cycle, sperm parameters, fertility indices, post-implantation losses, mean litter size, gross pathology and histopathology. Hematology and blood serum chemistry were only evaluated in parental animals. Offspring were evaluated for survival, number and sex of pups, body weight, and external and internal abnormalities. There were no treatment-related effects on any of the developmental indices measured. The study authors identified a developmental toxicity NOAEL of 15,000 ppm (corresponding to 1,124.6 mg/kg/day), which was the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2012 study).

- *Oral:* Propylparaben was evaluated in a previously summarized GLP-compliant extended one-generation reproductive toxicity study with both developmental neuro- and immunotoxicity (Cohorts 1A, 1B without extension, 2A, 2B, and 3) performed according to OECD TG 443. Wistar rats were administered propylparaben (99.7% purity) by gavage in 1% hydroxyethylcellulose at 0, 100, 300, or 1,000 mg/kg (25/sex/dose, plus an additional 5/sex/dose for the control and high dose groups). Parental (P1) males were dosed from 14 days pre-mating, through mating, and until terminal sacrifice, for a total of 10 weeks. P1 females were dosed from 14 days pre-mating, through mating, and gestation, and until weaning on PND 21, for a total of 8-10 weeks. Pups were dosed from weaning on PND 22 until sacrifice of the respective cohort. For all generations, there were no significant findings based on clinical observations, mortality, body weight and weight changes, food consumption, hematology, clinical chemistry, urinalysis, behavior (functional findings), organ weights, or histopathology. There were no significant findings on developmental toxicity, including developmental neurotoxicity, and developmental immunotoxicity parameters. The developmental toxicity NOAEL was at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2021 study).
- *Oral:* Propylparaben was evaluated in a previously summarized non-GLP compliant reproductive and developmental toxicity screening test performed in a manner equivalent or similar to OECD TG 421. Wistar rats were administered the test substance (purity not specified) by gavage (vehicle not specified) at 0, 500, or 1,000 mg/kg (5/sex/dose). Males were exposed for 21 days pre-mating, and a maximum of 14 days of mating, for a total of 35 days. Females were exposed for 21 days or pre-mating, and 14 days of mating. One dam per group was additionally exposed through gestation to GD 20, and the others were exposed through gestation and up through PND 21. Pups from 3 litters (one per group) were exposed from PND 13 to PND21, in accordance with the treatment group of the dam. The final administration for each animal was given 30 +/- 10 minutes prior to sacrifice and necropsy. There were no significant findings based on clinical signs, mortality, body weight and weight changes, food consumption, reproductive function and performance, or developmental toxicity parameters, for any group compared to controls. The NOAEL for developmental toxicity was reported at 1,000 mg/kg, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2018 study).
- *Subcutaneous:* Propylparaben was evaluated for estrogenicity in a non-GLP, non-guideline study. Pregnancy CF-1 mice were administered the test substance (purity not specified) in DMSO subcutaneously at 948.5 or 1,084 mg/kg on GD 1-4 (6 control animals, 5 at the low dose, and 7 at the highest dose). Dams were sacrificed two days after the last injection, the uteri were excised, and the number of visible intrauterine implantation sites was counted. There were no significant findings and authors assigned the NOAEL at 1,084 mg/kg, the highest dose tested (no further details provided) (Klimisch 2, reliable with restrictions) (Shaw and deCatanzaro 2009).

- CIR 2020
  - Several parabens were assessed for reproductive and developmental effects in a non-guideline study in prepubertal rats (Vo et al. 2010). Methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, and isobutylparaben were administered to groups of prepubertal Sprague Dawley rats (8 weeks old) at 0, 62.5, 250, or 1,000 mg/kg by gavage in corn oil once per day (10/group) on PND 21 to 40. EE was used as a positive control administered at 1 mg/kg/day. All rats were sacrificed at 24 hours following the final exposure.

- A statistically significant delay in vaginal opening was observed in rats exposed to methylparaben at 1,000 mg/kg, and to isopropylparaben at ≥ 250 mg/kg, whereas there was a statistically significant accelerated date of vaginal opening for the positive control animals. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens based on lack of reproducibility with ethylparaben, propylparaben, and butylparaben.*
- At 1,000 mg/kg, there was a statistically significant decrease in ovary weights for rats exposed to methylparaben and isopropylparaben; decreased kidney weights in rats exposed to ethylparaben and isopropylparaben; increases in adrenal gland weights in rats exposed to methylparaben, ethylparaben, and propylparaben, and increases in thyroid gland weights in rats exposed to methylparaben. Liver weights were increased for all doses of rats exposed to butylparaben. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there was no mention of corresponding pathological effects.*
- Decreased number of corpora lutea with increased number of cystic follicles and thinning of the follicular epithelium was observed in the ovaries of rats (test substance(s) and dose(s) not specified). Myometrial hypertrophy in the uterus was identified in rats exposed to propylparaben and isopropylparaben at 1,000 mg/kg, and in rats exposed to butylparaben and isobutylparaben at ≥ 62.5 mg/kg. *ToxServices notes the severity of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens.*
- Serum estradiol concentrations were significantly reduced in rats exposed to ethylparaben and isopropylparaben at 1,000 mg/kg, and prolactin concentrations were increased in rats exposed to methylparaben at 1,000 mg/kg. *ToxServices notes the severity and biological significance of these observations relative to the negative and positive controls was not reported, and there does not appear to be any particular trend among the parabens.*
- Serum concentrations of T4 were statistically significantly reduced in rats exposed to methylparaben at 1,000 mg/kg, propylparaben and isopropylparaben at ≥ 250 mg/kg, and isobutylparaben, propylparaben, and isopropylparaben at ≥ 62.5 mg/kg. The IC50 values for affinity to ERα and ERβ range from 2.07E-6 to 5.55E-5 in the following order: isobutylparaben > butylparaben > isopropylparaben = propylparaben > ethylparaben (the value for methylparaben was not reported); comparatively, the IC50 for 17 β-estradiol was approximately 3E-9. *ToxServices suggests these effects indicate the parabens have very weak affinity for ERα and Erβ.*

ToxServices notes the observations of reduced concentrations of serum T4, are of questionable toxicological significance particularly as the study was not guideline, has limited reporting (e.g. severities are not reported), and there do not appear to be any corresponding pathological effects. Furthermore, these effects have not been reproduced in the other more comprehensive guideline developmental toxicity studies.

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

Propylparaben was conservatively assigned a score of Moderate for endocrine activity based on weak evidence of endocrine activity and no indications of linked adverse health effects. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when there is evidence of endocrine activity and no corresponding adverse health effects have been identified. It may be noted that the SIN List Endocrine Disruptors, EU – Priority Endocrine Disruptors – Category 1 and TEDX ratings

correspond with High or Moderate hazard ratings (CPA 2018b). The confidence in the score is low because the level of endocrine activity in the one positive study was weak and may not be relevant to human health.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - ChemSec – SIN List – Endocrine Disruption.
    - EU – Priority Endocrine Disruptors – Category 1 – *In vivo* evidence of Endocrine Disruption Activity.
    - TEDX – Potential Endocrine Disruptors – Potential Endocrine Disruptor.
- ECHA 2023a[9]
  - *In vivo*: Propylparaben was evaluated in a uterotrophic bioassay in rats (GLP compliance and guideline not specified). Immature female Sprague Dawley rats were administered the test substance (purity not specified) by gavage in 1% hydroxyethylcellulose at 0, 10, 100, or 1,000 mg/kg, once daily, on PND 21 to 23 (6/group). 17α-ethinyl estradiol (E2) was used as the positive control substance and was administered subcutaneously at 0.001 mg/kg. Rats were evaluated daily for survival, clinical observations, and body weights. On PND 24, rats were examined for vaginal patency and euthanized, and the uteri were excised without the ovaries. There were no increases in uterus wet weight or uterine to body weight ratios in treated animals compared to vehicle controls. The positive control performed as expected (no further details provided) (Klimisch 2, reliable with restrictions) (Sivaramana et al. 2018).
  - *In vivo:* Propylparaben was evaluated in a uterotrophic bioassay performed in a manner equivalent or similar to OECD TG 440 (GLP compliance not specified). Immature female B6D2F1 mice and immature female Wistar rats were administered propylparaben (purity not specified) by gavage in a mixture of 10% ethanol in peanut oil, at 5 or 100 mg/kg for the subcutaneous administration, or 1, 10, or 100 mg/kg by gavage, once daily, for 3 days (10 animals/group). Estradiol benzoate was used as the positive control substance and was administered subcutaneously at 0.1 mg/kg/day for 3 days. Animals were sacrificed 24 hours after the final dose, the uteri were excised without the ovaries. There were no increases in uterus wet weight or uterine to body weight ratios in treated animals compared to vehicle controls. The positive control performed as expected. Authors concluded the test substance was not estrogenic under the conditions of the test (Klimisch 2, reliable with restrictions) (Hossaini et al. 2000).
  - *In vivo:* Propylparaben was evaluated in a GLP-compliant fish sexual development test performed according to OECD TG 234. *Danio rerio* (fish) were exposed to the test substance (99.7% purity) for 70 days under flow-through conditions. The 70-day NOEC and LOEC for sex ratio was 165 and 518 µg/L, respectively, based on 81.3% females to 18.7% males. The 70-day NOEC for mortality, number of males, vitellogenin (VTG) level in females, and VTG level in males, was 518 µg/L, the highest concentration tested. The ratio of 81.3% females to 18.7% males reflects a 20% increase in the number of females compared to concurrent controls, and 17% increase compared to historical controls. However, study authors noted an increase of female fish is not biologically relevant for species survival as there are still a sufficient number of males; therefore, this observation cannot be seen as an adverse effect. An estrogen modulated receptor interaction would be expected to result in a prominent VTG increase in male blood plasma, which did not occur, therefore the authors stated no feminization of male fish was caused by the test substance. There were no relevant lesions based on histopathology in treated fish compared to control fish, and no indications of feminization of the male fish (e.g. occurrence of testis-ova).

Authors concluded the test substance was not estrogenic under the conditions of the test (Klimisch 1, reliable without restriction) (Unnamed 2020 study).

- TEDX 2011
  - Propylparaben was placed on the TEDX list of potential endocrine disruptors in 2011. Abstract of studies cited by TEDX are summarized below:
    - *In vitro:* Byford et al. (2002) found evidence of estrogenic activity of parabens in MCF7 human breast cancer cells. The study authors reported that competitive inhibition of [^{3}H]estradiol binding to MCF7 cell estrogen receptors was detected at 1,000,000-fold molar excess of *n*-butylparaben (86%), *n*-propylparaben (77%), ethyl-paraben (54%), and methylparaben (21%). Parabens increased the expression of endogenous estrogen-regulated genes in MCF7 cells at concentrations ≥ 10^{-6} M. They also increased proliferation of cells in a monolayer culture in an estrogen receptor dependent manner.
    - *In vitro:* Chen et al. (2007) found evidence of anti-androgenic activity of parabens in an *in vitro* androgen receptor-mediated transcriptional activity assay. Methyl-, propyl- and butyl-4-hydroxybenzoate inhibited testosterone-induced transcriptional activity by 40%, 33%, and 19%, respectively. However, the major metabolite, 4-hydroxybenzoic acid had no effect on testosterone-induced transcriptional activity.
    - *In vitro:* Gomez et al. (2005) found evidence of estrogenic activity in three reporter cell lines. The parabens were found to activate the estrogen receptor-α (ERα) and ERβ similarly.
    - *In vitro:* Song et al. (1989) reported that parabens have potent *in vitro* spermicidal activity against human spermatozoa.
    - *In vivo:* As previously described, propylparaben was evaluated in a reproductive toxicity study conducted by Oishi (2002), groups of eight male Wistar rats aged 3 weeks were given diets containing 0, 0.01, 0.1, or 1% propylparaben for 4 weeks. The study authors estimated approximate intakes of 10, 100, and 1,000 mg/kg/day propylparaben, respectively. Following the 4-week treatment, rats were sacrificed, blood was collected for hormone assays, testes, epididymides, prostate, seminal vesicles, and preputial glands were weighed, and sperm counts in testes and epididymis were determined. Treatment had no effect on the weight of the reproductive organs. The authors found a significant decrease in cauda epididymal sperm reserves and concentrations in rats treated with 100 and 1,000 mg/kg/day. Daily sperm production and its efficiency in the testes were also significantly decreased in all treatment groups compared to controls. Daily sperm production was approximately 70% of control values in all treated groups; however, there was no dose-response relationship. The authors found a dose-dependent decrease in serum testosterone; the reduction was significant in high-dose animals (Klimisch 3 – not reliable) (ECHA 2023a, WHO 2007). ToxServices identified a NOAEL of 100 mg/kg/day and **LOAEL of 1,000 mg/kg/day based on decreased serum testosterone.**
- WHO 2007
  - *In vivo: <u>Mixed parabens</u>:* In a uterotrophic assay, immature B6D2F mice were administered oral or subcutaneous doses of methyl, ethyl, propyl, butyl *p*-hydroxybenzoate, or their shared metabolite, *p*-hydroxybenzoic acid at doses of 1, 10, or 100 mg/kg/day for 3 consecutive days (the authors did not report which parabens were administered orally vs. subcutaneously). Treatment did not produce an estrogenic response in mice (Hossaini et al. 2000).

- Gazin et al. 2013
    - *In vivo:* In a previously described juvenile toxicity study, male Wistar rats (20/dose) received 0, 3, 10, 100, or 1,000 mg/kg/day propylparaben (purity = 100%) via gavage at a dose volume of 10 ml/kg. Each group was divided into two subgroups of 10 animals: subgroup 1 was necropsied at the end of an 8 week treatment period and subgroup 2 was necropsied after a 26-week washout period. Dosing began on PND21. Blood samples were collected after 8 weeks of treatment for hormone analysis. The study authors found no changes in hormone levels (LH, FSH, and testosterone) at the end of the treatment period. The study authors identified a NOAEL of 1,000 mg/kg/day (highest dose tested).
- SCCS 2013
    - In an attempt to confirm or refute the findings of Oishi (2002) (summarized above, as cited in WHO 2007 and ECHA 2023a), Gazin et al. (2013) designed a study using a similar study design with minor modifications (gavage instead of dietary exposure, and some additional testing). The SCCS (2013) concluded the study by Gazin et al. (2013) was well conducted and provided sufficient information to refute the findings of Oishi (2002) who found effects of sperm parameters and plasma testosterone concentrations of juvenile male Wistar rats at doses of 100 mg/kg/day and above.
    - Although the Oishi (2002) study was discounted, SCCS in its conclusion notes data confirm that the toxicokinetics of parabens in rats and humans differ considerably, and the safety of propylparaben in cosmetic products particularly intended for use on children, has not been established.
- SCCS 2021
    - In its most recent opinion, SCCS reported "the available data on propylparaben provide some indications for potential endocrine effects. However, the current level of evidence is not sufficient to regard it as an endocrine disrupting substance, or to derive a toxicological point of departure based on endocrine disrupting properties for use in human health risk assessment."

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

Propylparaben was assigned a score of Low for acute toxicity based two oral LD_{50} values of 5,000 and > 8,000 mg/kg. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when the lowest oral LD_{50} is > 2,000 mg/kg (CPA 2018b). The confidence in the score is high based on reliable data for the target compound. Although no data were found for acute dermal toxicity, toxicokinetic data demonstrate slower and reduced absorption for dermal exposure, compared to oral exposure, and similar metabolites. Therefore, acute dermal toxicity is expected to be similarly low, or lower than that for the oral route. No data were found for acute inhalation toxicity.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a[9]
    - *Oral:* Propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed in a manner equivalent or similar to OECD TG 401. Wistar rats were administered propylparaben (purity not specified) by gavage in Lutrol at 5,000, mg/kg

(5/sex/dose) and were observed for 14 days post-administration. There were no mortalities and the LD_{50} was assigned at > 5,000 mg/kg (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).

- *Oral:* Propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed in a manner equivalent or similar to OECD TG 401. Albino mice (strain and sex not specified) were administered propylparaben (purity not specified) by gavage in propylene glycol or olive oil at up to 8,000 mg/kg (number of animals per dose not specified) and were observed for 7 days post-administration. The LD_{50} was assigned at > 8,000 mg/kg (no further details provided) (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).

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

Propylparaben is conservatively assigned a score of Moderate for systemic toxicity (single dose) based on a majority of notifiers in the ECHA Classification and Labeling Inventory indicating Hazard Statement H335 – May cause respiratory irritation, which corresponds to GHS Category 3 classification. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when data support GHS Category 3 classification for any route of exposure (CPA 2018b). Confidence is low as no supporting inhalation data were found. Available oral data suggest low concerns for systemic effects following single exposure. No data were found for acute dermal exposure, however, as noted previously, toxicokinetic data suggest toxicity following dermal exposure will be similar or lower than that for oral exposure, based on slower and less extensive absorption.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
  - *Other:*
    - EU – Manufacturer REACH hazard submissions – H335 – May cause respiratory irritation (unverified) [Specific target organ toxicity – single exposure; Respiratory tract irritation – Category 3].
- ECHA 2023a[9]
  - *Oral:* Propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed in a manner equivalent or similar to OECD TG 401. Wistar rats were administered propylparaben (purity not specified) by gavage in Lutrol at 5,000, mg/kg (5/sex/dose) and were observed for 14 days post-administration. There were no mortalities, no clinical signs of toxicity observed during the study period, and no significant findings based on necropsy at study termination (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).
  - *Oral:* Propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed in a manner equivalent or similar to OECD TG 401. Albino mice (strain and sex not specified) were administered propylparaben (purity not specified) by gavage in propylene glycol or olive oil at up to 8,000 mg/kg (number of animals per dose not specified) and were observed for 7 days post-administration (no further details provided) (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).

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

Propylparaben was assigned a score of Low for systemic toxicity (repeated dose) based on lack of indications of systemic toxicity in numerous studies, including some that are GLP-compliant and were

performed to recognized guidelines (e.g. OECD TG 408, 422, 443, 421), and several of these studies had doses > 1,000 mg/kg/day. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound.

- 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 2023a[9]
  - *Oral:* Propylparaben was evaluated in a GLP-compliant subchronic oral toxicity study performed according to OECD TG 408. Wistar rats were administered the test substance (99.7% purity) by gavage in 1% hydroxyethylcellulose at 0, 100, 300, or 1,000 mg/kg/day for 90 days (10/sex/group, plus an additional 5/sex for the control and high dose groups as recovery animals). Mid- and high-dose animals demonstrated slight-to-moderate salivation and moving the bedding, but as the timing was close to the test substance administration, investigators considered the effect to be local and not an indication of systemic toxicity. There were no further significant findings based on clinical observations. There were no significant findings based on mortality, body weight and weight changes, food consumption, ophthalmology, hematology, clinical chemistry, urinalysis, behavior (functional findings), immunology, organ weights, gross pathology, neuropathology, or histopathology. The NOAEL is reported at 1,000 mg/kg/day, the highest dose tested (Klimisch 1, reliable without restriction) (Unnamed 2019 study).
  - ToxServices notes no indications of systemic toxicity, organ toxicity, or immunotoxicity were identified in the previously summarized carcinogenicity/chronic exposure studies, reproductive toxicity studies, or developmental toxicity studies (see respective sections for details).
- CIR 2008
  - *Dermal:* Methylparaben and propylparaben were evaluated in numerous repeated dose toxicity studies presented in the CIR (2008) review. These studies used formulations containing methylparaben alone (up to 0.7%[12]), propylparaben alone (up to 0.3%), and product formulations containing multiple parabens (0.2% methylparaben and 0.2% propylparaben). Rats and/or rabbits were dermally exposed to the product formulation for up to 13 weeks. The studies occasionally found slight changes in hematologic and blood chemistry parameters; however, these changes were not accompanied by any significant gross or histopathological changes and were considered toxicologically insignificant. Treatment caused no changes in animal body weight or food consumption and no gross or histopathological changes were found. Treatment-related effects were limited to localized effects (i.e., mild to severe inflammation, moderate to well-defined erythema, slight edema, and slight to mild desquamation) of the treated skin. The study authors found no cumulative systemic toxic effects.
- NCI 1977
  - *Intramuscular injection:* Methylparaben and propylparaben were evaluated in a non-guideline antigen study in guinea pigs. Animals were injected a saline solution with 1.6 mg methylparaben and 0.4 mg propylparaben per 100 mg body weight (3/sex/treatment group and 2/sex as vehicle controls) once per day on Monday, Wednesday, and Friday of week 1, and Monday of the following week. A challenge dose was administered after a 14-day rest period directly into the heart of 6 test, and 4 control animals. Animals were observed for

[12] mg/kg/day dose cannot be calculated without information on the frequency and amount applied on the animals.

signs of respiratory distress and death within 1 hour post-administration. After one hour, animals were sacrificed and necropsied for gross pathological examination. One of the 6 exposed animals exhibited clonic-tonic convulsions and had bloody discharge from its mouth and nostrils, and also had massive cardiac hemorrhage and a large needle puncture wound in the heart identified at necropsy. Investigators reported the death was likely due to mechanical trauma to the heart, rather than an antigenic response. Necropsies of several control animals identified a few small hemorrhages on the lung, but no cardiac bleeding. Authors concluded the test substance was not antigenic under the conditions of the test.

Neurotoxicity (single dose, N-single) (Group II) Score (vH, H, M, or L): *L*
Propylparaben is assigned a score of Low for neurotoxicity (single dose) based on lack of indications of neurotoxicity following single exposure in rats and humans. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low as the rat and mouse data (OECD TG 401) are limited to clinical indications and necropsy and such studies do not typically assess additional neurotoxicity parameters (e.g. startle reflex, righting reflex, grip strength, etc.). It may be noted that only ECHA 51 notifiers indicate H statement H336, compared to over 2,000 that do not indicate this H statement (Pharos 2023). Furthermore, as no supporting data were found, the notified hazard phrase is not considered in the weight of evidence.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening list for this endpoint.
- ECHA 2023a[9]
  - *Oral:* As summarized previously, propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed in a manner equivalent or similar to OECD TG 401. Wistar rats were administered propylparaben (purity not specified) by gavage in Lutrol at 5,000, mg/kg (5/sex/dose) and were observed for 14 days post-administration. There were no mortalities, no clinical signs of toxicity observed during the study period, and no significant findings based on necropsy at study termination (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).
  - *Oral:* As summarized previously, propylparaben was evaluated in a non-GLP compliant acute oral toxicity study performed equivalent or similar to OECD TG 401. Albino mice (strain and sex not specified) were administered propylparaben (purity not specified) by gavage in propylene glycol or olive oil at up to 8,000 mg/kg (number of animals per dose not specified) and were observed for 7 days post-administration. There were no deaths (no further details provided) (Klimisch 2, reliable with restrictions) (Unnamed 1982 study).
- HSDB 2017
  - *Intravenous:* Methylparaben and propylparaben were evaluated in a non-guideline human exposure study designed to investigate effects on cerebral vasodilation and intracranial pressure. Healthy humans were administered intravenous injections of methylparaben and propylparaben, and Cerebral blood flow (CBF) and cerebral blood flow velocity (CBFV) were measured with inhaled ^{133}-Xenon and transcranial Doppler. There were no significant changes in CBF or CBFV identified for either test substance.

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): L
Propylparaben was assigned a score of Low for neurotoxicity (repeated dose) based on lack of indications of neurotoxicity in parental animals in the functional observation battery (FOB) of a GLP-compliant guideline study (OECD TG 422) in rats. GreenScreen® criteria classify chemicals as a Low

hazard for neurotoxicity (repeated dose) when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound.

- 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 2023a[9]
  - *Oral:* Propylparaben was evaluated in the previously described GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD TG 422. Male and female Wistar rats (11/sex/dose) were exposed to 0, 1,500, 4,500, or 15,000 ppm propylparaben in their feed (equivalent to 98.0, 305.1, and 980.0 mg/kg/day in males (pre-pairing); 59.3, 178.3, and 605.0 mg/kg/day in males (after pairing); 116.0, 341.9, and 1,076.4 mg/kg/day in females (pre-pairing); 121.6, 349.2, and 1,124.6 mg/kg/day in females (gestation); and 137.3, 431.8, and 1,380.0 mg/kg/day in females (lactation) (values were reported in the ECHA REACH Dossier)). Male rats were treated for 2 weeks prior to mating and throughout the mating period (a minimum of 28 days). Females were treated for 2 weeks prior to mating, through pregnancy, and then to postpartum day 4 (approximately 7 weeks). An FOB was performed in males (5/group) shortly before the scheduled sacrifice and in females (5/group) on post-partum day 3. The study authors performed cage-side observations and evaluated the quantity of feces and urine, posture, and resistance to removal. Hand-held observations were conducted and evaluated animals for muscle tone, pupil size, palpebral closure, lacrimation, salivation, reaction to handling, and general abnormalities. Open-field observations were conducted and evaluated animals for their level of ambulatory activity including rearing (one minute evaluation), unusual body movements (e.g. spasms and convulsions), gait, behavior, coat, respiration, and quantity of feces and urine. Evaluation of animal reflexes including assessment of blinking, palpebral closure, pinna reflex, extensor thrust response, paw pinch, responsiveness to sharp noise, righting reflex, and hearing ability. Rat hind limb and fore limb grip strength was measured, and rectal temperature was taken. Locomotor activity was also quantitatively measured. No treatment-related effects were reported. The study authors reported that the mean body temperature of high dose males was statistically significantly lower than control animals. However, the change was minor and it was within the range of historical controls; therefore, the study authors considered the change to be a results of biological variability and did not consider it to be treatment-related (Klimisch 1, reliable without restriction) (Unnamed 2012 study). *ToxServices identified a neurotoxicity NOAEL of 15,000 ppm propylparaben (corresponding to 1,124.6 mg/kg/day) (highest dose tested).*

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

Propylparaben was assigned a score of Low for skin sensitization based on measured data (multiple OECD TG 429 and 406 studies) for the target compound. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound. It may be noted that a screening list identifies propylparaben as a skin sensitizer (New Zealand). However, as there are high quality data demonstrating a lack of skin sensitization for propylparaben, and no supporting data to the contrary, the screening list is excluded from the weight of evidence.

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

  - *Screening:*
    - GHS – New Zealand – Skin sensitisation category 1.
- ECHA 2023a[9]
  - Propylparaben was not sensitizing in a mouse local lymph node assay conducted in a manner equivalent or similar to OECD TG 429 using (GLP compliance not specified). CBA/Ca mice (4/group) were dermally administered 25 µL of 5, 10, or 25% propylparaben (98% purity) in acetone/olive oil (4:1 v/v) on the dorsal surface of each ear for 3 consecutive days. Following the final application, the animals were sacrificed and the lymph nodes isolated to perform the proliferation assay. The stimulation indices for the 5, 10, and 25% doses were 1.3, 1.6, and 1.3, respectively. As all of the stimulation indices for the applied doses were less than 3, propylparaben was not sensitizing to the skin of mice in this study (Klimisch 2, reliable with restrictions) (Basketter and Scholes 1992).
  - Propylparaben was not sensitizing in a guinea pig maximization assay conducted according to OECD TG 406 (GLP compliance not specified). Dunkin-Hartley guinea pigs induced with propylparaben (> 98% purity) in physiological saline at 0.5% by intradermal injection, and 25% in acetone/polyethylene glycol 400 (70:30 v/v) by epicutaneous administration. The challenge was performed with 10% propylparaben in acetone/PEG 400 (70:30 v/v) by epicutaneous administration. No skin reactions were seen in any of the exposed animals at the 24 and 48 hour readings. 2-Mercaptobenzothiazole was the positive control substance and provided the expected results. Study authors concluded the test substance was not sensitizing by EU criteria (Klimisch 2, reliable with restrictions) (Basketter and Scholes 1992).
  - Propylparaben was not sensitizing in a mouse local lymph node assay conducted in a manner equivalent or similar to OECD TG 429 using (GLP compliance not specified). CBA/Ca mice (4/group) were dermally administered 25 µL of 5, 10, or 25% propylparaben (98% purity) in acetone/olive oil (4:1 v/v) on the dorsal surface of each ear for 3 consecutive days. Following the final application, the animals were sacrificed and the lymph nodes isolated to perform the proliferation assay. The stimulation indices for the 5, 10, and 25% doses were 1.4, 1, and 1.3, respectively. As all of the stimulation indices for the applied doses were less than 3, propylparaben was not sensitizing to the skin of mice in this study (Klimisch 2, reliable with restrictions) (Basketter et al. 1994).
  - Propylparaben was not sensitizing in a pre-GLP, pre-guideline guinea pig maximization assay conducted in a manner equivalent or similar to OECD TG 406. Hartley strain and Hartley-English short hair cross-strain guinea pigs (n=23) were induced with propylparaben (purity not specified) by intradermal injection at 3% (vehicle not specified), every other day for 10 injections. The challenge was performed by intradermal injection at 3% (vehicle not specified) and by epicutaneous administration at 3% (vehicle not specified) on day 34. There were no positive reactions in any exposed animals after the challenge. The substance is reported as not sensitizing (no further details provided) (Klimisch 2, reliable with restrictions) (Marzulli et al. 1968).
- CIR 2008
  - The CIR Expert Panel presented multiple clinical studies which found evidence that patients sensitive to one paraben show cross-reactivity to another paraben. They indicated that evidence of paraben sensitization was reported in case literature, but it primarily occurred when the exposure involved damaged or broken skin. Patch-testing data indicate that in patients with chronic dermatitis less than 4% of individuals were sensitive to parabens. Additionally, patch testing data over the past 20 years showed no significant change in the incidence of dermatitis patients that tested positive for parabens.

- HSDB 2017
    - In a repeated insult patch test, each paraben (methylparaben, ethylparaben, propylparaben, and butylparaben) were administered to the skin of 50 subjects (25/sex) for 4 to 8 hours every other day for 3 weeks (10 applications), followed by a 3-week rest period. The test substance was then reapplied and observations were recorded at 24 and 48 hours post exposure. There were no indications of sensitization in any subjects at 24 or 48 hours post-challenge.

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): *L*
Propylparaben was assigned a score of Low for respiratory sensitization in accordance with the guidance from ECHA (2017). Specifically, propylparaben has low concerns for respiratory sensitization based on extrapolation from negative skin sensitization data, lack of structural alerts for respiratory sensitization, and lack of indications of respiratory sensitization in the public literature despite long historical and widespread use. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low as this evaluation does not include non-immunologic mechanisms of respiratory sensitization, and no specific data are available for respiratory sensitization.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2022
    - Propylparaben does not contain any structural alerts for respiratory sensitization (Appendix D)
- The guidance from ECHA states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). As propylparaben was not sensitizing to the skin (see skin sensitization section above), a literature search did not find any human evidence of respiratory sensitization by propylparaben, and propylparaben does not contain any structural alerts for respiratory sensitization (OECD 2022), it is not expected to be a respiratory sensitizer.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
Propylparaben was conservatively assigned a score of Low for skin irritation/corrosivity based on surrogate ethylparaben being nonirritating to the skin of rabbits exposed to the undiluted test substance in a guideline study (OECD TG 404). This is consistent with the recent opinion of SCCS (2021) who concluded propylparaben was not a skin irritant. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low based on surrogate data, and the available data on the target compound indicate weak irritation potential but are insufficient to confirm if the irritation potential is below the threshold for GHS classification (UN 2021). Whereas the majority of EU notifiers report H315 – Causes skin irritation (Pharos 2023), substantiation for this rating was not found.

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

- CIR 2020
    - Methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzoparaben were evaluated for skin irritation and skin sensitization in a non-guideline *in vitro* study using cocultured human keratinocytes and peripheral blood mononuclear cells (PBMCs). The co-cultures were exposed to the parabens at unspecified concentrations in DMSO, and were incubated for 48 hours. Irritancy was assessed based on cell death and the corresponding EC_{50} value. EC_{50} values for irritating, weakly irritating, and non-irritating are ≤ 50 µM, >50 to ≤ 1,000 µM, and > 1,000 µM, respectively. Methylparaben and ethylparaben were not irritating, and propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzoparaben were weakly irritating (Sonnenburg et al. 2015). *ToxServices notes this non-guideline study does not appear to reflect a validated method, and is of low reliability. Additionally, the scoring system and results are not suitable for comparison to the GHS guidance. However, it does suggest propylparaben is weakly irritating to the skin.*
- HSDB 2017
    - Methylparaben, ethylparaben, propylparaben, and butylparaben were each applied to the backs of 50 volunteers at concentrations of 5, 7, 10, 12, and 15% in propylene glycol for 5 days under occlusive patches. The no effect levels for skin irritation of methylparaben, ethylparaben, propylparaben, and butylparaben were 5%, 7%, 12%, and 5%, respectively (no further details provided). *Although not stated as such, ToxServices notes this study summary implies propylparaben was irritating at ≥ 12%. However, due to lack of additional study details, ToxServices considered this study of low reliability.*
- CIR 2008
    - Propylparaben was evaluated in a clinical 24-hour single insult occlusive patch test. A formulation containing 0.3% propylparaben produced minimal irritation in 2 of 20 subjects with a primary irritation score of 0.1.
    - Methylparaben, butylparaben, and propylparaben were evaluated in a clinical 21-day cumulative irritancy study. Product formulations containing mixtures of methylparaben (0.2%), butylparaben (0.1%), or propylparaben (0.2%) produced no irritation to slight irritation. Volunteers were treated with the product formulation for 23 hours under occlusive conditions for 21 consecutive days.
    - Methylparaben and propylparaben were evaluated in a clinical controlled use test (4 weeks). An eye makeup formulation containing 0.2% methylparaben and 0.1% propylparaben caused no irritation.
    - Methylparaben or propylparaben were evaluated in a skin irritation study. A paste containing hydrophilic ointment and either 10% methylparaben or propylparaben was applied to the shaved backs of albino rabbits (number not reported) for 48 hours. The study summary did not indicate if treatment occurred under occlusive, semi-occlusive, or non-occlusive conditions. Treatment produced no irritation. No further details were provided.
    - Propylparaben was evaluated in a skin irritation study in rabbits. A product formulation containing 0.3% propylparaben was applied daily to the shaved skin of albino rabbits (n=9) for 4 consecutive days. Treatment produced minimal irritation. The authors reported a primary irritation index of 0.5 (maximum score = 4). No further details were provided.
    - Propylparaben was evaluated in a skin irritation study in rabbits. A product formulation containing 0.2% propylparaben produced minimal irritation. The authors reported a primary irritation index of 0.5. No further details were provided.

  - Propylparaben and butylparaben were evaluated in a skin irritation study (species not reported). A product formulation containing 0.2% propylparaben and 0.1% butylparaben was not irritating. No further details were provided.
  - Methylparaben and propylparaben were evaluated in a skin irritation study in rabbits. A product formulation containing 0.2% methylparaben and 0.1% propylparaben produced minimal irritation in rabbits, with a primary irritation index of 0.5. No further details were provided.
- ECHA 2023c[9]
  - *Surrogate Ethylparaben:* Ethylparaben was evaluated in a dermal irritation test conducted similarly to OECD TG 404 (GLP compliance not specified). Three male HC:NWZ rabbits were administered topical applications of 500 mg ethylparaben (purity not reported) moistened with water to clipped skin under semiocclusive dressing for 4 hours. An observation period of 7 days followed the exposure period. No edema or erythema was seen. The overall irritation score at 72 hours was 0 for both edema and erythema. The study authors concluded that ethylparaben was not irritating to the skin in this study (Klimisch 1, reliable without restriction) (Unnamed 1983 study).
- SCCS 2021
  - "Based on the weight of evidence, including *in silico* predictions with OECD Toolbox v4.0 and DEREK nexus v.6.0.1, profiling gives no evidence for skin irritation of propylparaben or any of the n-alkyl parabens."
  - SCCS noted the *in vivo* data on propylparaben (Unnamed 1983 study as cited in ECHA REACH dossier, Sokol 1952 as summarized in CIR 1984, Leberco Laboratories 1978, and CTFA 1979) suggest low concerns for skin irritation but the studies were not robust and/or had reporting deficiencies. Therefore, *in silico* modeling and read-across to methylparaben and ethylparaben, were included in the weight of evidence. SCCS concluded, based on the overall weight of evidence that "SCCS does not consider propylparaben as a skin irritant".

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

Propylparaben was assigned a score of Low for eye irritation/corrosivity based on high quality measured data from two GLP-compliant guideline studies in which the target compound was tested undiluted, and was not irritating. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation / corrosivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is high based on high quality data for the target compound. It may be noted that propylparaben is listed as an eye irritant by New Zealand (GHS Category 2), a majority of EU notifiers (H319 - Category 2A), and a minority of EU notifiers (H318 - Category 1) (Pharos 2023, ECHA 2023b). As no data were found to support these screening lists, and high quality data were found that support not classified, the screening list and self-classifications were discounted in the weight of evidence.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – New Zealand – Eye irritation Category 2.
- ECHA 2023a[9]
  - Propylparaben was evaluated in a GLP-compliant acute eye irritation study conducted according to OECD TG 405 and EU Method B.5. Undiluted propylparaben (0.1 g) (purity not reported) was instilled into the conjunctival sac of the left eye of three male New Zealand White rabbits. Irritation was scored at 1, 24, 48 and 72 hours, as well as 7 days after treatment. The mean irritation scores for all animals across all time points were 0.0 for corneal opacity, iris light reflex, and chemosis in all animals. Mean scores for conjunctivae

in the individual animals at 24, 48, and 72 hours were 1.0, 2.0, and 1.67, and effects were fully reversible within 7 days. The study authors concluded that propylparaben was not irritating to the eye and was not classified per CLP/GHS (Klimisch 1, reliable without restriction) (Unnamed 2012 study). *According to GHS criteria,* a *mean score for conjunctivae redness of ≥ 2 is required to classify to eye irritation Category 2B with effects being fully reversible within 7 days. Therefore, propylparaben is not classified per GHS.*

- Propylparaben was evaluated in a GLP-compliant, *in vitro* / *ex vivo* eye irritation study performed according to OECD TG 437, the bovine corneal opacity and permeability test (BCOP). Three bovine corneas were exposed to 0.75 mL of a 20% (w/v) suspension of propylparaben (purity not specified) in physiological saline solution for 240 minutes. At the end of the exposure period, the corneas were rinsed and opacity was determined. Ninety minutes after treatment, the permeability of the corneas was assessed through treatment with a fluorescein solution. Treatment with propylparaben caused a slight increase in corneal opacity, and no effect on permeability compared to the negative control. A mean *in vitro* irritation score of 13.03 was reported. The study authors concluded that propylparaben was not corrosive or severely irritating to the eye (Klimisch 1, reliable without restriction) (Unnamed 2012 study).

Ecotoxicity (Ecotox)

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

Propylparaben was assigned a score of High for acute aquatic toxicity based on a 96-hour LC_{50} of 6.4 mg/L in fish (OECD TG 203). GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when the most sensitive species has a LC/EC_{50} in the range of > 1.0 to 10 mg/L (CPA 2018b). The confidence in the score is high based on high quality data for the target compound for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a[9]
  - 96h LC_{50} = 6.4 mg/L (measured) (*Danio rerio*, fish) under static conditions (GLP, OECD TG 203 and EU Method C.1) (Klimisch 1, reliable without restriction) (Unnamed 2012 study).
  - 48h EC_{50} (mobility) = 15.4 mg/L (*Daphnia magna,* daphnia) (static or semi-static not specified) (ISO 6341) (Klimisch 2, reliable with restrictions) (Unnamed 2001 study).
  - 72h EC_{50} (growth rate) = 16 mg/L (nominal), (*Raphidocelis subcapitata,* algae) under static conditions (GLP, OECD TG 201, EU Method C.3) (Klimisch 1, reliable without restriction) (Unnamed 2012 study).
  - 72h EC_{50} = 15 mg/L (*R. subcapitata,* algae) (ISO 8692) (Klimisch 2, reliable with restrictions) (Unnamed 2001 study).
- ECHA 2021
  - In its review of the REACH dossier, there is discussion of "no effects at up to the limit concentration of 100 mg/L in terms of acute and chronic effects in Daphnia and algae and no acute effects in fish." No further details were provided. ECHA concluded the data were insufficient to support lack of chronic toxicity in fish, and requested submission of a study such as OECD TG 210. *Based on lack of additional details, ToxServices notes these comments regarding acute aquatic toxicity are not reliable and are therefore not included in the weight of evidence.*

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

Propylparaben was assigned a score of High for chronic aquatic toxicity based on an estimated chronic value of 0.396 mg/L in fish, and a measured NOEC of 0.25 mg/L in Daphnia. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when the most sensitive species has a NOEC value in the range of > 0.1 to 1.0 mg/L (CPA 2018b). The confidence in the score is low due to lack of reliable experimental data and reliance on modeled data for the fish trophic level.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS – New Zealand – Hazardous to the aquatic environment – chronic Category 2
- ECHA 2023a[9]
  - 21-day NOEC of 0.25 mg/L, and LOEC of 0.8 mg/L in *D. magna*, based on reproduction, immobility, and growth (GLP, OECD TG 211) (Klimisch 1, reliable without restrictions) (Unnamed 2019 study).
  - 72h NOEC (growth rate) = 2.1 mg/L (*R. subcapitata,* algae) under static conditions (GLP, OECD TG 201, EU Method C.3) (Klimisch 1, reliable without restriction) (Unnamed 2012 study).
  - 72h NOEC = 5 mg/L (*R. subcapitata,* algae) (ISO 8692) (Klimisch 2, reliable with restrictions) (Unnamed 2001 study).
- ECHA 2021
  - In its review of the REACH dossier, there is discussion of "no effects at up to the limit concentration of 100 mg/L in terms of acute and chronic effects in Daphnia and algae and no acute effects in fish." No further details were provided. ECHA concluded the data are insufficient to support lack of chronic toxicity in fish, and requires submission of a study such as OECD TG 210.
- AAICA 2020
  - 10-day LOEC in *D. magna* = 0.4 mg/L (no further details provided) (US EPA SERAS SOP 2028). *This study is reported with an incomplete reference and could not be found in the EPA's AQUIRE database (U.S. EPA 2018). Therefore, due to limited study details, ToxServices considered this study unreliable and did not include it in the weight of evidence.*
- HSDB 2017
  - Chronic toxicity was evaluated in non-guideline study with *Ceriodaphnia dubia* exposed to various parabens for 7 days under static conditions. The range of EC_{50} values for mortality, offspring number, and first brood production were 0.30-3.1, 0.047-12, and 1.3-6.3 mg/L, respectively. The NOEC and LOEC values for the number of neonates ranged from 0.63 to 10 mg/L, and 1.2 to 19 mg/L, respectively. The NOEC for methylparaben, benzylparaben, and dichlorinated benzoparaben was 1.3, 0.04, and 0.63 mg/L, respectively. NOEC and LOEC values could not be determined for propylparaben, chlorinated propylparaben, isopropylparaben, and chlorinated isopropylparaben as these compounds exhibited nonmonotonic concentration-dependent responses (no further details provided).
- U.S. EPA 2017b
  - Propylparaben belongs to the Esters and Phenols ECOSAR chemical classes. The most conservative estimated chronic values (ChVs) are 0.396 mg/L in fish, 0.456 mg/L in daphnia, and 1.28 mg/L in green algae (Appendix E).

Environmental Fate (Fate)

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

Propylparaben is assigned a score of Very Low for persistence based on measured data indicating ready biodegradability (>60% in 28 days), and it meets the 10-day window. Additionally, propylparaben is predicted to partition to soil with a half-life of 30 days. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when soil is the dominant compartment and the substances is readily biodegradable and meets the 10-day window (CPA 2018b). The confidence in the score is high based on measured data for the target compound.

- 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 2023a[9]
  - Propylparaben was evaluated in a ready biodegradability Manometric Respirometry Test performed according to OECD TG 301F (GLP compliance not specified). Biodegradation was measured based on oxygen consumption. Testing was performed with an initial concentration of 20 mg test substance/L, over 28 days, under aerobic conditions (inoculum not specified). Sodium benzoate was the reference substance. The test substance reached 61.1% by day 6, and 91.5% degradation by day 28, and the reference substance performed as expected. Authors concluded the test substance was readily biodegradable (Klimisch 2, reliable with restrictions) (Unnamed 2001 study). *ToxServices adds that test substance is readily biodegradable based on reaching >60% in 28 days, and it met the 10-day window (based on >60% in 6 days).*
- U.S. EPA 2017a
  - The Level III Fugacity model (MCI method) predicts 82% will partition to soil with a half-life of 30 days, 17.7% will partition to water with a half-life of 15 days, and <1% will partition to sediment and air (Appendix F).

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

Propylparaben was assigned a score of Very Low for bioaccumulation based on measured data indicating a log K_{ow} in the range of 2.34 to 3.04, and the most conservative predicted BCF of 10.073. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is ≤ 4 and the BCF is ≤ 100 (CPA 2018b). The confidence in the score is high based on a measured log K_{ow} and a conservatively modeled BCF.

- 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 2023a[9]
  - Propylparaben has a measured log K_{ow} values in the range of 2.34-3.04.
- U.S. EPA 2017
  - BCFBAF predicts a BCF of 28.08 using the regression based model based on a measured log K_{ow} of 2.7, and a BCF of 10.073 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix F).

Physical Hazards (Physical)

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

Propylparaben was assigned a score of Low for reactivity based on lack of reactive functional groups associated with explosivity and oxidizing potential. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score is low due to lack of experimental data. It may be noted that no data were found regarding corrosivity to metal.

- 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 measured data were identified. Therefore, screening procedures for explosivity were used here to estimate the reactivity property of propylparaben. These procedures are listed in the GHS (UN 2021).
  - Based on the structure of its components or moieties, propylparaben is not considered explosive or self-reactive due to lack of functional groups associated with explosive or self-reactive properties (See Appendix G).
  - Based on the structure of its components or moieties, propylparaben is not considered to have oxidizing properties as it does not contain any structural groups known to be correlated with a tendency to react exothermally with combustible materials. Specifically, organic substances which contain oxygen, fluorine, or chlorine where these elements are chemically bonded only to carbon or hydrogen, classification as an oxidizing liquid need not be applied. Therefore, as the molecular structure of propylparaben has 3 oxygens, which are all bonded only to carbon and hydrogen, classification is not warranted.
- ThermoFisher Scientific 2022
  - The safety data sheet (SDS) for Propyl 4-hydroxybenzoate (aka propylparaben) identifies a flash point of 180°C, autoignition temperature of 600°C, and NFPA ratings of 1 for flammability (flashpoint > 200°F, requires pre-heating to burn) and 0 for reactivity (normally stable).

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

Propylparaben is assigned a score of Low for flammability based on measured data indicating the substance is not flammable in a guideline test. GreenScreen® criteria classify chemicals as a Low hazard for flammability when adequate data exist and GHS classification is not warranted (CPA 2018b). The confidence in the score was high based on measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2023a
  - Propylparaben was evaluated in a GLP-compliant study for the flammability of solids, according to EU Method A.10. The test substance (≥ 99% purity) did not ignite on contact with air. In the course of the preliminary test, the item could not be ignited, but melted. Authors of the REACH dossier concluded the test substance was not flammable (no further details provided) (Klimisch 1, reliable without restriction) (Unnamed 2011 study).

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* testing for mutagenicity, endocrine activity, skin irritation, and eye irritation, and *in silico* modeling for respiratory sensitization, chronic aquatic toxicity, 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 (2018), uncertainty is "a general term referring to all types of limitations in available knowledge that affect the range and probability of possible answers to an assessment question." The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties (OECD 2020):

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

As shown in Table 4, Type I (input data) uncertainties in propylparaben's NAMs dataset include lack of, or insufficient experimental data for respiratory sensitization and chronic aquatic toxicity, and lack of validated methods for assessing respiratory sensitization. Propylparaben's Type II (extrapolation output) uncertainties include reliance on *in vitro* data in which the exogenous metabolic activation does not entirely mimic *in vivo* conditions, the limitation of the OECD TG 437 method to detect GHS Category 2 eye irritants, and extrapolation of skin sensitization data to respiratory sensitization which is incomplete in that it does not account for non-immunologic mechanisms of respiratory sensitization. Some of propylparaben's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 4: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses

Uncertainty Analyses (OECD 2020)	
Type I Uncertainty: Data/Model Input	**Respiratory sensitization**: No experimental data are available and there are no validated test methods. **Chronic aquatic toxicity:** No experimental data are available for fish and invertebrate trophic levels.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD TG 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 TG 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo* metabolism (i.e.,

[13] NAMs refers to any non-animal technology, methodology, approach, or combination thereof that inform chemical hazard and risk assessments. NAMs include *in silico*/computational tools, *in vitro* biological profiling (e.g., cell cultures, 2,3-D organotypic culture systems, genomics/transcriptomics, organs on a chip), and frameworks (i.e., adverse outcome pathways (AOPs), defined approaches (DA), integrated approaches to testing and assessment (IATA).

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

	the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[15] **Endocrine activity:** The exogenous metabolic activation system does not entirely mimic *in vivo* conditions. The relevance of available data to human health (e.g., weak endocrine activity *in vitro*) is not known. **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. **Eye irritation**: The BCOP (OECD TG 437) test is not recommended for identifying GHS Category 2A or 2B irritants[16].	
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
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In vitro* tests for estrogen receptor binding
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	Y	*In vitro* skin irritation study
Eye irritation	Y	*In vitro/ex vivo* BCOP test
Acute aquatic toxicity	N	
Chronic aquatic toxicity	Y	*In silico* modeling: ECOSAR
Bioaccumulation	Y	*In silico* modeling: EPI Suite™

[15] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[16] https://www.oecd-ilibrary.org/docserver/9789264203846-en.pdf?expires=1614095760&id=id&accname=guest&checksum=1613168F64BDB3558225572BDD75FC8D

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Propylparaben (CAS #94-13-3)

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	Propylparaben	94-13-3	*L*	L	L	L	*M*	L	*M*	L	*L*	L	L	*L*	*L*	L	H	H	vL	vL	*L*	L

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Propylparaben	2

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

Table 6

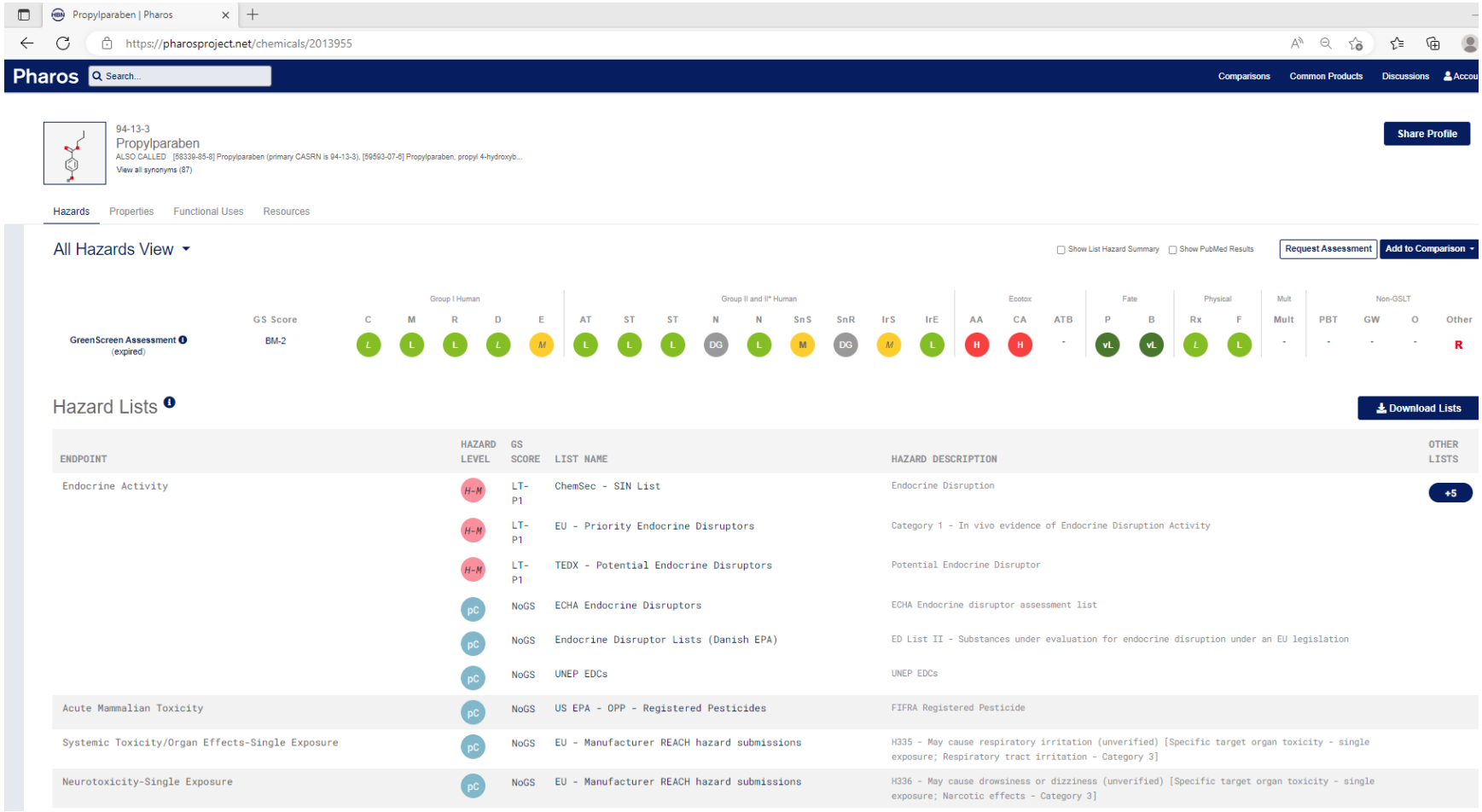
Chemical Name	Final GreenScreen® Benchmark Score
Propylparaben	2

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 Propylparaben (CAS #94-13-3)

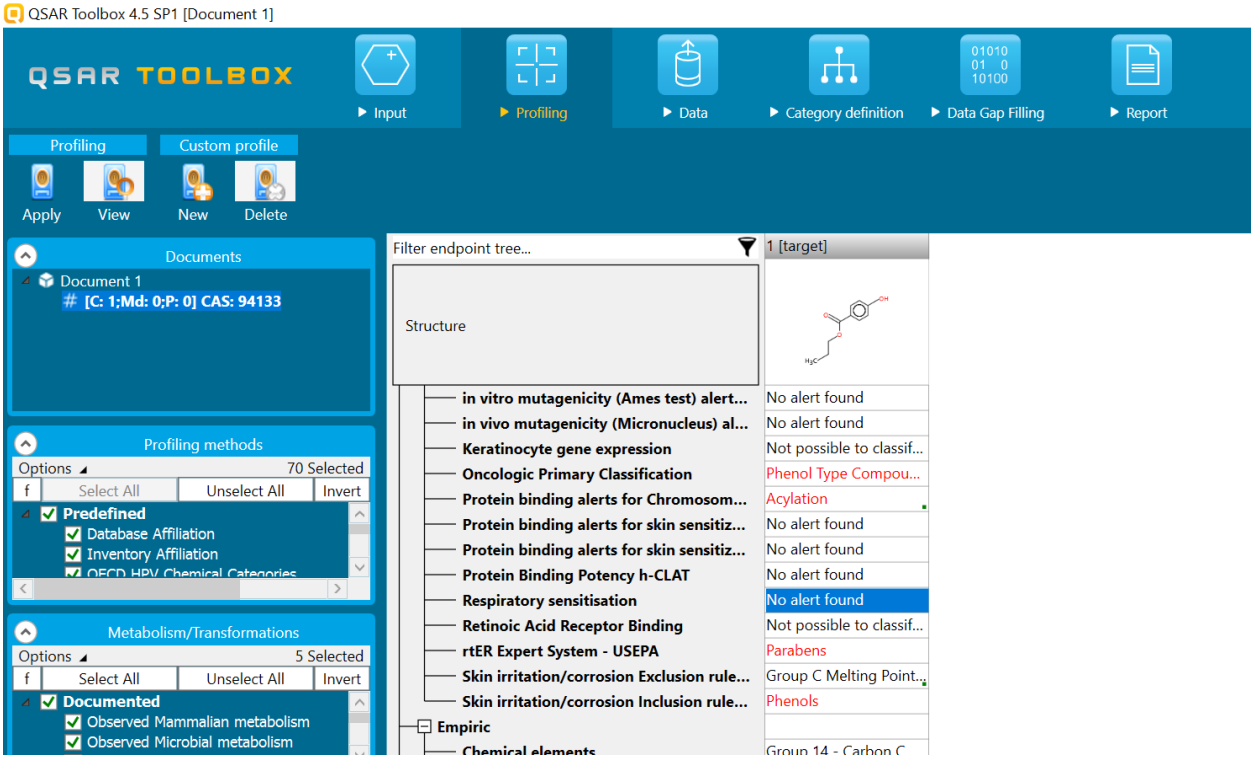


Skin Sensitization	H	LT-UNK	GHS - New Zealand	Skin sensitisation category 1	+2
	pC	NoGS	SCJ - Potential Skin Allergens	Potential Skin Allergens	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Skin Irritation/Corrosivity	pC	NoGS	EU - Manufacturer REACH hazard submissions	H315 - Causes skin irritation (unverified) [Skin corrosion/irritation - Category 2]	
Eye Irritation/Corrosivity	H	LT-UNK	GHS - New Zealand	Eye irritation category 2	+2
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H318 - Causes serious eye damage (unverified) [Serious eye damage/eye irritation - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	
Acute Aquatic Toxicity	pC	NoGS	DK-EPA - Danish Advisory List	Aquatic Acute1 - Very toxic to aquatic life (modeled)	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	vH	LT-P1	GHS - New Zealand	Hazardous to the aquatic environment - chronic category 2	+2
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H412 - Harmful to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 3]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H413 - May cause long lasting harmful effects to aquatic life (unverified) [Hazardous to the aquatic environment (chronic) - Category 4]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-UNK	German FEA - Substances Hazardous to Waters	Class 1 - Low Hazard to Waters	+1
	pC	NoGS	ChemSec - SIN List	Equivalent Concern	

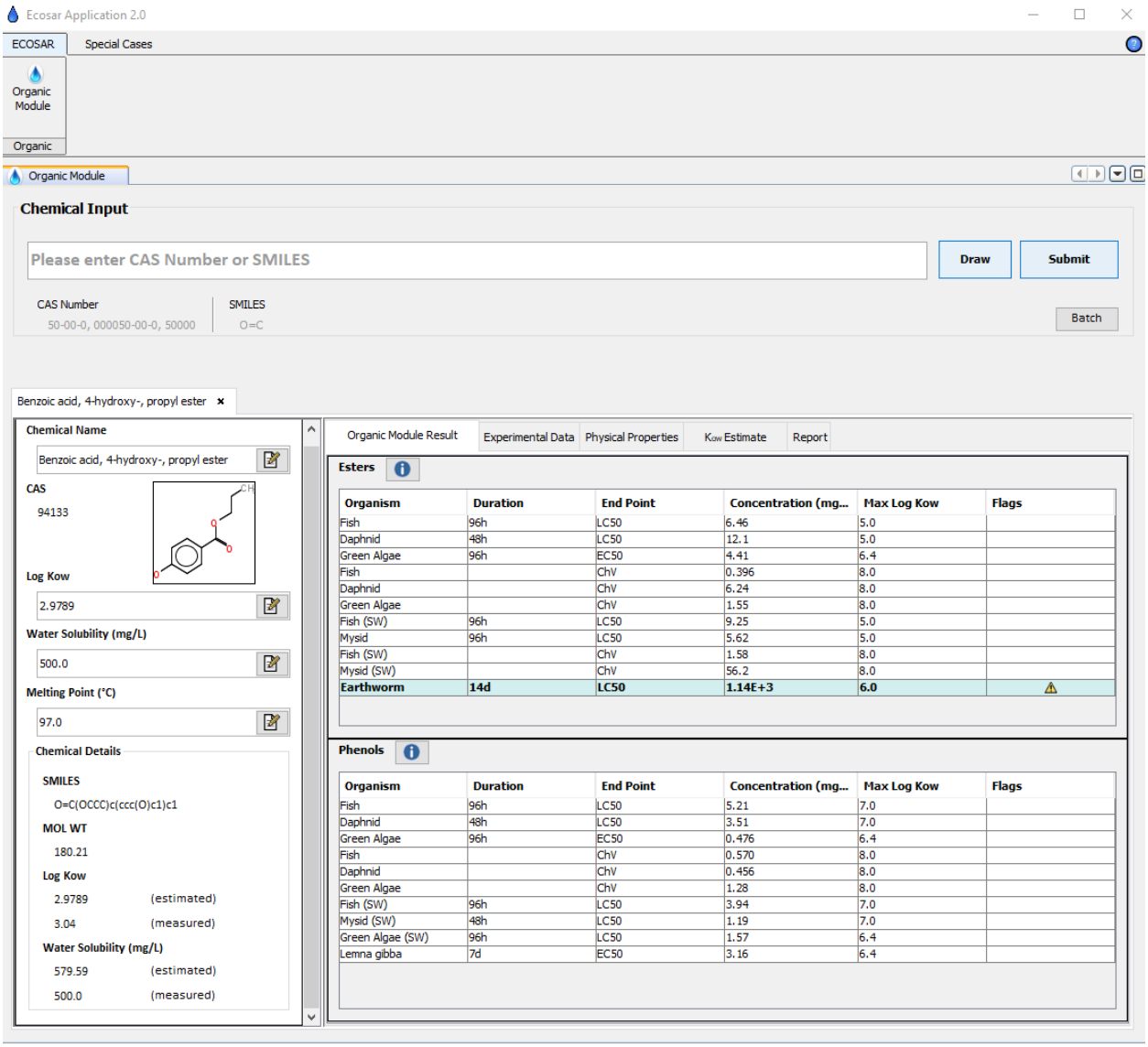
Restricted Substance Lists (17)

- CA SCP - Candidate Chemicals: Candidate Chemical List
- Campaign for Safe Cosmetics' Red List of Chemicals of Concern: Chemicals of Concern
- Credo Beauty's Restricted Substance List: Prohibited Chemicals
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Food Contact Chemicals Database (FCCdb): Food Contact Chemicals Database Version 5.0
- GreenScreen Certified Standard for Food Service Ware RSL: Ortho-Phthalates
- GreenScreen Certified Standard for Food Service Ware RSL: Parabens
- GSPI - Six Classes of Problematic Chemicals: Antimicrobials
- HEL LIST - Chemicals Prohibited by the Protect Land + Sea Certification: Prohibited Chemicals
- MDH - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern
- ME DEP - Chemicals of High Concern and Priority Chemicals: Chemicals of High Concern
- SCHF - Hazardous 100: Chemicals of high concern
- Sephora - High Priority Chemicals: High priority chemicals
- Target Corp - Target Priority Chemicals List (TPCL): Target Priority Chemicals List (TPCL)
- TSCA Chemical Substance Inventory (Active-Inactive): TSCA Chemical Substance Inventory - Active
- Vermont Chemicals of High Concern to Children: Chemicals of High Concern to Children
- WA DoE - Chemicals of High Concern to Children: Chemicals of High Concern to Children

APPENDIX D: OECD Toolbox Profiling Results for Propylparaben (CAS #94-13-3)



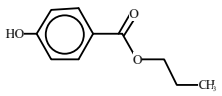
APPENDIX E: ECOSAR Modeling Results for Propylparaben (CAS #94-13-3)



APPENDIX F: EPI Suite™ Modeling Results for Propylparaben (CAS #94-13-3)

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

EPI Suite Results For CAS 94-13-3



```
SMILES : O=C(OCCC)c(ccc(O)c1)c1
CHEM   : Benzoic acid, 4-hydroxy-, propyl ester
MOL FOR: C10 H12 O3
MOL WT : 180.21
----------------------------- EPI SUMMARY (v4.11) -------------------------
Physical Property Inputs:
Log Kow (octanol-water):   2.70
Boiling Point (deg C)  :   301.00
Melting Point (deg C)  :   97.00
Vapor Pressure (mm Hg) :   ------
Water Solubility (mg/L):   ------
Henry LC (atm-m3/mole) :   ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) =  2.98
Log Kow (Exper. database match) =  3.04
Exper. Ref:  HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C):  285.14  (Adapted Stein & Brown method)
Melting Pt (deg C):  71.81  (Mean or Weighted MP)
VP(mm Hg,25 deg C):  0.000124  (Modified Grain method)
VP (Pa, 25 deg C) :  0.0165  (Modified Grain method)
MP  (exp database):  97 deg C
Subcooled liquid VP: 0.000618 mm Hg (25 deg C, Mod-Grain method)
: 0.0823 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L):  1229
log Kow used: 2.70 (user entered)
melt pt used: 97.00 deg C
Water Sol (Exper. database match) =  500 mg/L (25 deg C)
Exper. Ref:  YALKOWSKY,SH & HE,Y (2003)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) =  424.53 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Esters
Phenols
```

```
Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method :   6.37E-009  atm-m3/mole  (6.45E-004 Pa-m3/mole)
Group Method:   4.25E-009  atm-m3/mole  (4.31E-004 Pa-m3/mole)
For Henry LC Comparison Purposes:
User-Entered Henry LC:  not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC:  2.392E-008 atm-m3/mole  (2.424E-003 Pa-m3/mole)
VP:   0.000124 mm Hg (source: MPBPVP)
WS:   1.23E+003 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used:  2.70  (user entered)
Log Kaw used:  -6.584  (HenryWin est)
Log Koa (KOAWIN v1.10 estimate):  9.284
Log Koa (experimental database):  None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model)         :   0.9517
Biowin2 (Non-Linear Model)     :   0.9957
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model):   2.9975  (weeks       )
Biowin4 (Primary Survey Model) :   3.8564  (days        )
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model)    :   0.6329
Biowin6 (MITI Non-Linear Model):   0.7758
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model):  0.6793
Ready Biodegradability Prediction:   YES

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled):  0.0824 Pa (0.000618 mm Hg)
Log Koa (Koawin est  ): 9.284
Kp (particle/gas partition coef. (m3/ug)):
Mackay model           :  3.64E-005
Octanol/air (Koa) model:  0.000472
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model     :  0.00131
Mackay model           :  0.0029
Octanol/air (Koa) model:  0.0364

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant =  14.0678 E-12 cm3/molecule-sec
Half-Life =     0.760 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life =     9.124 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):
0.00211 (Junge-Pankow, Mackay avg)
0.0364 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
```

```
Koc    :  286.6  L/kg (MCI method)
Log Koc:  2.457       (MCI method)
Koc    :  331  L/kg (Kow method)
Log Koc:  2.520       (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C :  5.102E-003  L/mol-sec
Kb Half-Life at pH 8:       4.305  years
Kb Half-Life at pH 7:      43.052  years
(Total Kb applies only to esters, carbmates, alkyl halides)
```

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.448 (BCF = 28.08 L/kg wet-wt)

```
Log Biotransformation Half-life (HL) = -1.4714 days (HL = 0.03378 days)
```

Log BCF Arnot-Gobas method (upper trophic) = 1.031 (BCF = 10.73)

```
Log BAF Arnot-Gobas method (upper trophic) = 1.031 (BAF = 10.73)
log Kow used: 2.70 (user entered)

Volatilization from Water:
Henry LC:  4.25E-009 atm-m3/mole  (estimated by Group SAR Method)
Half-Life from Model River: 1.849E+005  hours   (7706 days)
Half-Life from Model Lake : 2.018E+006  hours   (8.407E+004 days)

Removal In Wastewater Treatment:
Total removal:               3.81  percent
Total biodegradation:        0.11  percent
Total sludge adsorption:     3.70  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	**0.0714**	**18.2**	**1000**
Water	**17.7**	**360**	**1000**
Soil	**82**	**720**	**1000**
Sediment	**0.222**	**3.24e+003**	**0**

```
Persistence Time: 746 hr

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

Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.0714	18.2	1000
Water	17.7	360	1000
water	(17.6)		
biota	(0.000442)		
suspended sediment	(0.00759)		
Soil	82	720	1000
Sediment	0.222	3.24e+003	0

```
Persistence Time: 746 hr

Level III Fugacity Model: (EQC Default)
```

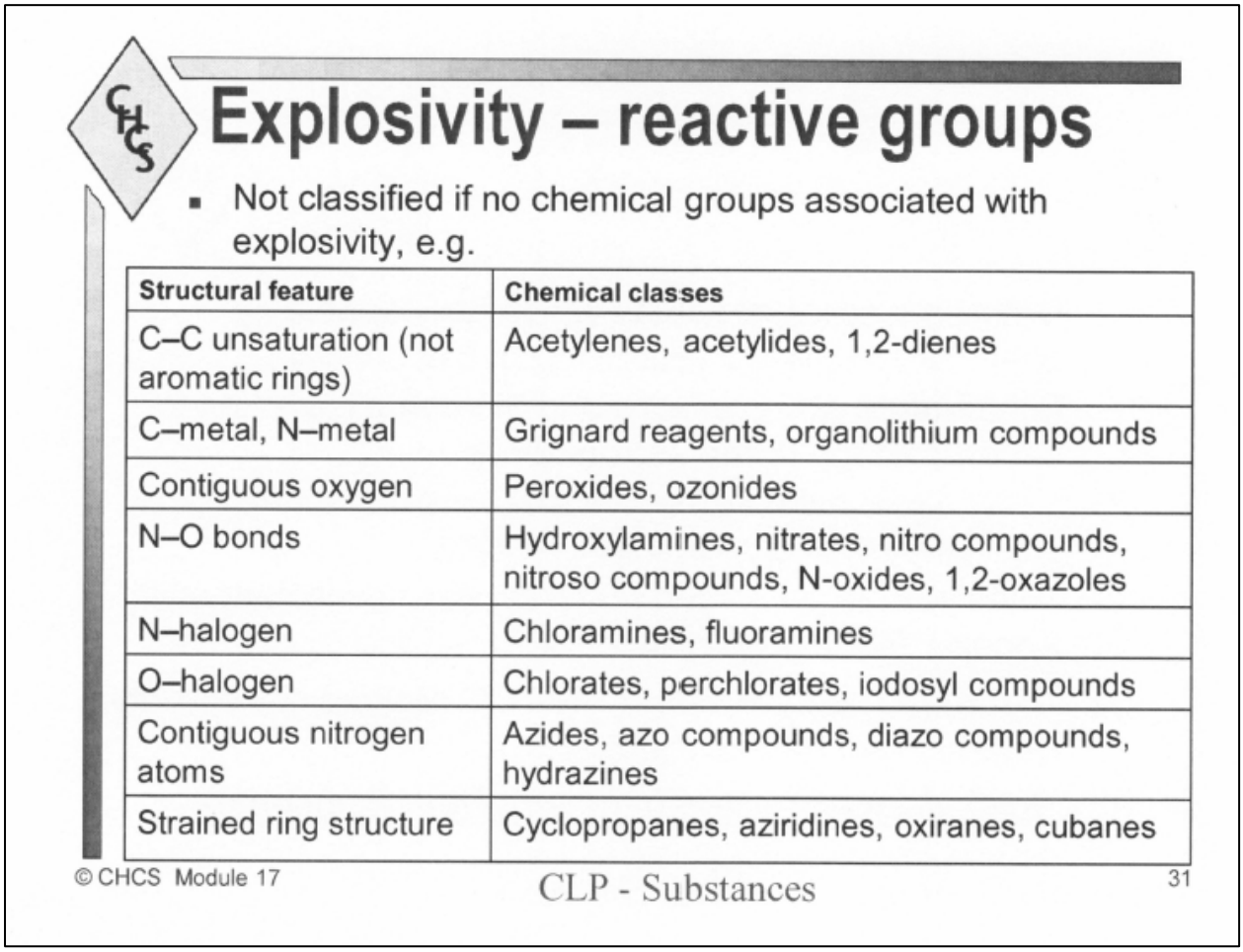
Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)	
Air	0.072	18.2	1000
Water	18.1	360	1000
water	(18.1)		

```
biota      (0.000455)
suspended sediment (0.00559)
Soil       81.6            720          1000
Sediment   0.177           3.24e+003    0
Persistence Time: 740 hr
```

....

APPENDIX G: 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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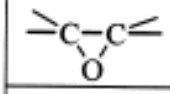
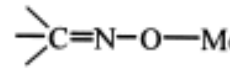
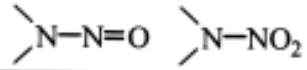
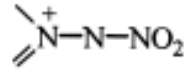
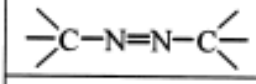
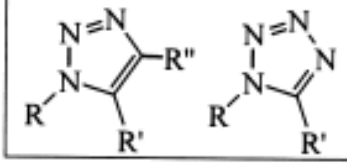
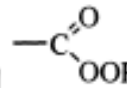
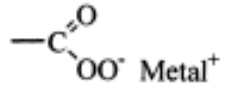
Explosivity – Full List

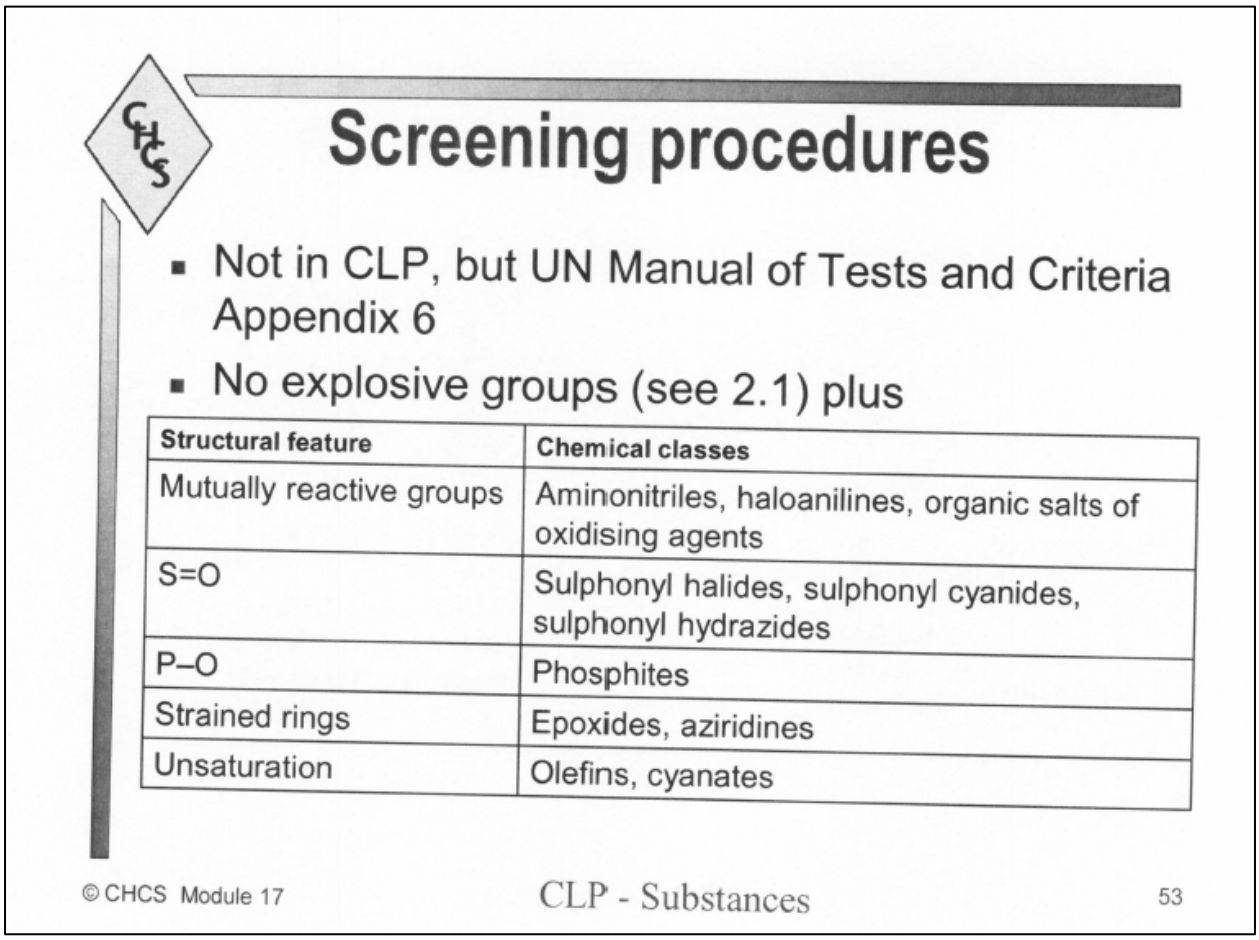
Table R.7.1-28 Chemical groups associated with explosive properties

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 H: Change in Benchmark Score

Table 5 provides a summary of changes to the GreenScreen® Benchmark™ for propylparaben. Although some of the hazard ratings for individual endpoints have changed over time, and all previous data gaps have been filled, the GreenScreen® Benchmark Score for propylparaben has not changed. The original GreenScreen® assessment was performed in 2015 under version 1.2 criteria and ToxServices assigned a Benchmark 2 (BM-2) score. The BM-2 score has been maintained with the version 1.3 update in 2016, and with the current version 1.4 update.

Table 5: Change in GreenScreen® Benchmark™ for Propylparaben

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
May 1, 2015	BM-2	v. 1.2	Original assessment
September 12, 2016	BM-2	v. 1.3	BM score unchanged. The hazard rating for system toxicity – single exposure (STs) changed from **Low** (high confidence) to *Moderat*e (low confidence). The hazard rating for skin sensitization (SnS) changed from *Moderate* (low confidence) to **Low** (high confidence).
March 30, 2023	BM-2	v. 1.4	BM score unchanged. Data gaps for neurotoxicity – single exposure (Ns) and respiratory sensitization (SnR) were filled. The hazard rating for skin irritation (IrS) changed from *Moderate* (low confidence) to *Low* (low confidence).
June 21, 2023	BM-2	v. 1.4	Minor changes to chronic aquatic toxicity are incorporated based on Washington Ecology's feedback. These changes do not affect the final Benchmark score.

Licensed GreenScreen® Profilers

Propylparaben GreenScreen® Evaluation Prepared by:

SIGNATURE BLOCK

Sara M. Ciotti, Ph.D.
Toxicologist
ToxServices LLC

Propylparaben GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC

Propylparaben GreenScreen® Evaluation Updated by:

SIGNATURE BLOCK

Mouna Zachary, Ph.D.
Toxicologist
ToxServices LLC

Propylparaben GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC

Propylparaben GreenScreen® Evaluation Updated by:

SIGNATURE BLOCK

Nancy Linde, M.S.
Senior Toxicologist
ToxServices LLC

Propylparaben GreenScreen® Evaluation QC'd by:

SIGNATURE BLOCK

Bingxuan Wang, Ph.D., D.A.B.T.
Senior Toxicologist
ToxServices LLC