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

Prepared for:

Environmental Defense Fund

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

Propylparaben is a chemical that functions as a preservative in food and cosmetics.

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

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

A data gap (DG) exists for respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), propylparaben meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gap. In a worst-case scenario, if propylparaben were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 2 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings 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
						single	repeated*	single	repeated*										
L	**L**	**L**	*L*	*M*	**L**	**L**	**L**	DG	**L**	**M**	DG	*M*	**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 estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard (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. Please see Appendix A for a glossary of hazard acronyms.

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

Method Version: GreenScreen® Version 1.2[1]
Assessment Type[2]: Certified

Chemical Name: Propylparaben

CAS Number: 94-13-3

GreenScreen® Assessment Prepared By:
Name: Sara M. Ciotti, Ph.D.
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Organization: ToxServices LLC
Date: April 24, 2015
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
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Organization: ToxServices LLC
Date: May 1 and Dec 4, 2015, Jan 29, 2016
Assessor Type: Licensed GreenScreen® Profiler

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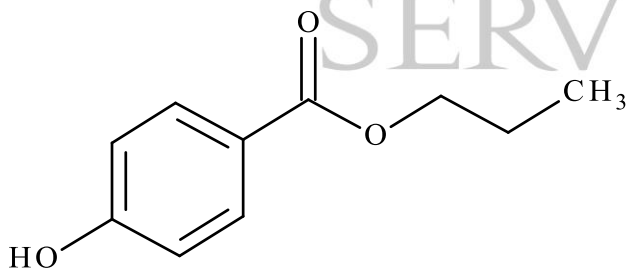
Title: Toxicologist
Organization: ToxServices LLC
Update Date: December 3, 2015
Assessor Type: Licensed GreenScreen® Profiler

Confirm application of the *de minimus* rule[3]: N/A (this assessment was conducted for the theoretically pure substance), No information was identified regarding the known impurities in propylparaben

Chemical Structure(s):



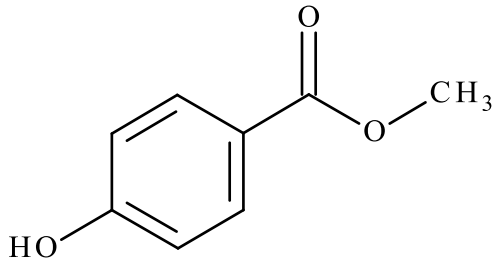
Also called: 4-Hydroxybenzoic acid, propyl ester; Benzoic acid, 4-hydroxy-, propyl ester; Propyl p-hydroxybenzoate; Propyl parahydroxybenzoate; Propylparaben; Propylparaben [USAN:NF]; 4-10-00-00374 (Beilstein Handbook Reference); 4-Hydroxybenzoic acid propyl ester; AI3-01341; Aseptoform P; Bayer D 206; Benzoic acid, p-hydroxy-, propyl ester; Betacide P; Betacine P; Bonomold OP; BRN 1103245; Caswell No. 714; Chemacide pk; Chemocide pk; EC 202-307-7; EINECS 202-307-7; EPA Pesticide Chemical Code 061203; FEMA No. 2951; FEMA Number 2951;

[1] Use GreenScreen® Assessment Procedure (Guidance) V1.2
[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)
[3] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

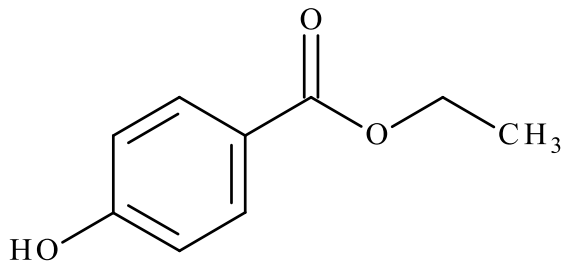
HSDB 203; n-Propyl p-hydroxybenzoate; N-Propyl p-hydroxybenzoate; Nipagin P; Nipasol; Nipasol M; Nipasol P; Nipazol; NSC 23515; p-Hydroxybenzoic acid propyl ester; p-Hydroxybenzoic propyl ester; p-Hydroxypropyl benzoate; p-Oxybenzoesaurepropylester; Paraben; Parasept; Paseptol; Preserval P; Propagin; Propyl 4-hydroxybenzoate; Propyl aseptoform; Propyl butex; Propyl chemosept; Propyl p-hydroxybenzoate; Propyl parahydroxybenzoate; Propyl Parasept; Propylester kyseliny p-hydroxybenzoove; Propylparasept; Protaben P; Pulvis conservans (VAN); Solbrol P; Tegosept P; UNII-Z8IX2SC1OH (ChemIDplus 2015)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
In the absence of available data for the chemical of interest, ToxServices searched for a suitable analog or class of analogs using guidance in the U.S. EPA's procedure for identifying analogs (U.S. EPA 2010), ECHA's read across assessment framework (ECHA 2015a) and OECD's guidance on grouping of chemicals (OECD 2014a). Resources used for the surrogate search included the ChemIDplus structural similarity search, OECD Toolbox, U.S. EPA's Analog Identification Methodology (AIM), and U.S. EPA's Chemical Assessment Clustering Engine (ChemACE). Surrogates were considered to be appropriate if they resemble the target in terms of molecular structure and size, contain a substructure of functional group that may play a critical toxicological role, share similar physicochemical properties (e.g. water solubility, partition coefficient), or have common or similar precursors, metabolites, or breakdown products. Where surrogates are used to fill data gaps or as supporting evidence, the use of a surrogate is clearly indicated for that endpoint.

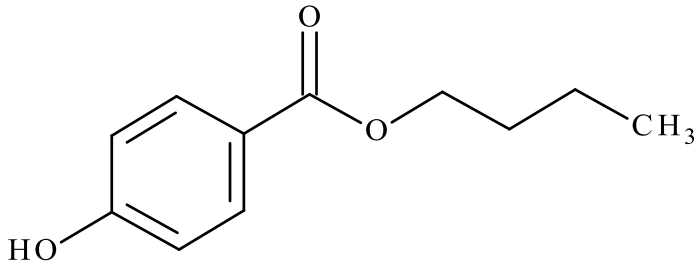
Propylparaben has a relatively complete dataset; however, a data gap existed for carcinogenicity and supporting data are needed for genotoxicity and chronic aquatic toxicity. Therefore, methylparaben (CAS# 99-76-3), ethylparaben (CAS# 120-47-8), butylparaben (CAS# 94-26-8), and isobutylparaben (CAS# 4247-02-3) were used as surrogates to fill a data gap or data from these compounds were used for supporting evidence. The available data indicate that the biological effects of parabens are related to the alkyl chain length (CIR 2008). For example, the SCCS (2013) has concluded that the use of methylparaben and ethylparaben as preservatives in cosmetics at the maximum authorized concentrations (0.4% for one ester or 0.8% when used in combination) is safe for human health. However, they express concern over the potential endocrine modifying effects of parabens with longer alkyl side chains, such as propylparaben, butylparaben, and isobutylparaben (SCCS 2013). As the endocrine activity of parabens appear to be related to the length of the alkyl chain length with an increased chain length producing greater toxicity, scores based entirely on surrogate data are reported with reduced confidence. Data for methylparaben were used as supporting evidence for various endpoints because it has the most complete dataset. Additionally, data from experiments using a mixed paraben solution were used as supporting evidence for various endpoints.



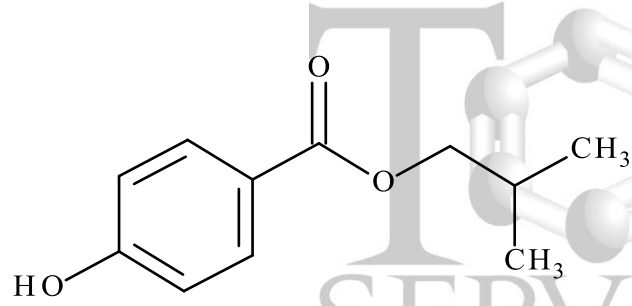
Methylparaben (CAS# 99-76-3)



Ethylparaben (CAS# 120-47-8)



Butylparaben (CAS# 94-26-8)



Isobutylparaben (CAS# 4247-02-3)

Identify Applications/Functional Uses: (SCCS 2013)
1. Preservative in food at a maximum concentration of 0.1% (21 CFR § 184.1670).
2. Preservative in cosmetics at a maximum concentration of 0.4% when used individually or 0.8% when used as a mixture of esters.

GreenScreen® Summary Rating for Propylparaben[4]: Propylparaben was assigned a **GreenScreen Benchmark Score™ of 2** ("Use but Search for Safer Substitutes") (CPA 2014). This score is based on the following hazard score:

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

A data gap (DG) exists for respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), propylparaben meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gap. In a worst-case

[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.

scenario, if propylparaben were assigned a High score for the data gap SnR*, it would still be categorized as a Benchmark 2 Chemical.

Figure 1: GreenScreen® Hazard Ratings 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
						single	repeated*	single	repeated*										
L	L	L	*L*	*M*	L	L	L	DG	L	M	DG	*M*	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 estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. 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. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[5]

Propylparaben is not expected to readily hydrolyze in the environment based on estimated hydrolysis half-lives of 4.3 and 43 years at pH levels of 8 and 7, respectively (HSDB 2007). OECD Toolbox (2014b) predicted that propylparaben will hydrolyze under acidic and basic conditions to form 4-hydroxybenzoic acid and n-propanol. Seawater is slightly basic with a pH of approximately 8.2 (7.5 – 8.5), while freshwater pH ranges from 6 to 8 (Christine 2013). Therefore, hydrolysis products may slowly form under environmental conditions. However, these products were not considered to relevant environmental transformation products, as biodegradation data detailed in the persistence section indicate that propylparaben is readily biodegradable and thus degradation products are considered to be transient. This means biodegradation will be the predominant environmental transformation pathway for propylparaben, and no relevant degradation products will be formed before it's rapidly and completely mineralized.

Table 1: Transformation Product Summary Table

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	Feasible and Relevant?	GreenScreen® List Translator Score or Benchmark Score[6,7]
Preservative	In use and disposal	Hydrolysis (acid and basic conditions)	4-Hydroxybenzoic acid	99-96-7	N	LT-P1
Preservative	In use and disposal	Hydrolysis (acid and basic conditions)	n-Propanol	71-23-8	N	LT-U

[5] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

[6] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2015) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.

[7] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

Introduction

Propylparaben is produced by the *n*-propanol esterification of *p*-hydroxybenzoic acid in the presence of sulfuric acid, with subsequent distillation. Propylparaben is an antimicrobial agent; its primary areas of application are foods and cosmetics (HSDB 2007). It is Generally Recognized as Safe (GRAS) as a direct food additive in the United States, and it is acceptable for use at a maximum level of 0.1% (21 CFR § 184.1670). It is permitted as an antimycotic in food-packaging materials with no limits or restrictions (21 CFR § 181.23). Propylparaben is not to exceed 0.1% when used as a preservative in fruit jelly (21 CFR § 150.141) and fruit preservatives and jams (21 CFR § 150.161). 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 stated an ADI of 0 to 10 mg/kg-day for the sum of methylparaben and ethylparaben (EFSA 2004). In their opinion EFSA stated propylparaben should not be included in the ADI due to the potential for endocrine effects (EFSA 2004).

In cosmetics marketed in the United States, the Cosmetics Ingredient Reviewed concluded that propylparaben was safe for use in cosmetics, and based their assessment of safety on use levels of up to 0.4% if used alone, and when present in a mixture of parabens at use levels up to 0.8% (CIR 2014). In cosmetics marketed in the European Union, propylparaben is listed in Annex V, Section 12 bis of EC Regulation No. 1223/2009 as a preservative that is acceptable for use in cosmetics, provided the sum of the individual concentrations of propylparaben and butylparaben does not exceed 0.14% (as acid) and the sum of all parabens does not exceed 0.8% (as acid) (EU 2009, 2014).

ToxServices assessed propylparaben against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

Preservative Spectrum of Effect:

As summarized below, propylparaben displays moderate to good preservative efficacy against microorganisms, with particular efficacy shown to control the growth of gram-positive bacteria, yeasts, and mold.

Propylparaben's Preservative Spectrum of Effect		
Microorganism	**Spectrum of Effect**	**Reference**
Gram-positive bacteria	Good	Siegert 2014
Gram-negative bacteria	Moderate	Siegert 2014
Yeasts/Molds	Good	Siegert 2014
Head-space protection	No	Siegert 2014

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 2012a). Pharos (Pharos 2015) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The Pharos output for propylparaben can be found in Appendix C, and a summary of the results can be found below.

Endocrine

EC – Priority Endocrine Disrupters – Category 1 – *In vivo* evidence of endocrine disruption activity

TEDX – Potential Endocrine Disruptors – Potential Endocrine Disruptor

SIN/ChemSec – Substitute List – Endocrine Disruption

Eye Irritation

New Zealand HSNO/GHS – 6.4A – Irritating to the eye

Skin Irritation

New Zealand HSNO/GHS – 6.5N (contact) – Contact sensitizers

Acute Aquatic

New Zealand HSNO/GHS – 9.1D (algal) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action

New Zealand HSNO/GHS – 9.1D (crustacean) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action

New Zealand HSNO/GHS – 9.1D (fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action

Restricted List

German FEA – Substances Hazardous to Waters (VwVwS) – Class 1 Low Hazard to Waters

When a classification from GHS New Zealand was available for any endpoint, it was converted to the harmonized GHS classifications using the "Correlation between GHS and New Zealand HSNO Hazard Classes and Categories" document from the New Zealand Environmental Protection Agency (EPA 2009):

Physicochemical Properties of Propylparaben

Propylparaben is a white crystalline solid at room temperature. Its vapor pressure (5.55×10^{-4} mm Hg) indicates that it can form a vapor at room temperature. It is moderately soluble in water and its partition coefficient (log K_{ow} = 3.04) indicates that it has a low potential for bioaccumulation.

Table 2: Physical and Chemical Properties of Propylparaben (CAS #94-13-3)

Property	Value	Reference
Molecular formula	C10-H12-O3	ChemIDplus 2015
SMILES Notation	c1c(O)ccc(C(OCCC)=O)c1	ChemIDplus 2015
Molecular weight	180.202	ChemIDplus 2015
Physical state	Solid	ECHA 2015b
Appearance	White crystalline solid	ECHA 2015b
Melting point	97ºC	ChemIDplus 2015
Vapor pressure	5.55×10^{-4} mm Hg at 25ºC	ChemIDplus 2015
Water solubility	500 mg/L at 25ºC	ChemIDplus 2015
Dissociation constant	8.87 7.9	ECHA 2015b HSDB 2007
Density/specific gravity	1.287 g/cm^3 at 20ºC	ECHA 2015b
Partition coefficient	Log K_{ow} = 3.04	ChemIDplus 2015

Hazard Classification Summary Section[8]:

[8] When original study reports were not available, ToxServices summarized study methodology, results, and study author conclusions as reported in secondary sources. In cases where conclusions were not reported or where ToxServices interpreted the results differently based on the information presented in the study summary, ToxServices' conclusions are clearly stated.

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 negative findings in carcinogenicity studies using propylparaben (non-standard exposure routes), butylparaben, and isobutylparaben. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and negative, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b). Confidence in the score is reduced because it is primarily based on surrogate data.

Propylparaben (CAS# 123-07-9)

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- CIR 2008
  - The carcinogenicity of propylparaben was investigated in a 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, including purity of the test compound, 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, including purity of the test compound, were provided.
- ECHA 2015b
  - *Oral:* In a 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[9]) (highest dose tested).
  - *Oral:* In a 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-

[9] 1,000 mg/kg/day * 6 days/7 days = 857 mg/kg/day

5.9 g/kg/day[10]) in their diet for 96 weeks. 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. 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).

- SCCP 2005a; CIR 2008
  - 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 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.
- OECD 2014b
  - Propylparaben contains no structural alerts for genotoxic or non-genotoxic carcinogenicity. See Appendix D for modeling results.
- Toxtree 2014
  - Propylparaben contains no structural alerts for genotoxic or non-genotoxic carcinogenicity. See Appendix E for modeling results.

Surrogate: Butylparaben (CAS# 94-26-8) and Isobutylparaben (CAS# 4247-02-3)

- CIR 2008
  - Male and female 8-week old ICR/Jcl mice (50/sex/group) were administered 0.15%, 0.3% or 0.6% butylparaben or isobutylparaben in their feed for 102 weeks. Animals surviving until the end of the study were sacrificed and necropsied. Data were compiled for animals surviving ≥ 78 weeks. Treatment did not significantly alter the incidence of tumors or the time to tumor development between treated mice and controls, or between different dose groups. Authors concluded that butylparaben and isobutylparaben were not carcinogenic under the conditions of this assay (Inai et al. 1985).
- Based on the weight of evidence, a score of Low was assigned. Limited carcinogenicity data were available for propylparaben, and included studies involving prenatal exposures and chronic oral studies in dogs and rats. Though limited by non-standard exposure routes and small sample sizes, these studies demonstrated no evidence of carcinogenicity. A lack of structural alerts and negative data in a chronic study for the surrogates butylparaben and isobutylparaben, which are likely conservative surrogates that are not likely to underestimate the toxicity of propylparaben, further indicate a lack of carcinogenic activity. The weight of evidence from the target compound and conservative surrogates collectively supports a high confidence score of score of Low, but confidence is reduced due to the potential for the chain length to influence toxicity.

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

Propylparaben was assigned a score of Low for mutagenicity/genotoxicity based on negative genotoxicity assays using propylparaben and methylparaben. GreenScreen® criteria classify

[10] Values reported in the ECHA REACH Dossier

chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and negative for both chromosomal aberrations and gene mutations, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b). Confidence in the score is high because it is based on several well conducted studies.

Propylparaben (CAS# 94-13-3)

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - *In vitro:* Negative results for mutagenicity were obtained in a GLP-compliant mammalian cell gene mutation test conducted according to OECD Guideline 476. Chinese hamster lung fibroblasts (V79) cells were exposed to propylparaben (purity not reported) in dimethyl sulphoxide (DMSO) at concentrations up to 448 μg/mL with metabolic activation and 224 μg/mL without metabolic activation. The first experiment involved a 4-hour treatment period, whereas the second experiment involved a 24-hour treatment period. No increase in the mutation frequency was observed in the presence or absence of metabolic activation.
  - *In vitro:* Negative results for mutagenicity were obtained in an Ames assay conducted according to guidelines similar to OECD 471. *S. typhimurium* tester strains TA1535, TA1537, and TA1538 were exposed to propylparaben (purity not reported) in DMSO at 0.075%, with and without metabolic activation. No increase in the mutation frequency was observed in the presence or absence of metabolic activation.
- OECD 2014b
  - *In silico:* Propylparaben possesses no structural alerts for bacterial mutagenicity (Ames assay); however, it contains a structural alert for the *in vivo* mouse micronucleus assay (H-acceptor – path3-H –acceptor). See Appendix D for modeling results.
- Toxtree 2014
  - *In silico:* Propylparaben possesses no structural alerts for bacterial mutagenicity (Ames assay) and no alerts for the *in vivo* mouse micronucleus assay. See Appendix F for modeling results.

Surrogate: Methylparaben (CAS# 99-76-3)

- ECHA 2015c
  - *In vivo:* In a dominant lethal assay conducted according to OECD Guideline 478, male Sprague-Dawley rats (10/group) were administered 0, 50, 500, or 5,000 mg/kg methylparaben (purity not reported) in 0.85% saline via oral gavage. In the acute study, animals received a single dose and in the subacute study animals were treated once per day on 5 consecutive days. Following treatment males were sequentially mated with 2 females per week for 8 (acute study) or 7 (subacute study) weeks. Females were sacrificed 14 days after separating from the treated male. At necropsy the uterus was examined for corpora lutea, early fetal deaths, late fetal deaths, and total implantations. No treatment-related effects were found. Authors concluded methylparaben was not mutagenic under the conditions of this assay.
  - *In vivo:* In a mammalian bone marrow chromosome aberration test conducted according to guidelines similar to OECD 475, male Sprague-Dawley rats were administered 0, 5, 50, or 500 mg/kg methylparaben (purity not reported) in 0.85% saline via oral gavage. Animals (10/dose) received a single oral dose (acute study) or were treated once per day on 5 consecutive days. Animals were sacrificed 6, 24, or 48 hours after administration. Methylparaben treatment did not alter the incidence of bone marrow cells with

chromosomal aberrations. Authors concluded that methylparaben was not clastogenic under the conditions of this assay.

- OECD 2014b
  - *In silico:* Methylparaben possesses no structural alerts for bacterial mutagenicity (Ames assay); however, it contains a structural alert for the *in vivo* mouse micronucleus assay (H-acceptor – path3-H –acceptor). See Appendix G for modeling results.
- Toxtree 2014
  - *In silico:* Methylparaben possess no structural alerts for bacterial mutagenicity (Ames assay) and no alerts for the *in vivo* mouse micronucleus assay. See Appendix H for modeling results.
- Based on the weight of evidence, a score of Low was assigned. Limited genotoxicity data were available for propylparaben. Negative findings from *in vitro* mutagenicity assays in mammalian and bacterial cells indicate that propylparaben is not mutagenic. Because no *in vitro* or *in vivo* chromosomal aberration assays were identified for propylparaben, ToxServices relied on surrogate data to evaluate the potential for clastogenicity. Supporting evidence from the surrogate methylparaben indicate that propylparaben is not clastogenic based on negative findings in an *in vivo* dominant lethal assay and an *in vivo* bone marrow chromosome aberration assay. Modeling produced mixed results for propylparaben and methylparaben, as OECD Toolbox (2014) identified the same structural alert for the *in vivo* mouse micronucleus assay for both chemicals, but Toxtree (2014) did not. Although modeling using OECD Toolbox identified the structural alert for the *in vivo* mouse micronucleus assay in both propylparaben and methylparaben, surrogate data are weighed more heavily than modeled data, and the negative findings in an *in vivo* chromosome aberration assay using methylparaben indicate that parabens are not clastogenic. Because the longer chain length for propylparaben compared to methylparaben is not likely to influence potential genotoxicity, the score is reported with high confidence.

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

Propylparaben was assigned a score of Low for reproductive toxicity based on the absence of adverse reproductive effects in well conducted, GLP-compliant reproductive toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate data are available and indicate that the chemical does not warrant GHS classification for reproductive toxicity and the chemical has no structural alerts (CPA 2012b). Confidence in the score is high because it is based on experimental data from well conducted studies.

Propylparaben (CAS# 94-13-3)

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - In a GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Wistar rats (11/sex/dose) were exposed to 0, 1,500, 4,500, or 15,000 ppm propylparaben (purity not reported) 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). 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, gross pathology and histopathology. Hematology and blood serum chemistry were only evaluated in parental animals. No treatment-related changes in clinical signs were reported in parental animals. High-dose parental males had slightly reduced body weight gain which occasionally reached statistical significance. No body weight changes were found in females. 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 a reproductive toxicity NOAEL of 15,000 ppm (corresponding to 1,124.6 mg/kg/day) (highest dose tested).

- WHO 2007
    - 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; there was no dose-response relationship (Oishi 2002, as cited in WHO 2007). ToxServices identified a LOAEL of 10 mg/kg/day (lowest dose tested) based on decreased daily sperm production and efficiency in the testes.
- Gazin et al. 2013
    - In a GLP-compliant reproductive toxicity study conducted by Gazin et al. 2013, male Wistar rats (20/dose) received 0, 3, 10, 100, or 1,000 mg/kg/day propylparaben (purity = 100%) via oral 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 weighted 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. 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), 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 and at doses of 100 mg/kg/day and above.

Surrogate: Methylparaben (CAS# 99-76-3)

- ECHA 2015c
    - In a prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female CD-1 mice (≥ 21/dose) received 0, 5.5, 25.5, 118, or 550 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 15. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 6, 11, 15, and 17. On day 17 all dams were subjected to a cesarean section and the numbers of corpora lutea, implantation sites, and resorption sites were recorded. Treatment did not alter maternal body weight and no adverse clinical signs were reported. Treatment had no effect on reproductive parameters (i.e., number of corpora lutea, implantation sites, and resorption sites). The study authors identified a maternal NOAEL of 550 mg/kg/day (highest dose tested).
    - In a prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female Wistar rats (≥ 23/dose) received 0, 5.5, 25.5, 118, or 550 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 15. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 6, 11, 15, and 20. On day 20 all dams were subjected to a cesarean section and the numbers of corpora lutea, implantation sites, and resorption sites were recorded. Treatment did not alter maternal body weight and no adverse clinical signs were reported. Treatment had no effect on reproductive parameters (i.e., number of corpora lutea, implantation sites, and resorption sites). The study authors identified a developmental NOAEL of 550 mg/kg/day (highest dose tested).
    - In a prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female CD-1 mice (≥ 21/dose) received 0, 3, 14, 65, or 300 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 10. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 8, 10, and 14. On day 14 all dams were subjected to a cesarean section and the numbers of corpora lutea, implantation sites, and resorption sites were recorded. Treatment did not alter maternal body weight and no adverse clinical signs were reported. Treatment had no effect on reproductive parameters (i.e., number of corpora lutea, implantation sites, and resorption sites). The study authors identified a developmental NOAEL of 300 mg/kg/day (highest dose tested).
- Based on the weight of evidence, a score of Low was assigned. A reproductive toxicity study conducted by Oishi et al. (2002) found effects on sperm parameters in juvenile Wistar rats treated with doses ≥ 10 mg/kg/day (lowest dose tested). However in a similar study, Gazin et al. found no adverse reproductive effects in male rats treated with doses up to 1,000 mg/kg/day for 8 weeks

(GLP-compliant study). In 2013 the SCCS evaluated both studies and concluded that the study by Gazin et al. (2013) was well conducted and provided sufficient information to refute the findings of Oishi et al. (2002). Additionally, no adverse reproductive effects were found in an OECD Guideline combined repeated dose toxicity study with a reproductive and developmental toxicity screening test using propylparaben. Surrogate data were also included as supporting information; treatment with methylparaben during gestation had no adverse effects on relevant reproductive parameters. Therefore, based on the weight of evidence indicating a lack of effects on reproductive parameters, a score of Low was assigned.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Propylparaben was assigned a score of Low for developmental toxicity based on the absence of adverse developmental effects in studies using propylparaben and methylparaben. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate negative data are available, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b). Confidence in the score is high because it is based on negative results for propylparaben with support from consistently negative results for the surrogate. Confidence in the score is reduced due to reliance on a screening study and surrogate data.

<u>Propylparaben (CAS# 94-13-3)</u>

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any screening lists
- ECHA 2015b
    - In a previously described GLP-compliant combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted according to OECD Guideline 422 (purity not reported), 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). 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, 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) (highest dose tested).

<u>Surrogate: Methylparaben (CAS# 99-76-3)</u>

- ECHA 2015c
    - In a previously described prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, Dutch-belted rabbits (≥9/group) were administered 3, 14, 65, or 300 mg/kg/day methylparaben (purity not reported) via oral gavage on gestation days 6 through 18. On gestation day 29, animals were subject to a cesarean section and reproductive parameters (described in the reproductive toxicity section) and

dead fetuses were evaluated. Pup body weight was recorded. Pups were evaluated for external abnormalities, visceral abnormalities, and skeletal defects. Treatment had no effect on the sex ratio or fetal body weight. The study authors found no abnormalities or skeletal defects. The study authors identified a developmental NOAEL of 300 mg/kg/day (highest dose tested).

- In a previously described prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female CD-1 mice (≥ 21/dose) received 0, 5.5, 25.5, 118, or 550 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 15. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 6, 11, 15, and 17. On day 17 all dams were subjected to a cesarean section and reproductive parameters (described in the reproductive toxicity section) and the numbers of live and dead fetuses were recorded. All pups were weighed and evaluated for external abnormalities. One-third of the pups underwent a detailed visceral examination under 10x magnification and the remaining two-thirds of the pups were examined for skeletal defects. Treatment did not alter maternal or fetal body weight, or sex ratio. There were no treatment-related increases in skeletal findings or soft tissue abnormalities. The study authors identified a developmental NOAEL of 550 mg/kg/day (highest dose tested).
- In a previously described prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female Wistar rats (≥ 23/dose) received 0, 5.5, 25.5, 118, or 550 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 15. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 6, 11, 15, and 20. On day 20 all dams were subjected to a cesarean section and reproductive parameters (described in the reproductive toxicity section) and the numbers of live and dead fetuses were recorded. All pups were weighed and evaluated for external abnormalities. One-third of the pups underwent a detailed visceral examination under 10x magnification and the remaining two-thirds of the pups were examined for skeletal defects. Treatment did not alter maternal or fetal body weight, or sex ratio. There were no treatment-related increases in skeletal findings or soft tissue abnormalities. The study authors identified a developmental NOAEL of 550 mg/kg/day (highest dose tested).
- In a prenatal developmental toxicity study conducted according to guidelines similar to OECD 414, female CD-1 mice (≥ 21/dose) received 0, 3, 14, 65, or 300 mg/kg methylparaben (purity not reported) via oral gavage on gestation days 6 through 10. Dams were monitored daily for changes in clinical signs and mortality. Dam body weight was measured on days 0, 8, 10, and 14. On day 14 all dams were subjected to a cesarean section and reproductive parameters (described in the reproductive toxicity section) and the numbers of live and dead fetuses were recorded. All pups were weighed and evaluated for external abnormalities. One-third of the pups underwent a detailed visceral examination under 10x magnification and the remaining two-thirds of the pups were examined for skeletal defects. Treatment did not alter maternal or fetal body weight, or sex ratio. There were no treatment-related increases in skeletal findings or soft tissue abnormalities. The study authors identified a developmental NOAEL of 300 mg/kg/day (highest dose tested).

- Based on the weight of evidence, a score of Low was assigned. There were no effects on developmental parameters in an oral study conducted according to OECD Guideline 422, but as this study is a screening study, data for the surrogate methylparaben were also evaluated. As these studies also showed a lack of effects on development, a score of Low was assigned.

Confidence in the score is reduced due to reliance on surrogate data.

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

Propylparaben was assigned a score of Moderate for endocrine activity based on associating with screening lists and evidence of endocrine activity. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine activity when the chemical is associated with screening lists and there is evidence of endocrine activity (CPA 2012b). Confidence in this endpoint was reduced due to reliance of screening lists and *in vitro* data.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* EU: Category 1 – *In vivo* evidence of endocrine disruption
  - *Screening:* TEDX – Potential endocrine disruptor
  - *Screening:* SIN/ChemSec – Endocrine disruption
- TEDX 2011
  - Propylparaben was placed on the TEDX list of potential endocrine disruptors in 2011 based on *in vitro* and *in vivo* evidence of endocrine disruption. The study abstracts were reviewed and 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 $\geq 10^{-6}$ 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 antiandrogenic 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 vivo:* Oishi (2002) reported that repeated oral exposure to propylparaben causes adverse effects on the male reproductive system. This study is summarized below.
    - *In vitro:* Song et al. (1989) reported that parabens have potent *in vitro* spermicidal activity against human spermatozoa.
- WHO 2007
  - In a previously described reproductive toxicity study, 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 and blood was collected for hormone assays. The authors found a dose-dependent decrease in serum testosterone; the reduction was significant in high-dose animals (Oishi 2002). ToxServices identified a NOAEL of 100 mg/kg/day and LOAEL of 1,000 mg/kg/day based on decreased serum testosterone.

- *Mixed parabens:* 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 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 oral 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), 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.
- Based on the weight of evidence, a score of Moderate was assigned. Oishi 2002 found a dose dependent decrease in serum testosterone levels in Wistar rats following repeated oral exposure to propylparaben, and the reduction was significant in animals exposed to 1,000 mg/kg/day. Gazin et al. (2013) found no changes in serum testosterone in animals treated with doses of 1,000 mg/kg/day. As previously discussed in the reproductive toxicity section above, the SCCS (2013) evaluated both the Oishi (2002) and the Gazin et al. (2013) study and concluded that the study performed by Gazin et al. (2013) provided sufficient information to refute the findings of Oishi (2002). Oral exposure to mixed parabens did not produce an estrogenic response in immature mice. Numerous *in vitro* studies have shown that parabens possess estrogenic/anti-androgenic properties, but reviewing the *in vitro* literature is outside of the scope of this GreenScreen®. Reviews of the *in vitro* and *in vivo* literature have been published by WHO (2007), SCCS (2013, 2011), SCCP (2005a), CIR (2008), EFSA (2004), and DTU (2009). Propylparaben is associated with the EU ED, TEDX, and SIN screening lists. Association with these screening lists warrants a Moderate to High score. GreenScreen® guidance indicates that chemicals should be assigned a Moderate hazard if there is an indication of endocrine activity in the scientific literature, and only when there is a plausible related adverse effect for carcinogenicity, reproductive toxicity, developmental toxicity, and/or systemic toxicity (repeated dose) and the scores for one of more of these endpoints is a High should the hazard level be modified from a Moderate to High. As there is evidence of endocrine activity and no related effect for carcinogenicity, reproductive toxicity, developmental toxicity, or systemic toxicity, a score of Moderate was assigned. Confidence in this endpoint was reduced due to reliance of screening lists and *in vitro* data.

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

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

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

Propylparaben was assigned a score of Low for acute toxicity based on oral LD_{50} values in rats, mice, and rabbits. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral LD_{50} values are greater than 2,000 mg/kg (CPA 2012b). Confidence in the score is high because it is based on experimental data from several studies.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - *Oral:* LD_{50} = > 5,000 mg/kg propylparaben (purity not reported) (male and female Wistar rat) (OECD 401)
  - *Oral:* LD_{50} = > 15,000 mg/kg propylparaben (purity not reported) (female albino rats) (similar to OECD 401)
- ECHA 2015b, CIR 2008, HSDB 2007
  - *Oral:* LD_{50} = > 8,000 mg/kg propylparaben (purity not reported) (albino mice) (OECD 401) (Matthews et al. 1956)
- HSDB 2007
  - *Oral:* LD_{50} = 6,000 mg/kg propylparaben (rabbit, strain not reported)
- CIR 2008
  - *Oral:* Oral exposure to products containing 0.2 – 0.3% propylparaben caused no deaths at doses of 15 g/kg (equivalent to 30 – 45 mg/kg propylparaben[11]). No further details were provided.
  - *Dermal:* The LD_{50} values of eye makeup formulations containing 0.2% butylparaben or 0.2% methylparaben and 0.1% propylparaben were > 2,000 mg/kg in rats (strain not reported) (the formulation contains 2 mg/kg propylparaben[12]).
- Smolinske 1992
  - *Oral:* LD_{50} = 6,332 mg/kg in mice(strain not reported) (purity not reported)
- U.S. FDA 1972
  - *Oral:* LD_{50} = > 8,000 mg/kg in mice (strain not reported) (purity not reported) (Sokol 1952)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

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

Propylparaben was assigned a score of Low for systemic toxicity (single dose) based on the absence of adverse effects at doses ≥ 5,000 mg/kg propylparaben in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when adequate data are available and no systemic effects are seen below the guidance value of 2,000 mg/kg/day for an acute oral study, the

[11] 15 g/kg * 0.002 * 1,000 mg/g = 30 mg/kg
15 g/kg * 0.003 * 1,000 mg/g = 45 mg/kg

[12] 2,000 mg/kg * 0.001 = 2 mg/kg

chemical has no structural alerts, and they chemical is not GHS classified (CPA 2012b). Confidence in the score is high because it is based on experimental data from several studies.

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any screening lists
- ECHA 2015b
    - *Oral:* In an acute oral toxicity study conducted according to OECD Guideline 401, male and female Wistar rats (5/sex) received a single oral dose of 5,000 mg/kg propylparaben (purity not reported) via oral gavage. Animals were observed for changes in clinical signs twice daily for 14 days. Animal body weights were recorded prior to treatment and then weekly thereafter. The study authors conducted necropsies on random survivors. Treatment caused no mortality or changes in clinical signs. No substance-related changes were found at necropsy. The study authors identified an LD_{50} > 5,000 mg/kg propylparaben.
    - *Oral:* In an acute oral toxicity study conducted according to guidelines similar to OECD 401, female albino rats (5/sex) received a single oral dose of 15,000 mg/kg propylparaben (purity not reported) via oral gavage. Animals were observed for mortality and signs of toxicity once daily for 7 days. Necropsies were performed on survivors. Treatment caused no mortality or changes in clinical signs. No substance-related changes were found at necropsy. The study authors identified an LD_{50} of > 15,000 mg/kg propylparaben.

Group II* Score (repeated dose) **(H, M, or L): L**

Propylparaben was assigned a score of Low or systemic toxicity (repeated dose) based on the absence of systemic toxicity following oral exposure to propylparaben and dermal exposure to formulations containing propylparaben, methylparaben, or propylparaben and methylparaben. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when no toxic effects are found at oral doses of 100 mg/kg/day and dermal doses of 200 mg/kg/day (CPA 2012b). Confidence in the score is high because it is based on experimental data from several well conducted studies.

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any screening lists
- ECHA 2015b
    - *Oral:* In a previously described GLP-compliant combined repeated dose toxicity study with a reproduction/developmental toxicity screening test conducted according to OECD Guideline 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). The parental animals were evaluated for clinical signs of toxicity, food consumption, body and organ weights, 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,

food consumption, organ weights, gross pathology, or histopathology. Body weight gain was slightly reduced in high dose males compared to controls and the reduction reached statistical significance on days 2, 5, 7, and 8 of the pre-pairing period and on days 3, 5, 6, 7, and 8 of the pairing period. There were no significant changes in absolute body weights in males at the high dose level (Mean percent weight gain was 10% in high dose compared to 11% in controls during days 1-13 of pre-pairing and 3% in high dose compared to 4% in controls during pairing). The study authors considered minimal changes in body weight gain to be treatment-related but not adverse. No changes in body weight 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. The study authors identified a systemic toxicity NOAEL of 15,000 ppm (980.9 mg/kg/day) (highest dose tested).

- *Oral:* In a previously described 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[13]) (highest dose tested).
- *Oral:* In a previously described 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[14]) in their diet for 96 weeks. 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. 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).

- CIR 2008
  - *Dermal:* Numerous repeated dose toxicity studies were presented in the CIR (2008) review. These studies used formulations containing methylparaben alone (up to 0.7%[15]),

[13] 1,000 mg/kg/day * 6 days/7 days = 857 mg/kg/day
[14] Values reported in the ECHA REACH Dossier
[15] mg/kg/day dose cannot be calculated without information on the frequency and amount applied on the animals.

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.

Neurotoxicity (N)

***Group II Score (single dose)* (vH, H, M, or L):** DG

Propylparaben was assigned a score of Data Gap for neurotoxicity (single dose) based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- No data were identified.

***Group II* Score (repeated dose)* (H, M, or L): L**

Propylparaben was assigned a score of Low for neurotoxicity (repeated dose) based on the absence of neurotoxicity following repeated oral exposure to up to 1,124.6 mg/kg/day propylparaben in rats. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and negative, the chemical has no structural alerts, and they chemical is not GHS classified (CPA 2012b). Confidence in the score is high because it is based on experimental data from a well conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - In a previously described GLP-compliant combined repeated dose toxicity study with the reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Wistar rats (11/sex/dose) were exposed to 0, 1,500, 4,500, or 15,000 ppm propylparaben (purity not reported) 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). A functional observational battery 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. 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): M

Propylparaben was assigned a score of Moderate for skin sensitization based on a low frequency of skin sensitization in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for skin sensitization when the chemical is classified as GHS Category 1B (CPA 2012b). Confidence in the score is high because it is based on experimental data with support from a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* GHS-New Zealand: 6.5B (contact) – Contact sensitizer – GHS Category 1
- EPA 2015
  - GHS-New Zealand classified propylparaben as a contact sensitizer based on the following information:
    - Propylparaben causes severe and intractable contact dermatitis. Parabens have been identified as the cause of chronic dermatitis in a number of cases and patients who are sensitized to one paraben may show cross-reactivity to others (HSDB 2007).
    - IV administration of a hydrocortisone preparation containing propylparaben produced bronchospasm and puritis in a 10 year old asthmatic patient. Dermal tests for immediate hypersensitivity to paraben were positive (HSDB 2007).
- ECHA 2015b
  - Propylparaben was not sensitizing in a mouse local lymph node assay conducted according to OECD Guideline 429 using CBA/Ca mice (4/group, sex not reported). CBA/Ca mice (4/group) were dermally administered 25 µL of 5, 10, or 25% propylparaben 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.
  - Propylparaben was not sensitizing in a guinea pig maximization assay conducted according to guidelines similar to OECD 406 performed with Dunkin-Hartley guinea pigs (number and sex of animals per group was not reported). Animals were intradermally and epicutaneously induced with 0.5% propylparaben in physiological saline and 25% propylparaben in acetone/polyethylene glycol 400 (70:30, v/v), respectively. Animals were epicutaneously challenged with 10% propylparaben in acetone/polyethylene glycol

400 (70:30, v/v) for 24 hours under occlusive conditions. No skin reactions were noted at the induction sites of any test group animals at the 24 or 48 hour mark. The study authors concluded that this substance is not sensitizing by EU criteria.
    - Propylparaben was not sensitizing in a mouse local lymph node assay conducted according to OECD Guideline 429 using CBA/Ca female mice. Mice (4/group) were dermally administered 25 µL of 5, 10, or 25% propylparaben 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, 1.0, 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.
    - Negative results were reported in four mouse local lymph node assays conducted according to guidelines similar to OECD 429. The assays were conducted in Laboratories A – D. In each assay CBA/Ca mice (4/group, sex not reported) were dermally administered 25 µL of 5, 10, or 25% propylparaben 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 following stimulation indices for the 5, 10, and 25% doses were 1.3, 1.6, and 1.3 (Laboratory A); 1.9, 2.2, and 1.3 (Laboratory B); 1.0, 1.2, and 1.5 (Laboratory C); and 1.2, 0.5, and 2.0 (Laboratory D). As all of the stimulation indices for the applied doses were less than 3, propylparaben was not sensitizing to the skin of mice in these studies.
- HSDB 2007; CIR 2008
    - In a HRIPT methylparaben (5%), ethylparaben (7%), propylparaben (12%), and butylparaben (5%) were applied daily to the skin of 50 humans (25/sex) for 4 to 8 hours every other day for 3 weeks (10 applications). Following a 3 week rest period, the test substances were reapplied at induction concentrations (concentrations not reported) for 24 to 48 hours. No sensitization reactions were reported. No further details were provided.
- HSDB 2007
    - Parabens are capable of causing skin sensitization reactions; however, the incidence of such reactions is low.
    - Patients sensitive to one paraben may show cross-reactivity to other parabens.
- CIR 2008
    - The CIR Expert Panel presented multiple clinical studies which found evidence that patients sensitive to one paraben showed cross-reactivity to another paraben. They indicated that evidence of paraben sensitization is reported in case literature, but it primarily occurs when the exposure involves damaged or broken skin. Patch-testing data indicate that in patients with chronic dermatitis less than 4% of individuals are sensitive to parabens. Additionally, patch testing data over the past 20 years show no significant change in the incidence of dermatitis patients that test positive for parabens.
- Based on the weight of evidence, a score of Moderate was assigned. Evidence from animal studies indicates that propylparaben is not sensitizing at concentrations of up to 25%; however, reports of sensitization in humans can be found in case report literature. Additionally, patients sensitive to one paraben may show cross-reactivity to other parabens. GHS-New Zealand classified propylparaben as a GHS Category 1 skin sensitizer. GHS-New Zealand classifications do not specify a sub-category; therefore, it is unclear if propylparaben is classifies as Category 1A or 1B. Category 1B skin sensitizers are "substances showing low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to produce

sensitization in humans. Severity of reaction may also be considered" (UN 2013). As a low frequency of skin sensitization reactions to propylparaben can be found in the case report literature, propylparaben was classified as GHS Category 1B (skin sensitizer).

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

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- No data were identified.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): *M*
Propylparaben was assigned a score of Moderate for skin irritation/corrosivity based on evidence of skin irritation in humans. GreenScreen® criteria classify chemicals as a Moderate hazard for skin irritation/corrosivity when the chemical is classified as a GHS Category 3 (mild skin irritant) (CPA 2012b). Confidence in the score is reduced due to the lack of a guideline (or comparable) study of the undiluted test substance and reliance on a screening list.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* GHS-New Zealand: 6.3B – Mildly irritating to the skin – GHS Category 3
- NZ EPA 2015
  - GHS-New Zealand classified propylparaben as GHS Category 3 (mild skin irritant) based on the following information:
    - Propylparaben causes skin irritation in humans (BIBRA 1989).
- HSDB 2007
  - Methylparaben, ethylparaben, propylparaben, and butylparaben were applied daily to the backs of humans for 5 days at concentrations of 5, 7, 10, 12, and 15% in propylene glycol. On the 5th day, patches were removed and the sites were scored. No skin irritation was reported at up to 5% methylparaben, 7% ethylparaben, 12% propylparaben, and 5% butylparaben. Exposure to higher concentrations caused skin irritation.
- CIR 2008
  - 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.
  - In clinical 21-day cumulative irritancy studies 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.
  - In a clinical controlled use test (4 weeks), an eye makeup formulation containing 0.2% methylparaben and 0.1% propylparaben caused no irritation.
  - 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.
  - 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.
    - A product formulation containing 0.2% propylparaben produced minimal irritation in rabbits. The authors reported a primary irritation index of 0.5. No further details were provided.
    - A product formulation containing 0.2% propylparaben and 0.1% butylparaben was not irritating. No further details were provided.
    - 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.
- Based on the weight of evidence, a score of Moderate was assigned. In a HRIPT, propylparaben concentrations ≤ 12% did not cause skin irritation, but exposure to 15% was irritating to the skin. Various other clinical tests found formulations that contain propylparaben at concentrations up to 0.3% caused no irritation to minimal irritation. Mixed results were found in animals studies. A formulation containing 10% propylparaben was not irritating to the skin or rabbits. However, minimal irritation was reported for formulations containing up to 0.3% propylparaben. GHS-New Zealand classified propylparaben as a mild skin irritant (GHS Category 3) based on reports of mild skin irritation in humans. Based on skin irritation in humans and mixed reports in animal studies, propylparaben was classified as a GHS Category 3 (mild skin irritant) and a score of Moderate was assigned. This is consistent with the classification made by GHS-New Zealand. Confidence in this endpoint was reduced due to the inconsistent results found in animal studies and the lack of a well-documented OECD guideline (or comparable) skin irritation study.

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 negative findings in a GLP-compliant OECD Guideline eye irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and negative, the chemical has no structural alerts, and the chemical is not GHS classified (CPA 2012b). Confidence in the score is high because it is based on high quality experimental data.

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* GHS-New Zealand: 6.4A – Irritating to the eye – GHS Category 2A or 2B
- NZ EPA 2015
    - GHS-New Zealand classified propylparaben as GHS Category 2A or 2B (irritating to the eye) based on the following information:
        - A saturated aqueous solution of propylparaben is moderately irritating to the eye (Grant 1986).
- ECHA 2015b
    - Propylparaben was not irritating to rabbit eyes in a GLP-compliant acute eye irritation study conducted according to OECD Guideline 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 New Zealand White rabbits (sex not reported). Irritation was scored at 1, 24, 48 and 72 hours, as well as 7 days after treatment. Treatment produced mild reddening of the conjunctivae, sclerae, and ocular discharge. These effects were transient and were not evident on day 7. The study authors found no abnormal findings in the cornea or for the iris light reflex in any of the treated animals. No corrosion was seen. Treatment produced no staining of the treated eyes, and no test item remnants were found in the treated eyes. The study authors calculated mean irritation scores for each animal

across three time points (24, 48, and 72 hours after instillation). The reported irritation scores were 0.0 for corneal opacity, iris light reflex, and chemosis in all animals. Mean scores of 1.00, 2.00, and 1.67 were reported for reddening of the conjunctivae. Effects resolved within 7 days. The study authors concluded that propylparaben does not have to be classified as an eye irritant.
    - Propylparaben was not corrosive in a GLP-compliant *in vitro* bovine corneal opacity and permeability test conducted according to OECD Guideline 437. Three bovine corneas were exposed to 0.75 mL of a 20% (w/v) suspension of propylparaben 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 compared to the negative control. No permeability effects were seen. A mean *in vitro* irritation score of 13.03 was reported. The study authors concluded that propylparaben is not corrosive or a severe irritant to the eye.
- Based on the weight of evidence, a high confidence Low score was assigned, based on the results from a GLP-compliant guideline study in rabbits. Although GHS-New Zealand classified propylparaben as a mild eye irritant, the basis of this classification is a qualitative description from old literature. ToxServices considered the well reported guideline study of the undiluted test substance with more weight and did not heavily weight GHS New-Zealand's classification because it could not be compared to GHS criteria due to the lack of detail provided.

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 an LC_{50} value of 6.4 mg/L in fish. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when the chemical is classified as GHS Category 2 (acute aquatic toxicant) based on L/EC_{50} values between 1 and 10 mg/L (CPA 2012b). Confidence in the score is high because it is based on experimental data from a reliable study.

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* GHS-New Zealand: 9.1D (algal) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action – GHS Category 2 or 3
    - *Screening:* GHS-New Zealand: 9.1D (crustacean) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action – GHS Category 2 or 3
    - *Screening:* GHS-New Zealand: 9.1D (fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action – GHS Category 2 or 3
- NZ EPA 2015
    - GHS-New Zealand hazard classifications are based on the following values:
        - 96h LC_{50} = 6.593 mg/L (fish) (U.S. EPA ECOSAR, software version and date not reported)
        - 48h EC_{50} = 15.4 mg/L (daphnia) (Danish EPA 2001)
        - 72h EC_{50} = 18 mg/L (algae) (Danish EPA 2001)
- ECHA 2015b
    - 96h LC_{50} = 6.4 mg/L (*Danio rerio*, fish) (GLP, OECD 203)
    - 48h EC_{50} (mobility) = 15.4 mg/L (*Daphnia magna,* daphnia) (ISO 6341 15)
    - 72h EC_{50} (growth rate) = 16 mg/L (nominal) (*Pseudokirchnerella subcapitata,* algae)

(GLP, OECD 201, EU Method C.3)
    - 72h EC_{50} = 15 mg/L (*Pseudokirchnerella subcapitata,* algae) (ISO 8692)
- Based on the weight of evidence, a score of High was assigned. Propylparaben is classified as an aquatic toxicant by GHS-New Zealand based on L/EC_{50} values ranging from 6.593 to 18 mg/L, which is consistent with classification as GHS Category 2 to 3. Measured L/EC_{50} values ranging from 6.4 to 16 mg/L were identified in fish, daphnia, and algae. Fish appear to be the most sensitive species with a 96h LC_{50} value of 6.4 mg/L. Based on the 96h LC_{50} value of 6.4 mg/L in fish, propylparaben was classified as GHS Category 2 (aquatic toxicant) and assigned a High score.

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

Propylparaben was assigned a score of High for chronic aquatic toxicity based on predicted chronic aquatic toxicity values in fish and daphnia for propylparaben and a measured 21 day NOEC value in daphnia for methylparaben. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic aquatic toxicity values are between 0.1 and 1.0 mg/L (CPA 2012b). Confidence in the score is high because it is based on experimental data with support from modeled data.

- Authoritative and Screening Lists
    - *Authoritative:* not on any authoritative lists
    - *Screening:* not on any screening lists

Propylparaben (CAS# 94-13-3)

- ECHA 2015b
    - 72h NOEC (growth rate) = 2.1 mg/L (nominal) (*Pseudokirchnerella subcapitata,* algae) (GLP, OECD 201, EU Method C.3)
- U.S. EPA 2012a
    - Propylparaben is designated to the ester and phenol ECOSAR chemical classes. The most conservative predicted chronic toxicity values are 0.360 mg/L in fish, 0.461 mg/L in daphnia, and 1.435 mg/L in green algae. See Appendix I for modeling results.

Surrogate: Methylparaben (CAS# 99-76-3)

- ECHA 2015c
    - 21d NOEC (reproduction) = 0.2 mg/L (*Daphnia magna,* daphnia) (GLP, OECD 211)
    - 72h NOEC (growth rate) = 20 mg/L (*Pseudokirchneriella subcapitata*, algae) (ISO 8692)
- Based on the weight of evidence, a score of High was assigned. Very limited chronic aquatic toxicity data were available for propylparaben. A measured 72 hour NOEC of 2.1 mg/L was identified in algae, which is consistent with the predicted value of 1.435 mg/L, indicating that the model appears to perform well for algae for these compounds. Studies using the surrogate methylparaben identified a 21 day NOEC of 0.2 mg/L in daphnia and a 72 hour NOEC of 20 mg/L in algae. Modeling was performed for propylparaben because no chronic aquatic toxicity data were located for fish, and acute aquatic toxicity data indicate that fish is the most sensitive species. Modeling predicted chronic toxicity values ranging from 0.36 mg/L in fish to 1.435 mg/L in green algae. Based on the predicted chronic toxicity values of 0.36 and 0.461 in fish and daphnia for propylparaben and the measured 21 day NOEC value of 0.2 mg/L in daphnia for methylparaben, a score of High was assigned.

Environmental Fate (Fate)

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

Propylparaben was assigned a score of Very Low for persistence based on the findings of an OECD Guideline 301F ready biodegradation study. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when the major compartment is soil and the chemical meets the 10-day window (CPA 2012b). Confidence in the score is high because it is based on experimental biodegradation data.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - Propylparaben was readily biodegradable in a Manometric Respirometry Test conducted according to guidelines similar to OECD 301F, with 73% degradation after 10 days and 91.5% degradation after 28 days. The reference substance, sodium benzoate, was > 60% degraded after 14 days.
- U.S. EPA 2012b
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that propylparaben is expected to be readily biodegradable. Fugacity modeling predicts 75% will partition to soil with a half-life of 30 days, 23.6% will partition to water with a half-life of 15 days, and 1.12% will partition to air with a half-life of 18.2 hours. See Appendix J for modeling results.
- Based on the weight of evidence, a score of Very Low was assigned. Fugacity modeling predicts that propylparaben will partition primarily to soil. Propylparaben was readily biodegradable and met the 10-day window in an OECD Guideline 301F study. When the major compartment is soil, GreenScreen® criteria specify a score of Very Low if the chemical meets the 10-day window.

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

Propylparaben was assigned a score of Very Low for bioaccumulation based on its measured log K_{ow} of 3.04 and estimated BCF values of 15.62 and 44. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is less than 4 and the BCF is less than 100 (CPA 2012b). Confidence in the score is high because it is based on an experimental log K_ow with support from modeled BCF values.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ChemIDplus 2015, HSDB 2007
  - log K_{ow} = 3.04
- HSDB 2007
  - Propylparaben is not expected to bioaccumulate based on its log K_{ow} of 3.04 and estimated BCF value of 44.
- U.S. EPA 2012b
  - BCFBAF predicts a BCF of 15.62 based on a log K_{ow} of 3.04. See Appendix J for modeling results.

Physical Hazards (Physical)

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

Propylparaben was assigned a score of Low for reactivity based on its HMIS reactivity rating. Confidence in this endpoint was reduced due to the lack of measured data. GreenScreen® criteria

classify chemicals as a Low hazard for reactivity when the chemical is not self-reactive, explosive, or oxidizing (CPA 2012b). Confidence is reduced due to the lack of experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- Smolinske 1992
  - Concentrated dust may present an explosion hazard. *Dust explosion is not considered under GHS criteria and therefore ToxServices did not use this information to classify this endpoint.*
  - Propylparaben has an HMIS (Hazardous Materials Identification System) reactivity rating of 0. An HMIS reactivity rating of 0 corresponds to "Materials which are normally stable even under fire conditions, and which will not react with water" (Paint.org 2015).

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

Propylparaben was assigned a score of Low for flammability based on the findings of a flammability test. GreenScreen® criteria classify chemicals as a Low hazard for flammability when the chemical is not a flammable solid (CPA 2012b). Confidence in the score is high because it is based on experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* not on any authoritative lists
  - *Screening:* not on any screening lists
- ECHA 2015b
  - Propylparaben was not flammable in a flammability test conducted according to EU Method A.10. Propylparaben could not be ignited with a flame.
- Smolinske 1992
  - Propylparaben has an HMIS (Hazardous Materials Identification System) flammability rating of 0. An HMIS flammability rating of 0 corresponds to "Materials that will not burn" (Paint.org 2015).

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21 CFR § 150.161. Code of Federal Regulations Title 21 Section 150.161 Artificially Sweetened Fruit Preserves and Jams. Available at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=150.161.

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APPENDIX A: Hazard Benchmark 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)

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	L	L	DG	L	M	DG	*M*	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)

[94-13-3] Propylparaben; propyl 4-hydroxybenzoate

General Information | Hazards | Compound Groups | Life Cycle Research | GreenScreen

Direct Hazards:

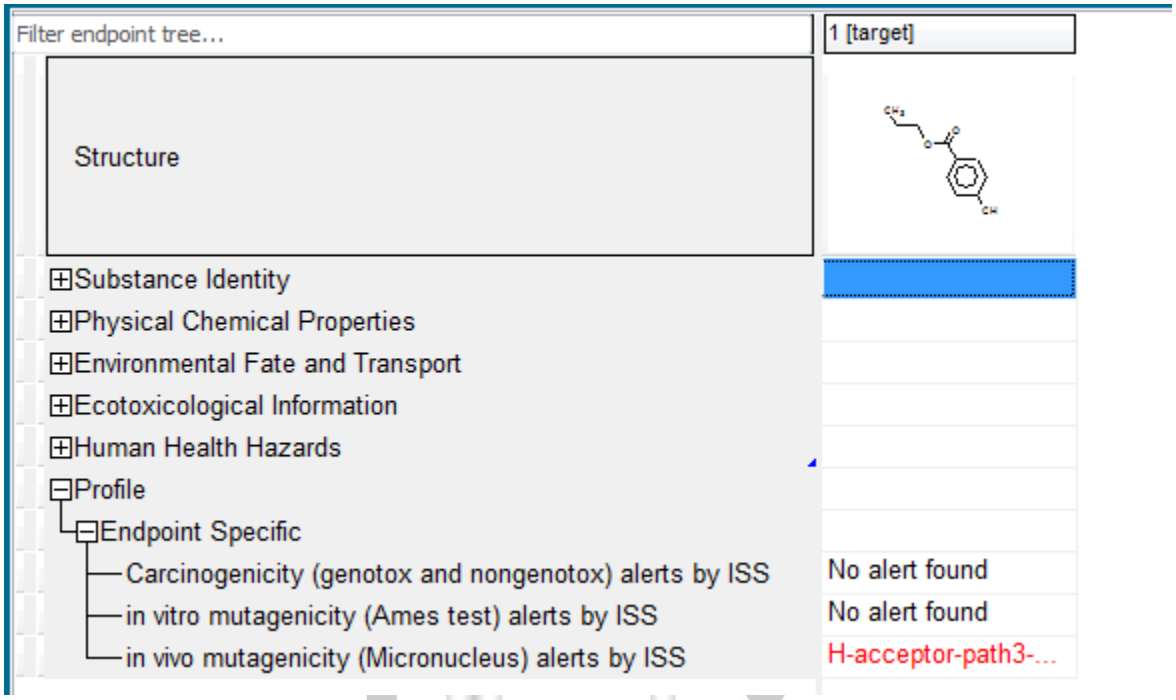
ENDOCRINE	EC - Priority Endocrine Disrupters - Category 1 - In vivo evidence of endocrine disruption activity TEDX - Potential Endocrine Disruptors - Potential Endocrine Disruptor ChemSec - Substitute List - Endocrine Disruption	+2
EYE IRRITATION	New Zealand HSNO/GHS - 6.4A - Irritating to the eye	
SKIN IRRITATION	New Zealand HSNO/GHS - 6.3B - Mildly irritating to the skin	
SKIN SENSITIZE	New Zealand HSNO/GHS - 6.5B (contact) - Contact sensitisers	
ACUTE AQUATIC	New Zealand HSNO/GHS - 9.1D (algal) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action New Zealand HSNO/GHS - 9.1D (crustacean) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action New Zealand HSNO/GHS - 9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	+2
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS) - Class 1 Low Hazard to Waters Hazardous 100 - Chemicals of high concern ChemSec - Substitute List - Equivalent Concern CA SCP Candidate Chemicals - Full Candidate Chemical List	+3

Potential Residual Hazards:

See Life Cycle Research tab for details on residuals and other substances used in manufacture.

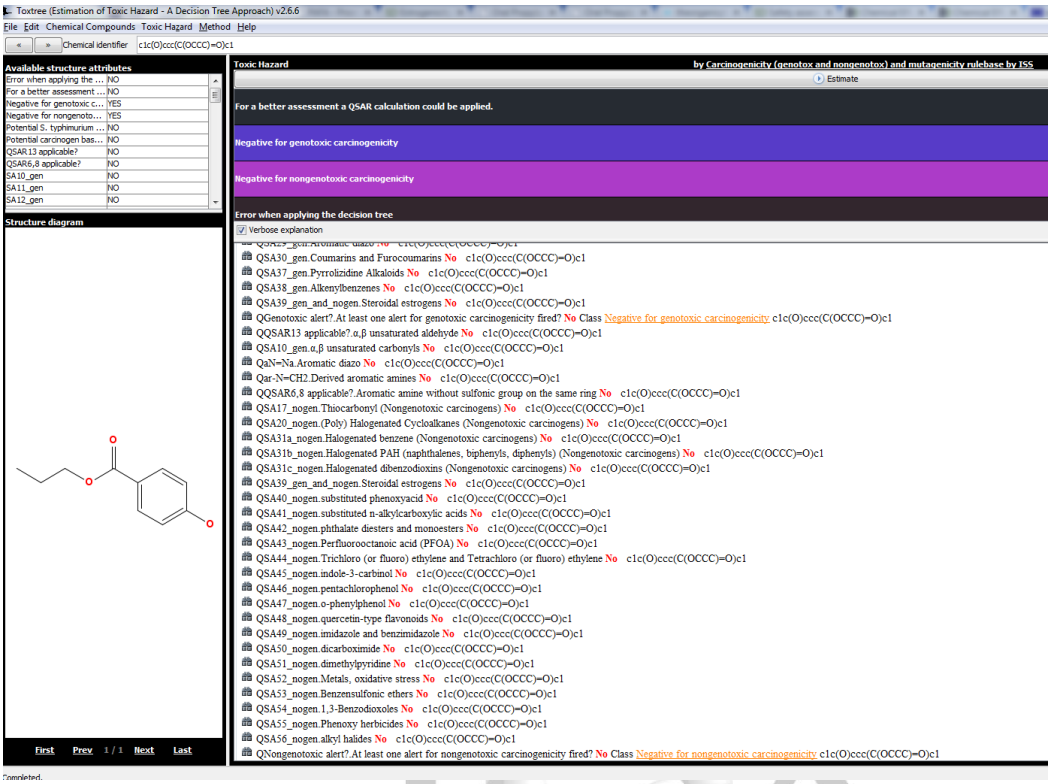
None identified

APPENDIX D: OECD Toolbox Carcinogenicity and Genotoxicity Modeling Results for Propylparaben (CAS #94-13-3)

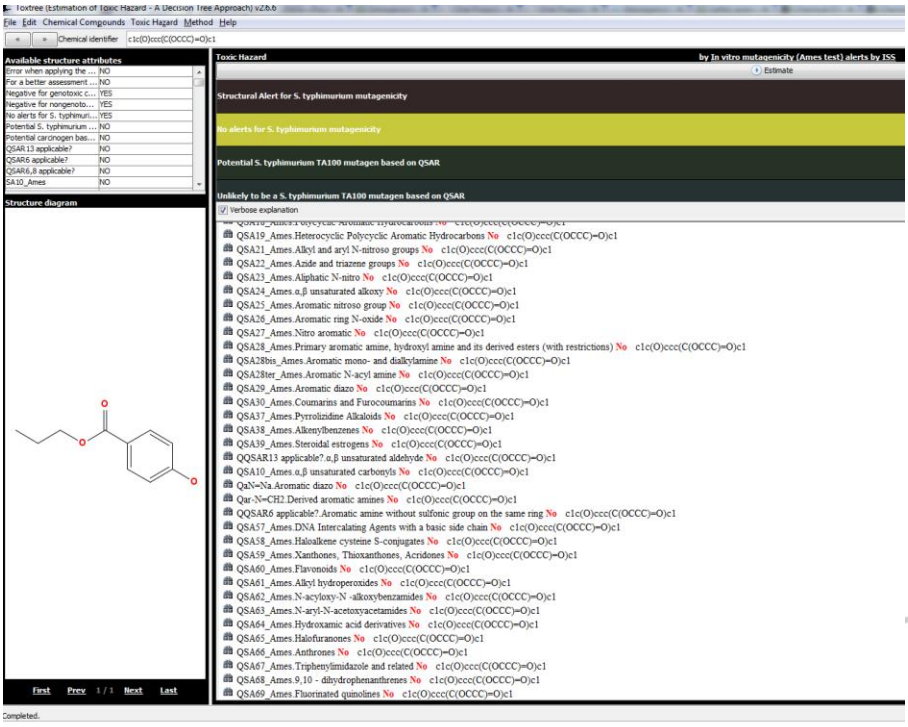


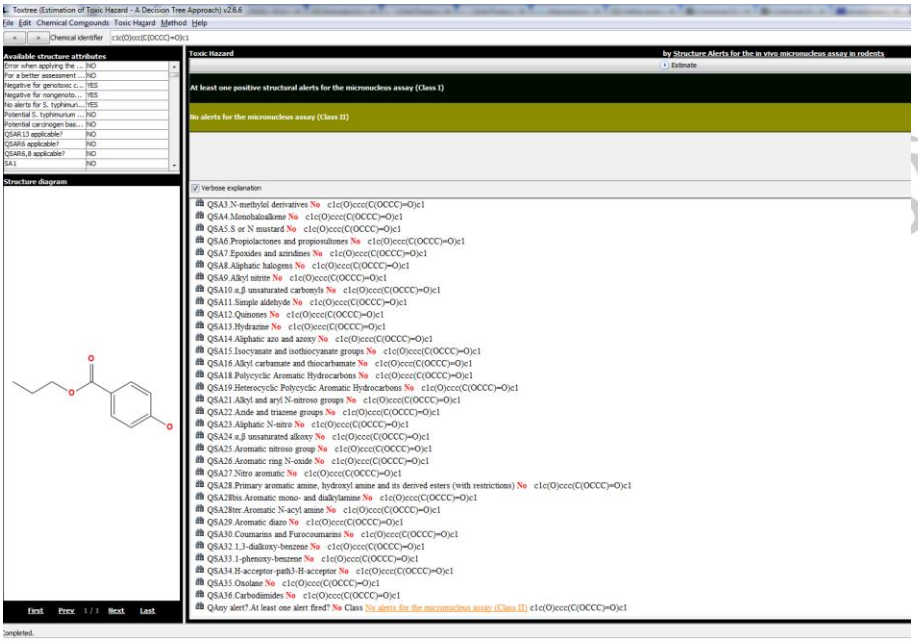
Filter endpoint tree...	1 [target]
Structure	
⊞Substance Identity	
⊞Physical Chemical Properties	
⊞Environmental Fate and Transport	
⊞Ecotoxicological Information	
⊞Human Health Hazards	
⊟Profile	
⊟Endpoint Specific	
Carcinogenicity (genotox and nongenotox) alerts by ISS	No alert found
in vitro mutagenicity (Ames test) alerts by ISS	No alert found
in vivo mutagenicity (Micronucleus) alerts by ISS	H-acceptor-path3-...

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

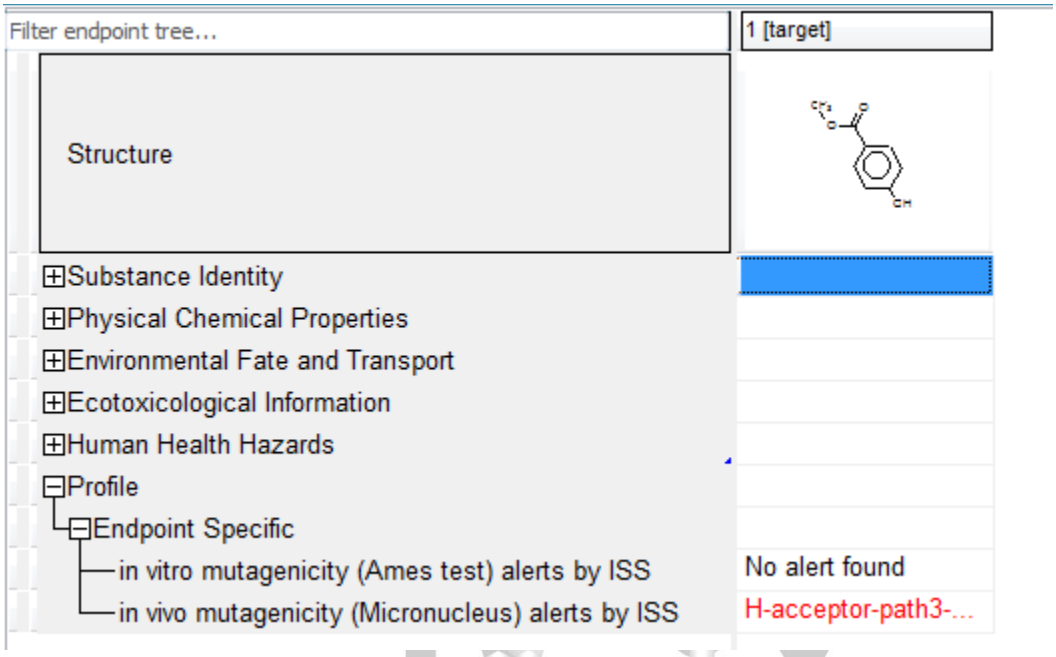


APPENDIX F: Toxtree Genotoxicity Modeling Results for Propylparaben (CAS #94-13-3)

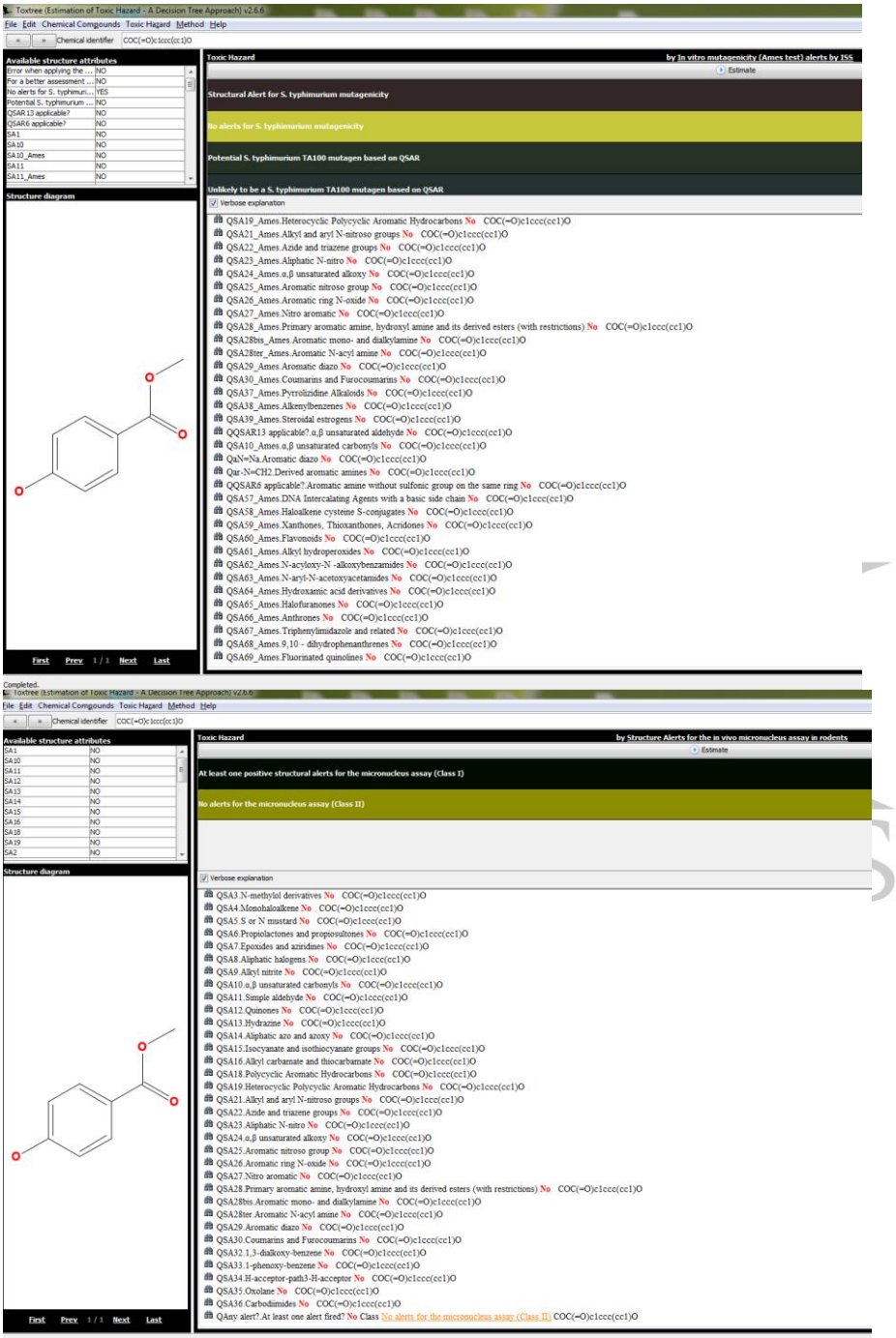


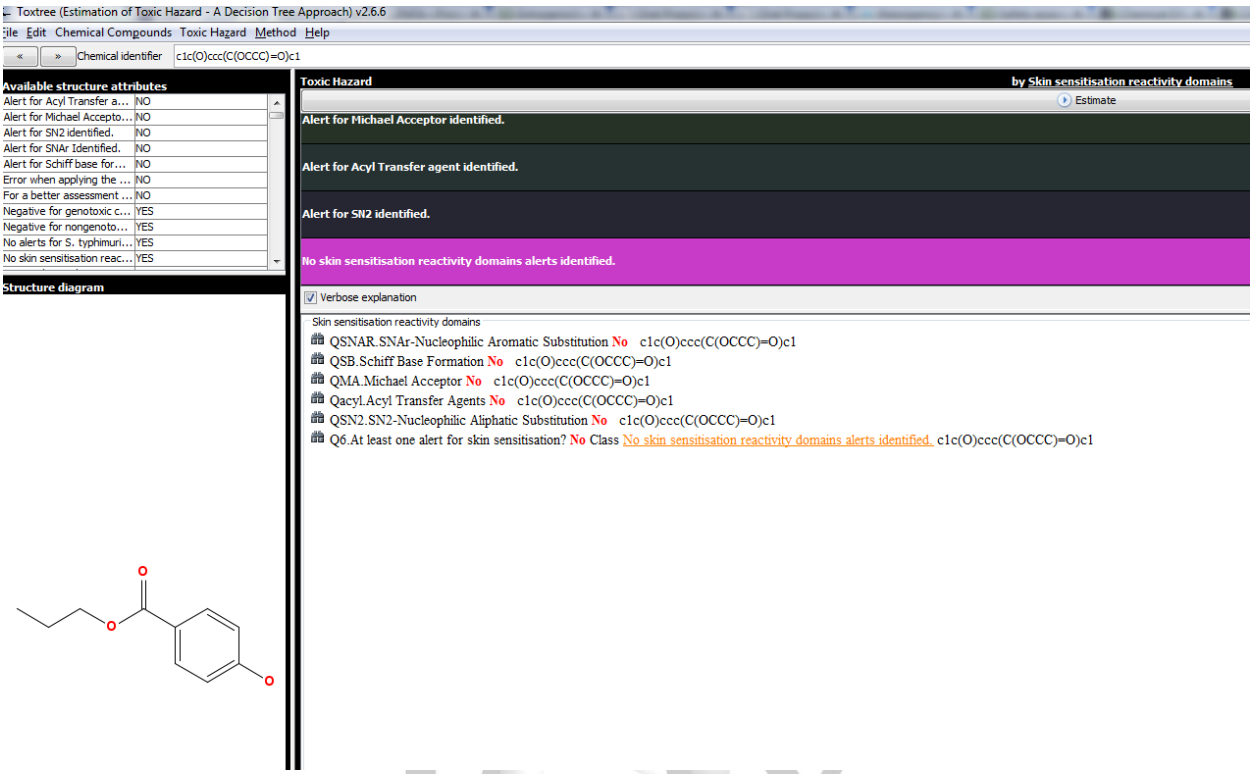


APPENDIX G: OECD Toolbox Genotoxicity Modeling Results for Methylparaben (CAS #99-76-3)



APPENDIX H: Toxtree Genotoxicity Modeling Results for Methylparaben (CAS #99-76-3)





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

ECOSAR Version 1.11 Results Page

SMILES: c1c(O)ccc(C(=O)(OCCC))c1
CHEM:
CAS Num:
ChemID1:
MOL FOR: C10 H12 O3
MOL WT: 180.21
Log K_{ow}: 2.979 (EPISuite K_{ow}win v1.68 Estimate)
Log K_{ow}: 3.040 (User Entered)
Log K_{ow}: 3.04 (PhysProp DB exp value - for comparison only)
Melt Pt: 97.00 (deg C, User Entered for Wat Sol estimate)
Melt Pt: 97.00 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 579.6 (mg/L, EPISuite WSK_{ow}win v1.43 Estimate)
Wat Sol: 500 (mg/L, User Entered)
Wat Sol: 500 (mg/L, PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log K_{ow}: 3.040 (User Entered)
Wat Sol: 500 (mg/L, User Entered)

Available Measured Data from ECOSAR Training Set

No Data Available

ECOSAR v1.1 Class-specific Estimations

Esters
Phenols

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Esters	: Fish	96-hr.	LC50	5.950
Esters	: Daphnid	48-hr.	LC50	11.065
Esters	: Green Algae	96-hr.	EC50	3.994
Esters	: Fish		ChV	0.360
Esters	: Daphnid		ChV	5.610
Esters	: Green Algae		ChV	1.435

Esters	: Fish (SW)	96-hr.	LC50	8.493
Esters	: Mysid	96-hr.	LC50	5.004
Esters	: Fish (SW)		ChV	1.468
Esters	: Mysid (SW)		ChV	44.216
Esters	: Earthworm	14-day	LC50	1085.604 *
Phenols	: Fish	96-hr.	LC50	5.071
Phenols	: Daphnid	48-hr.	LC50	2.426
Phenols	: Green Algae	96-hr.	EC50	10.086
Phenols	: Fish		ChV	0.596
Phenols	: Daphnid		ChV	0.461
Phenols	: Green Algae		ChV	4.676
Phenols	: Fish (SW)	96-hr.	LC50	1.886
Phenols	: Earthworm	14-day	LC50	62.880
Phenols	: Lemna gibba	7-day	EC50	2.799

Neutral Organic SAR (Baseline Toxicity)	: Fish	96-hr.	LC50	17.232
	: Daphnid	48-hr.	LC50	10.771
	: Green Algae	96-hr.	EC50	11.934
	: Fish		ChV	1.886
	: Daphnid		ChV	1.372
	: Green Algae		ChV	3.870

Note: * = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

Class Specific LogK_{ow} Cut-Offs

If the log K_{ow} of the chemical is greater than the endpoint specific cut-offs presented below, then no effects at saturation are expected for those endpoints.

Esters:

Maximum LogK_{ow}: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogK_{ow}: 6.0 (Earthworm LC50)
Maximum LogK_{ow}: 6.4 (Green Algae EC50)
Maximum LogK_{ow}: 8.0 (ChV)

Phenols:

Maximum LogK_{ow}: 7.0 (Fish 96-hr LC50, Daphnid LC50)
Maximum LogK_{ow}: 6.4 (Earthworm, Lemna)
Maximum LogK_{ow}: 7.0 (Green Algae EC50

Maximum $LogK_{ow}$: 8.0 (ChV)
Maximum $LogK_{ow}$: 5.0 (Fish (SW) 96-hr LC50, Mysid)

Baseline Toxicity SAR Limitations:

Maximum $LogK_{ow}$: 5.0 (Fish 96-hr LC50; Daphnid LC50)
Maximum $LogK_{ow}$: 6.4 (Green Algae EC50)
Maximum $LogK_{ow}$: 8.0 (ChV)

APPENDIX J: EPISuite Modeling Results for Propylparaben (CAS #94-13-3)

CAS Number: 000094-13-3
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 K_{ow} (octanol-water): 3.04
Boiling Point (deg C): 301.00
Melting Point (deg C): 97.00
Vapor Pressure (mm Hg): 0.000555
Water Solubility (mg/L): 500
Henry LC (atm-m^3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{ow}WIN v1.68 estimate) = 2.98
Log K_{ow} (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: 0.00286 mm Hg (-999 deg C, user-entered VP)
: 0.381 Pa (-999 deg C, user-entered VP)

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 579.6
log K_{ow} used: 3.04 (user entered)
melt pt used: 97.00 deg C
Water Sol (Exper. database match) = 500 mg/L (25 deg C)
Exper. Ref: YALKOWSKY, S.H. & 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-m^3/mole (6.45E-004 Pa-m^3/mole)
Group Method: 4.25E-009 atm-m^3/mole (4.31E-004 Pa-m^3/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: 2.632E-007 atm-m^3/mole (2.667E-002 Pa-m^3/mole)
VP: 0.000555 mm Hg (source: User-Entered)
WS: 500 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: 3.04 (user entered)
Log K_{aw} used: -6.584 (HenryWin est)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 9.624
Log K_{oa} (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): 0.7161
Biowin6 (MITI Non-Linear Model): 0.8344
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): 0.381 Pa (0.00286 mm Hg)
Log K_{oa} (K_{oa}win est): 9.624
Kp (particle/gas partition coef. (m^3/µg)):
Mackay model: 7.87E-006
Octanol/air (K_{oa}) model: 0.00103
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model: 0.000284
Mackay model: 0.000629
Octanol/air (K_{oa}) model: 0.0763

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 14.0678 E-12 cm^3/molecule-sec
Half-Life = 0.760 Days (12-hr day; 1.5E6 OH/cm^3)
Half-Life = 9.124 Hrs.
Ozone Reaction:
No Ozone Reaction Estimation
Reaction With Nitrate Radicals May Be Important!
Fraction sorbed to airborne particulates (phi):

0.000457 (Junge-Pankow, Mackay avg)
0.0763 (K_{oa} method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc}: 286.6 L/kg (MCI method)
Log K_{oc}: 2.457 (MCI method)
K_{oc}: 510.3 L/kg (K_{ow} method)
Log K_{oc}: 2.708 (K_{ow} 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 = 1.673 (BCF = 47.08 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.3669 days (HL = 0.04297 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.194 (BCF = 15.62)
Log BAF Arnot-Gobas method (upper trophic) = 1.194 (BAF = 15.62)
log K_{ow} used: 3.04 (user entered)

Volatilization from Water:
Henry LC: 2.63E-007 atm-m^3/mole (calculated from VP/WS)
Half-Life from Model River: 2988 hours (124.5 days)
Half-Life from Model Lake: 3.27E+004 hours (1363 days)

Removal In Wastewater Treatment:
Total removal: 6.06 percent
Total biodegradation: 0.13 percent
Total sludge adsorption: 5.92 percent
Total to Air: 0.01 percent
(using 10000 hr. Bio P,A,S)

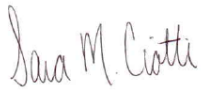
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr.)	Emissions (kg/hr.)
Air	1.12	18.2	1000
Water	23.6	360	1000
Soil	75	720	1000
Sediment	0.297	3.24e+003	0

Persistence Time: 513 hr.

Licensed GreenScreen® Profilers

Propylparaben GreenScreen® Evaluation Prepared by:



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Propylparaben GreenScreen® Evaluation QC'd by:

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