BENZOYL PEROXIDE

(CAS #94-36-0)

GREENSCREEN® FOR SAFER CHEMICALS (GREENSCREEN®) ASSESSMENT

Prepared by:

ToxServices LLC

Assessment Date: November 15, 2021

Expiration Date: November 15, 2026

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TABLE OF CONTENTS

TABLE OF FIGURES

TABLE OF TABLES

GreenScreen® Executive Summary for Benzoyl Peroxide (CAS #94-36-0)

Benzoyl peroxide is an organic peroxide that has a variety of uses including: a bleaching agent for fats, flour, oils, and waxes; a drying agent for unsaturated oils and rubber vulcanization; a burn out agent for acetate yarns; a polymerization catalyst; a catalyst for the hardening of fiberglass resins; an oxidizing agent; and a topical non-prescription medication for the treatment of acne. Benzoyl peroxide is a granular solid or powder at room temperature. Its low vapor pressure indicates it is unlikely to volatilize. It has very low water solubility and in solid form, may explode if exposed to heat, shock, or friction.

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

- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
  - High Group II* Human Toxicity (skin sensitization-SnS*)
- Benchmark 2g
  - Very High Physical Hazard (reactivity-Rx)

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

New Approach Methodologies (NAMs) used in this GreenScreen® include *in silico* modeling for endocrine activity and sensitization, and *in vitro* data for genotoxicity and endocrine activity. The quality, utility, and accuracy of NAM predictions are greatly influenced by two primary types of uncertainties:

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

Type I (input data) uncertainties in benzoyl peroxide's NAMs dataset include lack of *in vivo* data for endocrine activity and respiratory sensitization, and lack of validated test methods for respiratory sensitization. Benzoyl peroxide's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, the uncertain *in vivo* relevance of *in silico* modeling and *in vitro* assays of endocrine receptor binding, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, and OECD Toolbox not accounting for non-immunologic mechanisms of respiratory sensitization. Some of benzoyl peroxide's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

GreenScreen® Hazard Summary Table for Benzoyl Peroxide

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

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

GreenScreen® Chemical Assessment for Benzoyl Peroxide (CAS #94-36-0)

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

GreenScreen® Assessment (v.1.4) Prepared By:
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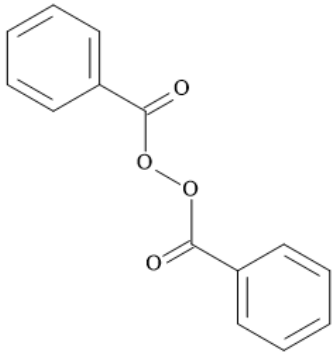
Organization: ToxServices LLC
Date: August 18, 2021, November 15, 2021

Expiration Date: November 15, 2026[2]

Chemical Name: Benzoyl Peroxide

CAS Number: 94-36-0

Chemical Structure(s):



Also called: Abcat 40; Acetoxyl; Acne-Aid Cream; Acnegel; Akneroxid 5; Akneroxide L; Aksil 5; Asidopan; Aztec BPO; B 75W; Benbel C; Benox 50; Benoxyl; Benoxyl (5&10) Lotion; Benprox; Benzac; Benzac W; Benzagel; Benzagel 10; Benzaknen; Benzashave; Benzefoam; Benzoic acid, peroxide; Benzol peroxide; Benzoperoxide; Benzoyl superoxide; BPO; Brevoxyl; BZF-60; Cadat BPO; Cadox 40E; Cadox B; Cadox B 40E; Cadox B 50P; Cadox B 70W; Cadox B-CH 50; Cadox BS; Chaloxyd BP 50FT; Clear By Design; Clearasil Antibacterial Acne Lotion; Clearasil BP Acne Treatment Cream; Debroxide; Desanden; Desquam E; Desquam X; Desquam-X; Dibenzoyl peroxide; Diphenylglyoxal peroxide; Dry and Clear; Duresthin 5; Eloxyl; Epi Clear Antiseptic Lotion; Epi-Clear; Fostex; Fostex BPO Bar, Gel, and Wash; G 20; Garox; Incidol; Lavoclen; Loroxide; Lucidol; Lucidol (peroxide); Lucidol 50P; Lucidol B 50; Lucidol G 20; Lucidol KL 50; Lucidol-70; Luperco AA; Luperco AST; Luperox FL; Mytolac; Nayper B and BO; Nayper bo; Neobenz micro; Norox bzp-250; Norox bzp-C-35; Novadelox; Oxy-10; Oxy-10 Cover; Oxy-5; Oxylite; Pacnex; PanOxyl; Persa-Gel; Persadox; Quinolor compound; Resdan Akne; Stri-dex B.P.; Superox 744; Theraderm; Topex; Vanoxide; Xerac; Benzamycin; pHisoAc BP; Sulfoxyl; Xerac BP (ChemIDplus 2021).

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

Suitable surrogates or moieties of chemicals used in this assessment (CAS #'s):
A surrogate was not used as part of this assessment as benzoyl peroxide has a relatively complete toxicological dataset, and no data were identified that could fill the data gaps.

Identify Applications/Functional Uses:
1. Bleaching agent for fats, flour, oils, and waxes
2. Drying agent for unsaturated oils, rubber vulcanization
3. Burn out agent for acetate yarns
4. Polymerization catalyst
5. Catalyst for hardening of fiberglass resins
6. Oxidizing agent
7. Topical non-prescription medications for treatment of acne
(Pharos 2021, HSDB 2018)

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

GreenScreen® Summary Rating for Benzoyl Peroxide[4,5 6,7]: Benzoyl peroxide was assigned a **GreenScreen Benchmark™ Score of 2** ("Use but Search for Safer Substitutes") (CPA 2018b). This score is based on the following hazard score combinations:

- Benchmark 2e
  - Moderate Group I Human Toxicity (developmental toxicity-D)
- Benchmark 2f
  - Very High Ecotoxicity (acute aquatic-AA and chronic aquatic-CA)
  - High Group II* Human Toxicity (skin sensitization-SnS*)
- Benchmark 2g
  - Very High Physical Hazard (reactivit-Rx)

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

Figure 1: GreenScreen® Hazard Summary Table for Benzoyl Peroxide

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

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

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

Environmental Transformation Products

In a preliminary hydrolysis study conducted under GLP according to OECD Guideline 111, >50% hydrolysis occurred after 2.4 hours at pHs of 4, 7, and 9 at 50°C. Benzoic acid is the expected main hydrolysis product and was measured at each tested pH. Study authors concluded that benzoyl peroxide is hydrolytically unstable (ECHA 2021). Using OECD Toolbox, ToxServices predicted three hydrolysis products, including benzoic acid, hydrogen peroxide, and peroxybenzoic acid, as shown in Table 1 below (OECD 2020a). Per GreenScreen® guidance (CPA 2018b), chemicals that degrade rapidly and completely (i.e., meet criteria for Very Low for persistence) are not likely to form persistent biodegradation intermediates because the degradation intermediates will not persist long enough to be encountered after use or release of the parent chemical (i.e., relevant). As benzoyl peroxide is readily biodegradable, it is not expected to have relevant transformation products.

Table 1: Environmental Transformation Product Summary

Life Cycle Stage	Transformation Pathway	Environmental Transformation Product	CAS #	Feasible (Yes or No)	Relevant (Yes or No)	GreenScreen® List Translator Score or GreenScreen® Benchmark™ Score[8,9]
End	Hydrolysis	Benzoic acid	65-85-0	Yes	No	LT-P1
End	Hydrolysis	Hydrogen peroxide	7722-84-1	Yes	No	LT-UNK
End	Hydrolysis	Peroxybenzoic acid	93-59-4	Yes	No	No GS

Introduction

Benzoyl peroxide has a variety of uses including: a bleaching agent for fats, flour, oils, and waxes; a drying agent for unsaturated oils and rubber vulcanization; a burn out agent for acetate yarns; a polymerization catalyst; a catalyst for the hardening of fiberglass resins; an oxidizing agent; and a topical non-prescription medication for the treatment of acne (Pharos 2021). It is prepared by the interaction of benzoyl chloride and a cooled solution of sodium peroxide (HSDB 2018). ToxServices assessed benzoyl peroxide against GreenScreen® Version 1.4 (CPA 2018b) following procedures outlined in ToxServices' SOPs (GreenScreen® Hazard Assessment) (ToxServices 2020).

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

The SCIL is a list of chemicals that meet the Safer Choice standard (U.S. EPA 2021a). It can be accessed at: http://www2.epa.gov/saferchoice/safer-ingredients. Chemicals on the SCIL have been assessed for compliance with the Safer Choice Standard and Criteria for Safer Chemical Ingredients (U.S. EPA 2015).

Benzoyl peroxide is not listed on the U.S. EPA SCIL.

[8] The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to screen for GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against the lists in the List Translator electronically.
[9] A GreenScreen® assessment of a transformation product depends on the Benchmark score of the parent chemical (see GreenScreen® Guidance).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen Benchmark™ 1 chemicals (CPA 2018b). Pharos (Pharos 2021) is an online list-searching tool that is used to screen chemicals against all of the lists in the List Translator electronically. ToxServices also checks the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b),[10] which are not considered GreenScreen® Specified Lists but are additional information sources, in conjunction with the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for benzoyl peroxide can be found in Appendix C.

- Benzoyl peroxide is an LT-P1 chemical when screened using Pharos, and therefore a full GreenScreen® is required.
- Benzoyl peroxide is not listed on the U.S. DOT list.
- Benzoyl peroxide is on the following lists for multiple endpoints:
  - German FEA – Substances hazardous to waters: Class 2 – Hazard to Waters.
  - Quebec CSST – WHMIS 1988: Class D2B – Toxic material causing other toxic effects.
- Specified lists for single endpoints are reported in individual hazard endpoints in the hazard assessment section below.

Hazard Statement and Occupational Control

The Globally Harmonized System of Classification and Labelling of Chemicals (GHS) hazard statements that were harmonized across the European Union (EU) for benzoyl peroxide are indicated in Table 2. General personal protective equipment (PPE) recommendations and occupational exposure limits (OELs) are presented in Table 3, below.

Table 2: GHS H Statements for Benzoyl Peroxide (CAS #94-36-0) (Pharos 2021, ECHA 2021)

H Statement	H Statement Details
H317	May cause an allergic skin reaction (Skin sensitization – Category 1)
H319	Causes serious eye irritation (Serious eye damage/irritation – Category 2A)
H241	Heating may cause a fire or explosion (Self-reactive substances and mixtures; and organic peroxides – Type B)

Table 3: Occupational Exposure Limits and Recommended Personal Protective Equipment for Benzoyl Peroxide (CAS #94-36-0)

Personal Protective Equipment (PPE)	Reference	Occupational Exposure Limits (OEL)	Reference
Respiratory: Effective dust mask, recommended filter type: P2. In case of hazardous fumes, use self-contained breathing apparatus	ECHA 2021	PEL: 8h TWA: 5 mg/m^3	HSDB 2018
Hand: Gloves (nitrile rubber, neoprene) tested EN374			
Eye/face: Safety glasses/goggles and face mask		TLV: 8h TWA: 5 mg/m^3	
Skin and body: Protective suit			

PEL: Permissible Exposure Limit
TLV: Threshold Limit Value
TWA: Time Weighted Average

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

Physicochemical Properties of Benzoyl Peroxide

Benzoyl peroxide is a granular solid or powder at room temperature. Its low vapor pressure indicates it is unlikely to volatilize. It has very low water solubility and in solid form, may explode if exposed to heat, shock, or friction. Its log K_{ow} indicates that benzoyl peroxide is not expected to bioaccumulate.

Table 4: Physical and Chemical Properties of Benzoyl Peroxide (CAS #94-36-0)

Property	Value	Reference
Molecular formula	$C_{14}H_{10}O_4$	ChemIDplus 2021
SMILES Notation	O=C(OOC(=O)c1ccccc1)c2ccccc2	ChemIDplus 2021
Molecular weight	242.229 g/mol	ChemIDplus 2021
Physical state	Solid	ECHA 2021
Appearance	White crystalline powder	ECHA 2021
Melting point	103-108°C	ECHA 2021
Boiling point	N/A; decomposes before boiling	ECHA 2021
Vapor pressure	7.32E-005 mm Hg @ 25°C (estimated)	U.S. EPA 2017
Water solubility	0.35 mg/L @ 20°C	ECHA 2021
Dissociation constant	N/A; no ionic structure	ECHA 2021
Density/specific gravity	1.33 @ 20°C	ECHA 2021
Partition coefficient	log K_{ow} = 2.3 @ 20°C	ECHA 2021

Toxicokinetics

Absorption:

- *Oral:* No oral absorption data were available for benzoyl peroxide. However, as benzoyl peroxide is hydrolytically unstable, it is expected to undergo hydrolysis to form benzoic acid in the stomach after oral administration. Benzoic acid is 100% absorbed based on experimental data in humans and rats (ECHA 2021).
- *Dermal:* In an *in vitro* dermal penetration and disposition study (non-GLP, non-guideline), excised human skin was exposed to C14-labeled benzoyl peroxide under occlusive conditions for 8 hours at 900 µg/cm^2. 4.5% of the benzoyl peroxide administered penetrated into the skin, either through the stratum corneum or the follicular openings, or both, and appeared on the other side of the skin as benzoic acid. Study authors concluded that only benzoic acid enters systemic circulation (Klimisch 2, reliable with restrictions) (ECHA 2021). *In vivo* studies conducted using hairless Sprague-Dawley rats, mice, New Zealand rabbits, rhesus monkeys, and human volunteers indicate that benzoyl peroxide is absorbed through the skin as benzoic acid which is then converted to benzoate (ECHA 2021).

Distribution

- Due to its instability, benzoyl peroxide is not systemically absorbed or distributed unchanged, but as benzoic acid (ECHA 2021).

Metabolism

- Benzoyl peroxide is metabolized by cleavage of the peroxide bond, resulting in benzyloxyl radicals; these radicals will then either degrade to phenyl radicals and carbon dioxide, or remove hydrogen from molecules such as nicotinamide adenine dinucleotide and reduced NADH to form benzoic acid. Peroxidases catalyze the insertion of two hydrogen ions donated by NADH between the oxygen atoms of hydrogen peroxide to form two molecules of water. Benzoyl peroxide is converted to benzoic acid by the same mechanism, indicating benzoic acid is its major metabolite (JECFA 2006).

Elimination

- Benzoic acid is excreted in the urine, either as benzoate or as hippuric acid (benzoic acid conjugated with glycine) (JECFA 2006).
- A study in rhesus monkeys showed that the benzoic acid is systemically absorbed as benzoate and rapidly excreted in urine in an unchanged form (i.e., benzoate), without being conjugated to hippuric acid (ECHA 2021).

Hazard Classification Summary

Group I Human Health Effects (Group I Human)

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

Benzoyl peroxide was assigned a score of Low for carcinogenicity based on negative results in chronic dietary studies in rats and mice and being classified as Group 3 by the International Agency for Research on Cancer (IARC). GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate negative data are available and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* IARC Group 3: Agent is not classifiable as to its carcinogenicity to humans.
  - *Screening:* Not present on any screening lists for this endpoint.
- IARC 1999
  - Two case–control studies have evaluated exposure to benzoyl peroxide among cases of malignant melanoma. One of these studies suggested a greater frequency of exposure among cases than controls. A third large population-based case–control study, designed specifically to evaluate the possible risk of benzoyl peroxide used as an acne medication among young persons, included largely cases of basal-cell carcinoma of the skin. There was no association of cancers with use of benzoyl peroxide in this study.
  - Two dermal carcinogenicity studies in mice were identified which reported benign and malignant skin tumors in one study and only benign skin tumors in the other. Several skin-painting studies in mice and hamsters were identified in combination with exposure to known carcinogens. Benzoyl peroxide was determined to be a skin tumor promoter in several strains of mice.
  - There is inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of benzoyl peroxide.
  - Benzoyl peroxide is classified as Group 3: not classifiable as to its carcinogenicity to humans.
- JECFA 2006
  - *Oral*: Benzoyl peroxide was not carcinogenic in a dietary study where groups of male and female albino mice (25/sex/dose) received benzoyl peroxide at doses of 28, 280, or 2,800 mg/kg in diet (equivalent to 4.2, 42, and 420 mg/kg bw/day) for 80 weeks. No further details were provided.
- ECHA 2021, JECFA 2006
  - *Oral:* A non-GLP compliant combined feeding toxicity and carcinogenicity study was conducted according to an unspecified guideline. Male and female albino rats (25/sex/dose) were fed a diet containing 28, 280, and 2,800 mg benzoyl peroxide/kg diet (equivalent to 1.9, 19, or 190 mg/kg bw/day in males and 2.3, 23, and 230 mg/kg bw/day in females, respectively). Body weight gains of rats were noted weekly for the first 18 weeks, and then monthly; animals were examined twice daily regarding general health; and animals were

examined for benign and malignant tumors. There were no signs of carcinogenicity seen (Klimisch 2, reliable with restrictions).

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

Benzoyl peroxide was assigned a score of Low for mutagenicity/genotoxicity based on a weight of evidence of *in vitro* bacterial reverse mutation assays, mammalian cell mutation assay, *in vitro* chromosomal aberration assay, an *in vitro* mammalian cell mutation assay, and an *in vivo* mouse micronucleus assay. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data are available for both gene mutations and chromosome aberrations, and they are not GHS classified (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *In vitro*: Negative results for mutagenicity were obtained in a bacterial reverse mutation assay conducted according to OECD Guideline 471 (GLP compliance not reported). *Salmonella typhimurium* test strains TA97, TA98, TA100, TA102, TA104, and TA1535 were exposed to benzoyl peroxide (75% purity in dimethyl sulfoxide (DMSO)) at undisclosed concentrations both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 1, reliable without restriction).
  - *In vitro*: Negative results for mutagenicity were obtained in a bacterial reverse mutation assay conducted according to OECD Guideline 471 (GLP compliance not reported). *S. typhimurium* test strains TA98, TA100, TA1535, and TA1537 were exposed to benzoyl peroxide (purity not reported) in acetate at concentrations up to 500 µg/plate both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a GLP-compliant bacterial reverse mutation assay conducted according to OECD Guidelines 471 and 472. *S. typhimurium* test strains TA98, TA100, TA1535, and TA1537, as well as *Escherichia coli* strain WP_2 *uvr*A, were exposed to benzoyl peroxide (71.8% purity in DMSO) at concentrations up to 60 µg/plate both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a bacterial reverse mutation assay conducted using the preincubation method modified by Ames (GLP compliance not reported). *S. typhimurium* test strains TA97a, TA100, TA102, and TA104 were exposed to benzoyl peroxide (purity unknown) at concentrations of 1-100 µg/plate both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a bacterial reverse mutation assay conducted according to OECD Guideline 471 (GLP compliance not reported). *S. typhimurium* test strains TA92, TA94, TA98, TA100, TA1535, and TA1537 were exposed to benzoyl peroxide (purity not reported) in DMSO at concentrations up to 2,500 µg/plate both in the presence and absence of metabolic activation. No increases in the mutation

frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a reverse mutation assay (GLP compliance and method not reported). *S. typhimurium* test strains TA1535, TA1537, and TA1538, as well as *Saccharomyces cerevisiae*, were exposed to benzoyl peroxide (78% purity) in DMSO at concentrations up to 0.1875% both in the presence and absence of metabolic activation. No increases in the mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro*: Negative results for mutagenicity were obtained in a mammalian cell gene mutation assay conducted according to OECD Guideline 476/EU Method B.17. Mouse lymphoma L5178Y cells ($TK^{+/-}$) cells were exposed to benzoyl peroxide (74.6% purity in DMSO) at concentrations up to 100 µg/mL in the presence of metabolic activation and 50 µg/mL in the absence of metabolic activation. No increases in mutation frequency were observed in the presence and absence of metabolic activation (Klimisch 1, reliable without restriction).
  - *In vitro:* Negative results for clastogenicity were obtained in a chromosomal aberration assay; the test method and GLP compliance were not reported. Chinese hamster fibroblasts (CHL) were exposed to benzoyl peroxide (purity not reported) at concentrations up to 200 µg/mL in the absence of metabolic activation. There were no increases in the number of structural aberrations seen in the absence of metabolic activation (Klimisch 2, reliable with restrictions).
  - *In vitro:* Ambiguous results for clastogenicity were obtained in a chromosomal aberration assay conducted in method similar to OECD Guideline 473 (GLP compliance not reported). Human peripheral lymphocytes were exposed to benzoyl peroxide (purity not reported) at concentrations up to 100 µg/mL in the presence and absence of metabolic activation. Treatment induced a weak increase in the frequency of chromosomal aberrations and was cytotoxic at the highest test concentration (Klimisch 2, reliable with restrictions).
  - *In vitro:* Ambiguous results for clastogenicity were obtained in a mammalian cell micronucleus assay conducted in method similar to OECD Guideline 487 (GLP compliance not reported). Human peripheral lymphocytes were exposed to benzoyl peroxide (purity not reported) at concentrations up to 100 µg/mL in the presence and absence of metabolic activation. Treatment induced a weak increase in the frequency of micronuclei formation (Klimisch 2, reliable with restrictions).
  - *In vivo*: Negative results for clastogenicity were obtained in a GLP-compliant mouse micronucleus assay conducted according to OECD Guideline 474. Male ICR (SPF) mice (6/dose) were exposed to benzoyl peroxide (71.8% purity) at doses of 0, 50, 100, or 200 mg/kg via intraperitoneal (i.p.) injection. There were no increases in micronuclei formation seen at all doses levels (Klimisch 1, reliable without restriction).
- Based on the weight of evidence, benzoyl peroxide is not expected to be genotoxic. Although benzoyl peroxide was weakly clastogenic in an *in vitro* chromosomal aberration assay and in an *in vitro* mammalian cell micronucleus assay, an *in vivo* mouse micronucleus assay was negative for clastogenicity. As the *in vivo* study was negative, benzoyl peroxide is not expected to be mutagenic or genotoxic.

Reproductive Toxicity (R) Score (H, M, or L): *L*
Benzoyl peroxide was assigned a score of Low for reproductive toxicity based on the lack of effects on reproductive parameters seen in an OECD Guideline 422 study in rats. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when adequate negative data are available and they

are not GHS classified (CPA 2018b). The confidence in the score is low as it is based on results of a screening study that evaluates a limited number of relevant parameters.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* In a GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Sprague-Dawley rats (10/sex/dose) received doses of 0, 250, 500, and 1,000 mg/kg/day benzoyl peroxide (purity not reported) via gavage. Although not specifically mentioned, other sections of the study description suggest that a recovery group was also included. Males received doses during the premating period of 2 weeks then the mating period for 15 days for a total of 29 days; females received doses during the premating period of 2 weeks then mating, pregnancy, and 3 days of the lactation period for a total of 41-51 days. The systemic effects are discussed in the systemic toxicity (repeat) section below. Reproductive parameters evaluated include sperm parameters, litter observations, postmortem examinations of both parents and offspring, reproductive indices, and offspring viability indices, but fertility was not affected. One high dose male had reduced testes and epididymis eights and study authors considered this to be sporadic as opposed to treatment related. Severe testis atrophy was observed in one high dose male and minimal tests degeneration was observed in several high dose males; however, these effects are reversible in the recovery group, and fertility was not affected. Therefore, study authors did not consider this effect to be adverse. A reproductive NOAEL of 1,000 mg/kg/day was established, as there were no treatment-related effects seen on reproductive parameters (Klimisch 1, reliable without restriction).

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *M*
Benzoyl peroxide was assigned a score of Moderate for developmental toxicity based on incomplete ossification in a prenatal developmental toxicity study at 1,000 mg/kg/day in the presence of maternal toxicity and increased birthrate of runt and decreased body weight gain in an OECD 422 study in rats at 1,000 mg/kg/day in the absence of apparent maternal systemic toxicity. These effects warrant classification to GHS Category 2. GreenScreen® criteria classify chemicals as a Moderate hazard for developmental toxicity when they are classified to GHS Category 2 (CPA 2018b). The confidence in the score is reduced as effects were observed at a high dose of 1,000 mg/kg/day and maternal toxicity was observed in one of the two studies at this dose. Therefore, it could not be completely ruled out that the observed developmental effects are secondary to maternal toxicity.

- Authoritative and Screening Lists
  - Authoritative: Not present on any authoritative lists for this endpoint.
  - Screening: Not present on any screening lists for this endpoint.
- ECHA 2021
  - Oral: In a GLP-compliant developmental toxicity study conducted according to OECD Guideline 414, pregnant Sprague-Dawley rats (24/dose) received doses of 100, 300, and 1,000 mg/kg benzoyl peroxide (74.8% purity) in 0.5% methylcellulose gavage on gestation days (GD) 6-20. Parameters evaluated include maternal examinations, ovaries and uterine content, fetal examinations, and percentage pre- and post-implantation loss. There was a lower mean gravid uterus weight seen in high-dose animals; there were no other treatment-related effects seen in the maternal animals. In the fetuses, there was an increased number of litters with incomplete ossification of various parts of the skeleton seen in high-dose

animals. Based on these effects, a maternal and fetotoxic NOAEL of 300 mg/kg/day was established (Klimisch 1, reliable without restriction).

- *Oral:* In a GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Sprague-Dawley rats (10/sex/dose) received doses of 0, 250, 500, and 1,000 mg/kg/day benzoyl peroxide (purity not reported) via gavage. Males received doses during the premating period of 2 weeks then the mating period for 15 days for a total of 29 days; females received doses during the premating period of 2 weeks then mating, pregnancy, and 3 days of the lactation period for a total of 41-51 days. The systemic effects are discussed in the systemic toxicity (repeat) section below. Developmental parameters evaluated include sex ratio, body weight on postnatal day (PND) 0 and PND 4, and gross external, soft tissue and skeletal abnormalities. High dose offspring had a significant decrease in body weight gain and increase in birthrate of runt. A developmental NOAEL of 500 mg/kg/day was established by the study authors (Klimisch 1, reliable without restriction).

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

Benzoyl peroxide was assigned a score of Data Gap for endocrine activity based on a lack of sufficient data for this endpoint. While *in silico* modeling and *in vitro* high throughput receptor reactivity screening data do not suggest a concern for interaction with the estrogen, androgen, and thyroid pathways, no *in vivo* data are available that measured endocrine levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- U.S. EPA 2021b
  - Benzoyl peroxide was active in 0/28 estrogen receptor (ER) assays, 0/10 androgen receptor (AR) assays, 0/2 steroidogenesis assays, and 0/6 thyroid receptor assays performed as part of the U.S. EPA's Endocrine Disruptor Screening Program (EDSP) in the 21st Century.
- DTU 2021 (only results that are in domain are described below)
  - Benzoyl peroxide and its predicted metabolites have no structural alerts for estrogen receptor binding (Appendix D).
  - Benzoyl peroxide is predicted to be negative for estrogen receptor α binding (full and balanced training set, human *in vitro*) by the model batteries consisting of in domain and negative predictions by Leadscope and SciQSAR.
  - Benzoyl peroxide is predicted to be negative for estrogen receptor α activation in two models by Leadscope (human *in vitro* and CERAPP data *in vitro*)
  - Benzoyl peroxide is predicted to be negative for androgen receptor inhibition (human *in vitro*) by the model battery consisting of negative and in domain predictions by Case Ultra, Leadscope and SciQSAR (Appendix D).
  - Benzoyl peroxide is predicted to be negative for androgen receptor binding, inhibition and activation (CoMPARA data *in vitro*) by the Leadscope model (Appendix D).
  - Benzoyl peroxide is predicted to be negative for thyroperoxidase (TPO) inhibition QSAR 2 (rat *in vitro*) model in Leadscope (Appendix D).

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

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

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

Benzoyl peroxide was assigned a score of Low for acute toxicity based on oral LD_{50} values >2,000 mg/kg and an inhalation (dust) LC_{50} >24.3 mg/L. GreenScreen® criteria classify chemicals as a low hazard for acute toxicity when oral LD_{50} values >2,000 mg/kg and inhalation (dust) LC_{50} >5 mg/L (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* LD_{50} >2,000 mg/kg, GLP-compliant, OECD Guideline 401, ICR mouse, male and female (Klimisch 1, reliable without restriction)
  - *Oral:* LD_{50} >5,000 mg/kg, non-GLP compliant, no guideline followed, albino Spartan rat, male only (Klimisch 2, reliable with restrictions)
  - *Inhalation:* LC_{50} (4-hr) >24.3 mg/L (dust, whole body), non-GLP compliant, similar to OECD Guideline 403, albino Spartan rat, male only (Klimisch 2, reliable with restrictions)

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

Benzoyl peroxide was assigned a score of Moderate for systemic toxicity (single dose) based on respiratory irritation experienced by workers. No adverse systemic toxic effects were observed following acute oral and inhalation exposures in animal studies. This suggests classification to GHS Category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are classified to GHS Category 3 (CPA 2018b). The confidence in the score is high as it is based on reliable human data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
    - *Screening:* GHS Japan: H336 – Specific target organs/systemic toxicity following single exposure – Category 3 (respiratory irritation): based on nose and throat irritation experienced humans (NITE 2006).
- ECHA 2021
  - *Oral:* A GLP-compliant study conducted according to OECD Guideline 401 found no deaths or adverse effects on clinical signs, body weight development, and gross pathology examinations when male and female ICR mice (5/sex) received benzoyl peroxide (79% purity) in 0.5% methylcellulose via gavage at 2,000 mg/kg = (Klimisch 1, reliable without restriction).
  - *Oral:* A non-GLP compliant study conducted according to no specified guidelines found no deaths or adverse effects on clinical signs and body weight development (gross pathology not performed) when male albino Spartan rats (n=5) received benzoyl peroxide (78% purity) in corn oil via gavage at 5,000 mg/kg (Klimisch 2, reliable with restrictions).
  - *Inhalation:* In a non-GLP compliant study according to a guideline similar to OECD Guideline 403, male albino Spartan rats were exposed to benzoyl peroxide (78% purity) via inhalation of a dust. Animals (n=10) were exposed whole body to 24.3 mg/L air continuously for 4 hours. This concentration was chosen as the physical properties of the

test material prohibited exposure of the test animals to the highest atmospheric concentrations, and no deaths or adverse effects on clinical signs and body weights were noted over the 14-day observation period (Klimisch 2, reliable with restrictions).

- HSDB 2018
  - Overexposure to benzoyl peroxide may cause irritation to the mucus membranes.
  - In a study of occupational experience at an industrial plant processing benzoyl peroxide formulations, dust concentrations of 1.34-5.25 mg/m^3 benzoyl peroxide did not lead to any symptoms by workers. However, concentrations of 12.2 mg/m^3 and above caused pronounced irritation of the nose and throat.

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

Benzoyl peroxide was assigned a score of Low for systemic toxicity (repeated dose) based on ToxServices not classifying it under GHS criteria for this endpoint. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when adequate data are available and they are not classified under GHS (CPA 2018b). The confidence in the score is high as it is based on reliable experimental data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021, JECFA 2006
  - *Oral:* A non-GLP compliant combined feeding toxicity and carcinogenicity study was conducted according to an unspecified guideline. Male and female albino rats (25/sex/dose) were fed a diet containing 28, 280, and 2,800 mg benzoyl peroxide/kg diet (equivalent to 1.9, 19, or 190 mg/kg bw/day in males and 2.3, 23, and 230 mg/kg bw/day in females, respectively) for 80 weeks. Body weight gains of rats were noted weekly for the first 18 weeks, and then monthly; animals were examined twice daily regarding general health; and animals were examined for benign and malignant tumors. The carcinogenic effects were discussed in the Carcinogenicity section above. Any treatment-related effects seen were considered to be limited and/or indirect effects; therefore, a systemic NOAEL of 190 mg/kg/day was established (Klimisch 2, reliable with restrictions).
    - As the study is longer than 90 days, the oral GHS Category 2 guidance value of 100 mg/kg/day is adjusted to 16.25 mg/kg/day (100 mg/kg/day x 13 weeks/80 weeks). As the NOAEL of 190 mg/kg/day is greater than the duration-adjusted guidance value, benzoyl peroxide is not classified under GHS.
- ECHA 2021
  - *Oral:* In a GLP-compliant combined repeated dose toxicity study with reproduction/developmental toxicity screening test conducted according to OECD Guideline 422, male and female Sprague-Dawley rats (10/sex/dose) received doses of 0, 250, 500, and 1,000 mg/kg/day benzoyl peroxide (purity not reported) via gavage. Males received doses during the premating period of 2 weeks then the mating period for 15 days for a total of 29 days; females received doses during the premating period of 2 weeks then mating, pregnancy, and 3 days of the lactation period for a total of 41-51 days. Although not specifically mentioned, other sections of the study description suggest that a recovery group was also included. The reproductive effects are discussed in the reproductive toxicity section above. Parameters evaluated include clinical observations and body weight, organ weights, hematology and clinical chemistry, gross pathology, and histopathology. No

relevant treatment-related effects were seen. *ToxServices identified a NOAEL of 1,000 mg/kg/day, the highest dose tested, for systemic toxicity.*

- As the study is less than 90 days, the oral GHS Category 2 guidance value of 100 mg/kg/day is adjusted to 300 mg/kg/day (100 mg/kg/day x 3 months/ 1 month, as 29 days is approximately 1 month). As the NOAEL of 1,000 mg/kg/day is greater than the duration-adjusted guidance value, benzoyl peroxide is not classified under GHS.

- *Dermal:* A GLP-compliant dermal chronic toxicity study was conducted according to OECD Guideline 451. Male and female B6C3F1 mice (60/sex/dose) were administered doses of dibenzoyl peroxide (purity not reported) in aqueous Carbopol gel at concentrations of 1, 5, and 15/25% (equivalent to 33, 166, and 833 mg/kg/day in males and 40, 200, and 1,000 mg/kg/day in females, respectively according to the ECHA record) 7 days a week for at least 104 weeks. The test substances were applied topically once a day to a 2x3 cm area on the dorsal side of mice. Parameters evaluated include body weights, food consumption, macroscopic and microscopic observations, and organ weights. There were no treatment-related effects seen at all dose levels; therefore, a NOAEL of 833 mg/kg/day was established (Klimisch 1, reliable without restriction).
  - As the study is longer than 90 days, the dermal GHS Category 2 guidance value of 200 mg/kg/day is adjusted to 25 mg/kg/day (200 mg/kg/day x 13 weeks/104 weeks). As the NOAEL of 833 mg/kg/day is greater than the duration-adjusted guidance value, benzoyl peroxide is not classified under GHS.
- *Dermal:* A GLP-compliant dermal chronic toxicity study was conducted according to OECD Guideline 451. Male and female Fischer 344 rats (60/sex/dose) were administered doses of dibenzoyl peroxide (purity not reported) in aqueous Carbopol gel at concentrations of 1.67, 5, and 15% (equivalent to 11, 33, and 100 mg/kg/day in males and 17, 50, and 150 mg/kg/day in females, respectively according to ECHA record) 7 days a week for at least 104 weeks. The test substances were applied topically daily at a volume of 0.3 mL. Parameters evaluated include body weights, food consumption, macroscopic and microscopic observations, and organ weights. There were no treatment-related effects seen at all dose levels; therefore, a NOAEL of 100 mg/kg/day was established (Klimisch 1, reliable without restriction).
  - As the study is longer than 90 days, the dermal GHS Category 2 guidance value of 200 mg/kg/day is adjusted to 25 mg/kg/day (200 mg/kg/day x 13 weeks/104 weeks). As the NOAEL of 100 mg/kg/day is greater than the duration-adjusted guidance value, benzoyl peroxide is not classified under GHS.

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

Benzoyl peroxide was assigned a score of Low for neurotoxicity (single dose) based on a lack of effects on clinical signs and gross pathology suggestive of neurotoxicity in acute toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (single dose) when they are not classified under GHS for neurotoxicity (CPA 2018b). The confidence in the score is low as specific neurotoxicity examinations are not carried out in standard acute toxicity studies.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - *Oral:* A GLP-compliant study conducted according to OECD Guideline 401 found no deaths or adverse effects on clinical signs, body weight development, and gross pathology examinations when male and female ICR mice (5/sex) received benzoyl peroxide (79%

purity) in 0.5% methylcellulose via gavage at 2,000 mg/kg (Klimisch 1, reliable without restriction).
    - *Oral:* A non-GLP compliant study conducted according to no specified guidelines found no deaths or adverse effects on clinical signs and body weight development (gross pathology not performed) when male albino Spartan rats (n=5) received benzoyl peroxide (78% purity) in corn oil via gavage at 5,000 mg/kg (Klimisch 2, reliable with restrictions).
    - *Inhalation:* In a non-GLP compliant study according to a guideline similar to OECD Guideline 403, male albino Spartan rats were exposed to benzoyl peroxide (78% purity) via inhalation of a dust. Animals (n=10) were exposed whole body, and exposed to 24.3 mg/L air continuously for 4 hours. This concentration was chosen as the physical properties of the test material prohibited exposure of the test animals to the highest atmospheric concentrations, and no deaths or adverse effects on clinical signs and body weights were noted over the 14-day observation period (Klimisch 2, reliable with restrictions).

Neurotoxicity (repeated dose, N-repeated) (Group II*) Score (H, M, or L): DG
Benzoyl peroxide was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of data for this endpoint.

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

Skin Sensitization (SnS) (Group II*) Score (H, M, or L): H
Benzoyl peroxide was assigned a score of High for skin sensitization based on being listed with EU GHS H-Statement H317 and classified as Category 1A (EC3 < 2%) based on a positive result in a local lymph node assay in mice. GreenScreen® criteria classify chemicals as a High hazard for skin sensitization when classified as Category 1A and listed on EU GHS with H-Statement H317 (CPA 2018b). The confidence in the score is high as it is on an authoritative list and is based on reliable experimental data.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU GHS: H317 – May cause an allergic skin reaction (Skin sensitization – Category 1)
    - *Screening:*
        - GHS (Japan, Korea, Australia, Malaysia): H317 – May cause an allergic skin reaction (Skin sensitization – Category 1).
        - GHS New Zealand: 6.5B (Contact) – Contact sensitizers (Category 1)
- ECHA 2021
    - In a GLP-compliant local lymph node assay (LLNA) conducted according to OECD Guideline 429 (GLP compliance not reported), benzoyl peroxide (70% purity) was applied to CBA female mice (5/dose) at concentrations of 0.5, 1, 2.5, 5, and 10% in acetone. Benzoyl peroxide was found to be a skin sensitizer under the conditions of this study, with stimulation indices (SIs) of 14.6-24.4, 17.2-22.8, 18.1-33.7, 20.2-31.4, and 18.6% at the 0.5, 1, 2.5, 5, and 10% concentrations, respectively. As all SI values are greater than 3, an EC3 value could not be calculated. Therefore, a GHS score of Category 1A is assigned (Klimisch 1, reliable without restriction). *As the SI was > 3 even at the lowest concentration of 0.5%, ToxServices concludes that the EC3 value is <0.5%. Therefore, benzoyl peroxide is classified to GHS Category 1A (EC3 <2) (UN 2019).*

- In a Buehler assay conducted according to OECD Guideline 406 (GLP compliance not reported), benzoyl peroxide (purity not reported) at a concentration of 10% was applied to the skin of 20 guinea pigs (sex and strain not reported) under epicutaneous and occlusive conditions. One patch per week was applied to the dorsal surface of animals for three weeks. The challenge dose was applied at a 10% concentration after an undisclosed time frame after the last induction dose. Eight of the 20 animals were found to have positive reactions. Under the test conditions, benzoyl peroxide was considered as sensitizing in the Buehler assay and would be classified as a skin sensitizer according to the threshold defined by the CLP regulation and the directive 67/548/EC (>15%) (Klimisch 2, reliable with restrictions). *Based on 40% reaction rate at 10% induction dose, ToxServices classified benzoyl peroxide to GHS Category 1B (15 – 60% reaction rate at topical induction dose of 0.2 – 20% (UN 2019).*

Respiratory Sensitization (SnR) (Group II*) Score (H, M, or L): DG
Benzoyl peroxide was assigned a score of Data Gap for respiratory sensitization based on positive skin sensitization results and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- OECD 2020a
  - Benzoyl peroxide does not contain any structural alerts for respiratory sensitization (Appendix E).
- No data were identified for the target compound for this endpoint. Therefore, ToxServices attempted to evaluate the respiratory sensitization potential of benzoyl peroxide according to ECHA's guideline (ECHA 2017), which states that the mechanisms leading to respiratory sensitization are essentially similar to those leading to skin sensitization (ECHA 2017). ECHA recommended that if a chemical is not a dermal sensitizer based on high quality data, it is unlikely to be a respiratory sensitizer. ECHA also noted that this rationale does not cover respiratory hypersensitivity caused by non-immunological mechanisms, for which human experience is the main evidence of activity (ECHA 2017). Benzoyl peroxide does not contain any structural alerts, but is a skin sensitizer based on positive experimental data. According to the ECHA guidance, the positive skin sensitization results in animals and lack of structural alerts and evidence of respiratory sensitization indicate that there is insufficient positive data for the chemical to be classified as a respiratory sensitizer. However, the guidance requires negative skin sensitization data in order to conclude that the chemical is not a respiratory sensitizer. GreenScreen® criteria require negative data in order to assign a Low (i.e., a lack of alerts is not sufficient). Due to the positive experimental skin sensitization results and uncertainty regarding whether the mechanisms of sensitization could correspond to respiratory sensitization, a Data Gap was assigned.

Skin Irritation/Corrosivity (IrS) (Group II) Score (vH, H, M, or L): *L*
Benzoyl peroxide was assigned a score of Low for skin irritation/corrosivity based on the absence of skin irritation seen in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available, studies are negative, and is not GHS classified (CPA 2018b). The confidence in the score is low as the highest concentration tested was 78%.

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

- ECHA 2021
    - In a skin irritation study conducted according to a method similar to OECD Guideline 404 (GLP compliance not reported), three male and three female New Zealand white rabbits were administered benzoyl peroxide (78% purity) at an undisclosed dose on abraded and intact skin for four hours under semiocclusive conditions. Skin was examined 24, 48, and 72 hours after the removal of the dressing. The mean erythema and edema scores were 0 in all six animals when measured up to 72 hours after treatment. The study authors concluded that benzoyl peroxide was not irritating to skin (Klimisch 2, reliable with restrictions).
    - In a skin irritation study following the method for a 24-hour patch test (GLP compliance not reported), ten rabbits (sex and strain not reported) were administered benzoyl peroxide (purity not reported) at concentrations of 0.1, 1, 5, 10, 15, and 30% on shaved skin for 24 hours under occlusive conditions. Skin was examined immediately after the dressing was removed. Scores for individual animals were not reported. Instead, study authors calculated a concentration leading to an irritant reaction in 50% animals (IC50) of 2.52%, the number of days necessary to induce irritation in 50% of the animals after daily application (IT50) of 8.35 days. ECHA dossier authors concluded that benzoyl peroxide was slightly irritating but did not meet GHS classification criteria based on the results of this study (Klimisch 2, reliable with restrictions).

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

Benzoyl peroxide was assigned a score of Moderate for eye irritation/corrosivity based on being associated with EU GHS H-Statement H319. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when the chemical is associated with H-Statement H319 (CPA 2018b). The confidence in the score is high as it is based on its presence on an authoritative list.

- Authoritative and Screening Lists
    - *Authoritative:*
        - EU GHS: H319 – Causes serious eye irritation (Serious eye damage/eye irritation – Category 2A)
    - *Screening:*
        - GHS (Australia, Malaysia, Japan): H319 – Causes serious eye irritation (Serious eye damage/eye irritation – Category 2A)
        - GHS New Zealand: 6.4A – Irritating to the eye (Category 2A)
- ECHA 2021
    - In a GLP-compliant eye irritation study conducted according to OECD Guideline 405, eyes of four male New Zealand white rabbits were instilled with 100 mg benzoyl peroxide (70% purity) into the conjunctival sac of the left eye; the eyes of three animals were washed 30 seconds after instillation, while the eye of the fourth animal was not rinsed. Eyes were observed from 1 hour to 72 hours post-instillation. In the animals with rinsed eyes, there were no clinical signs seen. In the animal whose eye was not rinsed, an opaque cornea was observed until 48 hours after treatment, as well as deepened rugae in the iris after 48 hours and redness, swelling, and excrement in the conjunctivae; these effects were reversed after 72 hours. Based on these effects, benzoyl peroxide was found to be a slight ocular irritant (Klimisch 1, reliable without restriction).
    - In an eye irritation study conducted according to U.S. FDA 21 CFR §119 (GLP compliance not reported), eyes of New Zealand white rabbits (sex not reported) were instilled with 0.1 mL of benzoyl peroxide (78% purity) into the conjunctival sac of the right eye; 5 rabbits had their eyes rinsed after 5 minutes, and 3 had their eyes rinsed after 24 hours. Eyes were observed at 1, 24, 48, 72 hours, and 7 days post-instillation. In the first group, there was

very minor conjunctivitis and swelling seen in 1 of 5 and 2 of 5 animals respectively, but it cleared in 24 hours. In the second group, there was grade 2 redness in 2 of 3 animals at 48 hours, but it degraded to grade 1 at 72 hours, and completely cleared by day 7. Based on the results in the second group of animals, benzoyl peroxide was determined to be a moderate ocular irritant (Klimisch 2, reliable with restrictions).

Ecotoxicity (Ecotox)

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

Benzoyl peroxide was assigned a score of Very High for acute aquatic toxicity based on L/EC_{50} values of 0.06 mg/L, 0.11 mg/L, and 0.042-0.071 mg/L in fish, daphnid, and algae, respectively. GreenScreen® criteria classify chemicals as a Very High hazard for acute aquatic toxicity when L/C_{50} values are <1 mg/L (CPA 2018b). The confidence in the score is high as measured data are available for all three trophic levels.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:*
    - GHS New Zealand: 9.1D (algal, crustacean, fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action.
- ECHA 2021
  - 96-hour mortality LC_{50} (*Oncorhynchus mykiss*) = 0.06 mg/L (GLP-compliant, EU Method C.1/OECD Guideline 203) (Klimisch 1, reliable without restriction)
  - 48-hour mobility EC_{50} (*Daphnia magna)* = 0.11 mg/L (GLP-compliant, EU Method C.2/OECD Guideline 202) (Klimisch 1, reliable without restriction)
  - 72-hour growth rate EC_{50} (*Pseudokirchneriella subcapitata*, algae) = 0.071 mg/L (GLP-Compliant, EU Method C.3/OECD Guideline 201) (Klimisch 1, reliable without restriction)
  - 72-hour cell number EC_{50} (*P. subcapitata*, algae) = 0.042 mg/L (GLP-Compliant, EU Method C.3/OECD Guideline 201) (Klimisch 1, reliable without restriction)
  - 72-hour yield EC_{50} (*P. subcapitata*, algae) = 0.042 mg/L (GLP-Compliant, EU Method C.3/OECD Guideline 201) (Klimisch 1, reliable without restriction)

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

Benzoyl peroxide was assigned a score of Very High for chronic aquatic toxicity based on chronic NOEC values of 0.076 mg/L, and 0.001 mg/L in algae and daphnid, respectively. GreenScreen® criteria classify chemicals as a Very High hazard for chronic aquatic toxicity when NOEC values are <0.1 mg/L (CPA 2018b). The confidence in the score is high as measured data are available to assign the most conservative score.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - 21-day reproduction EC_{10} (*D. magna*) = 0.001 mg/L (GLP-Compliant, OECD Guideline 211) (Klimisch 1, reliable without restriction)
  - 72-hour growth rate, cell number, and yield NOEC (*P. subcapitata*, algae) = 0.02 mg/L (GLP-Compliant, EU Method C.3/OECD Guideline 201) (Klimisch 1, reliable without restriction)

Environmental Fate (Fate)

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

Benzoyl peroxide was assigned a score of Low for persistence based on it reaching the pass level of 60% and meeting the 10-day window in an OECD 301D test, and on being predicted to mainly partition to sediment. GreenScreen® criteria classify chemicals as a Low hazard for persistence when Very Low hazard for persistence when they meet the 10-day window in ready degradability studies and mainly partition to water, soil or sediment (CPA 2018b). The confidence in the score is high as it is based on reliable measured data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301D (Closed Bottle Test) was performed with secondary activated sludge (non-adapted) exposed to benzoyl peroxide (purity not reported) at 2 mg/L for 28 days. At the end of the exposure period, the level of degradation was 71%, with over 60% biodegradation occurring in 10 days (Klimisch 1, reliable without restriction).
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301D (Closed Bottle Test) was performed with activated domestic sludge (non-adapted) exposed to benzoyl peroxide (purity not reported) at 4 mg/L for 28 days. At the end of the exposure period, the level of degradation was 68%. According to the guidelines, benzoyl peroxide is not readily biodegradable, as the 10-day biodegradation window was not met. However, as the pass criteria was met, benzoyl peroxide is inherently biodegradable (Klimisch 1, reliable without restriction).
  - A GLP-compliant ready biodegradability test conducted according to OECD Guideline 301D (Closed Bottle Test) was performed with secondary activated domestic sludge (adapted) exposed to benzoyl peroxide (purity not reported) at 1,000 mg/L for 28 days. At the end of the exposure period, the level of biodegradation was 56%, meaning that benzoyl peroxide is not readily biodegradable (Klimisch 2, reliable with restrictions).
- U.S. EPA 2017
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that benzoyl peroxide is not expected to be readily biodegradable. Fugacity modeling (MCI method) predicts 24.6% will partition to water with a half-life of 37.5 days, 0.155% will partition to sediment with a half-life of 337.5 days, and 73.4% will partition to soil with a half-life of 75 days (Appendix F).
- Based on the weight of evidence, a score of Very Low was assigned. Available ready biodegradability studies indicate benzoyl peroxide is degradable. Per OECD guidance, when conflicting data are available from multiple biodegradability tests, the positive tests (i.e., readily biodegradable) of acceptable reliability could be considered valid regardless of the negative studies (OECD 2001). Therefore, the score for this endpoint is based on the best-performing tests. In the best-performing test, an OECD 301D study, benzoyl peroxide met the pass level, and met the 10-day window.

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

Benzoyl peroxide was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 2.3. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the

measured log Kow is <4 (CPA 2018b). The confidence in the score is high as it is based on measured log K_{ow} data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists for this endpoint.
  - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
  - Log K_{ow} = 2.3 (measured)
- U.S. EPA 2017
  - BCFBAF predicts a BCF/BAF of 15.29 using the regression-based model based on a measured log K_{ow} of 2.3, and a BCF of 14.84 using the Arnot-Gobas model for the upper trophic level, taking metabolism into consideration (Appendix E).

Physical Hazards (Physical)

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

Benzoyl peroxide was assigned a score of Very High for reactivity based on being associated with EU GHS H-Statement H241 for explosiveness and being a Type B organic peroxide. GreenScreen® criteria classify chemicals as a Very High hazard for reactivity when associated with EU H-phrase H241 (CPA 2018b). The confidence in the score was high as it is based on being listed on an authoritative list.

- Authoritative and Screening Lists
  - *Authoritative:*
    - EU GHS: H241 – Heating may cause a fire or explosion (Self-reactive substances and mixtures; Organic peroxides – Type B)
  - *Screening:*
    - GHS (Australia, Japan, Malaysia): H241– Heating may cause a fire or explosion (Self-reactive substances and mixtures; Organic peroxides – Type B)
    - GHS New Zealand: 5.2B – Organic peroxides– Type B
    - GHS New Zealand: 5.2B – Organic peroxides– Type C
    - Quebec CSST – WHMIS 1988 – Class C – Oxidizing Materials
    - Quebec CSST – WHMIS 1988 – Class F – Dangerously Reactive Materials
- ECHA 2021
  - Benzoyl peroxide can explode spontaneously when dry (<1% water) (Klimisch 2, reliable with restrictions).
  - Benzoyl peroxide may explode spontaneously when heated above its melting point or when overheated under confinement. It is moderately sensitive to heat, shock, friction, or contact with combustible materials. Explosive decomposition above the melting point forms flammable products (Klimisch 2, reliable without restrictions).
  - Decomposition above the melting point is instantaneous and explosive (Klimisch 2, reliable without restrictions).

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

Benzoyl peroxide was assigned a score of Low for flammability based on its flammability and explosivity having been accounted for under the reactivity endpoint. GreenScreen® criteria classify chemicals as a Low hazard for flammability when they are not classified under GHS as flammable solids, aerosols, or pyrophoric solids (CPA 2018b). The confidence in the score is low as no experimental data are available.

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

    - *Screening:* Not present on any screening lists for this endpoint.
- ECHA 2021
    - Benzoyl peroxide is flammable and decomposes upon heating (Klimisch 2, reliable without restrictions).
    - Benzoyl peroxide is highly flammable in the dry state (Klimisch 2, reliable without restrictions).
    - The study to determine the flammability of benzoyl peroxide is waived as it is an organic peroxide and is explosive. Organic peroxides are not classified as flammable solids. Based on the molecular structure and experience in handling the substance, benzoyl peroxide has no pyrophoric properties and does not react with water.

Use of New Approach Methodologies (NAMs)[11] in the Assessment, Including Uncertainty Analyses of Input and Output

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

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

As shown in Table 5, Type I (input data) uncertainties in benzoyl peroxide's NAMs dataset include lack of *in vivo* data for endocrine activity and respiratory sensitization, and lack of validated test methods for respiratory sensitization. Benzoyl peroxide's Type II (extrapolation output) uncertainties include the limitations of *in vitro* genotoxicity assays in mimicking *in vivo* metabolic systems, the uncertain *in vivo* relevance of *in silico* modeling and *in vitro* assays of endocrine receptor binding, the limitation of OECD Toolbox in identifying structural alerts without defining the applicability domain, and OECD Toolbox not accounting for non-immunologic mechanisms of respiratory sensitization. Some of benzoyl peroxide's type II uncertainties were alleviated by the use of *in vitro* test batteries and/or in combination of *in vivo* data.

Table 5: Summary of NAMs Used in the GreenScreen® Assessment, Including Uncertainty Analyses	
Uncertainty Analyses (OECD 2020b)	
Type I Uncertainty: Data/Model Input	**Endocrine activity:** No *in vivo* experimental data are available. **Respiratory sensitization**: No experimental data are available and there are no validated test methods.
Type II Uncertainty: Extrapolation Output	**Genotoxicity:** The bacterial reverse mutation assay (as defined in OECD Guideline 471) only tests point-mutation inducing activity in non-mammalian cells, and the exogenous metabolic activation system does not entirely mimic *in vivo* conditions[12]. The mammalian cell gene mutation assay (as defined in OECD Guideline 476) only detects gene mutations, and the exogenous metabolic activation system does not entirely mirror *in vivo*

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

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

	metabolism (i.e. the liver S9 mix contains enzymes present in the endoplasmic reticulum but not the cytosol of liver cells).[13] The *in vitro* chromosome aberration assay (OECD 473) does not measure aneuploidy and it only measures structural chromosomal aberrations. The exogenous metabolic activation system does not entirely mirror *in vivo* metabolism[14]. **Endocrine activity:** The *in vivo* relevance of *in silico* receptor binding activity prediction and *in vitro* receptor binding data is unclear due to lack of sufficient data on toxicokinetics. **Respiratory sensitization**: The OECD Toolbox only identifies structural alerts and does not define applicability domains. Additionally, the ECHA guidance (2017), on which the use of OECD Toolbox structural alerts is based, does not evaluate non-immunologic mechanisms for respiratory sensitization.	
Endpoint	**NAMs Data Available and Evaluated? (Y/N)**	**Types of NAMs Data (*in silico* modeling/*in vitro* biological profiling/frameworks)**
Carcinogenicity	N	
Mutagenicity	Y	*In vitro* data: Bacterial reverse mutation assay/*in vitro* gene mutation assay/*in vitro* chromosome aberration assay
Reproductive toxicity	N	
Developmental toxicity	N	
Endocrine activity	Y	*In silico* modeling: Danish QSAR; *In vitro* high throughput data: EDSP 21 data
Acute mammalian toxicity	N	
Single exposure systemic toxicity	N	
Repeated exposure systemic toxicity	N	
Single exposure neurotoxicity	N	
Repeated exposure neurotoxicity	N	
Skin sensitization	N	
Respiratory sensitization	Y	*In silico* modeling: OECD Toolbox structural alerts
Skin irritation	N	
Eye irritation	N	

[13] https://www.oecd-ilibrary.org/docserver/9789264264809-en.pdf?expires=1614097800&id=id&accname=guest&checksum=C0DE371FB9C5A878E66C9AB7F84E6BBE
[14] https://www.oecd-ilibrary.org/docserver/9789264264649-en.pdf?expires=1614098015&id=id&accname=guest&checksum=6A4F9CE52EA974F5A74793DD54D54352

Acute aquatic toxicity	N	
Chronic aquatic toxicity	N	
Persistence	N	
Bioaccumulation	N	

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APPENDIX A: Hazard Classification Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Benzoyl Peroxide (CAS #94-36-0)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Benzoyl peroxide / 94-36-0	L	L	*L*	*M*	DG	L	M	L	*L*	DG	H	DG	*L*	H	vH	vH	vL	vL	vH	*L*

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Benzoyl peroxide	2

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

Table 6

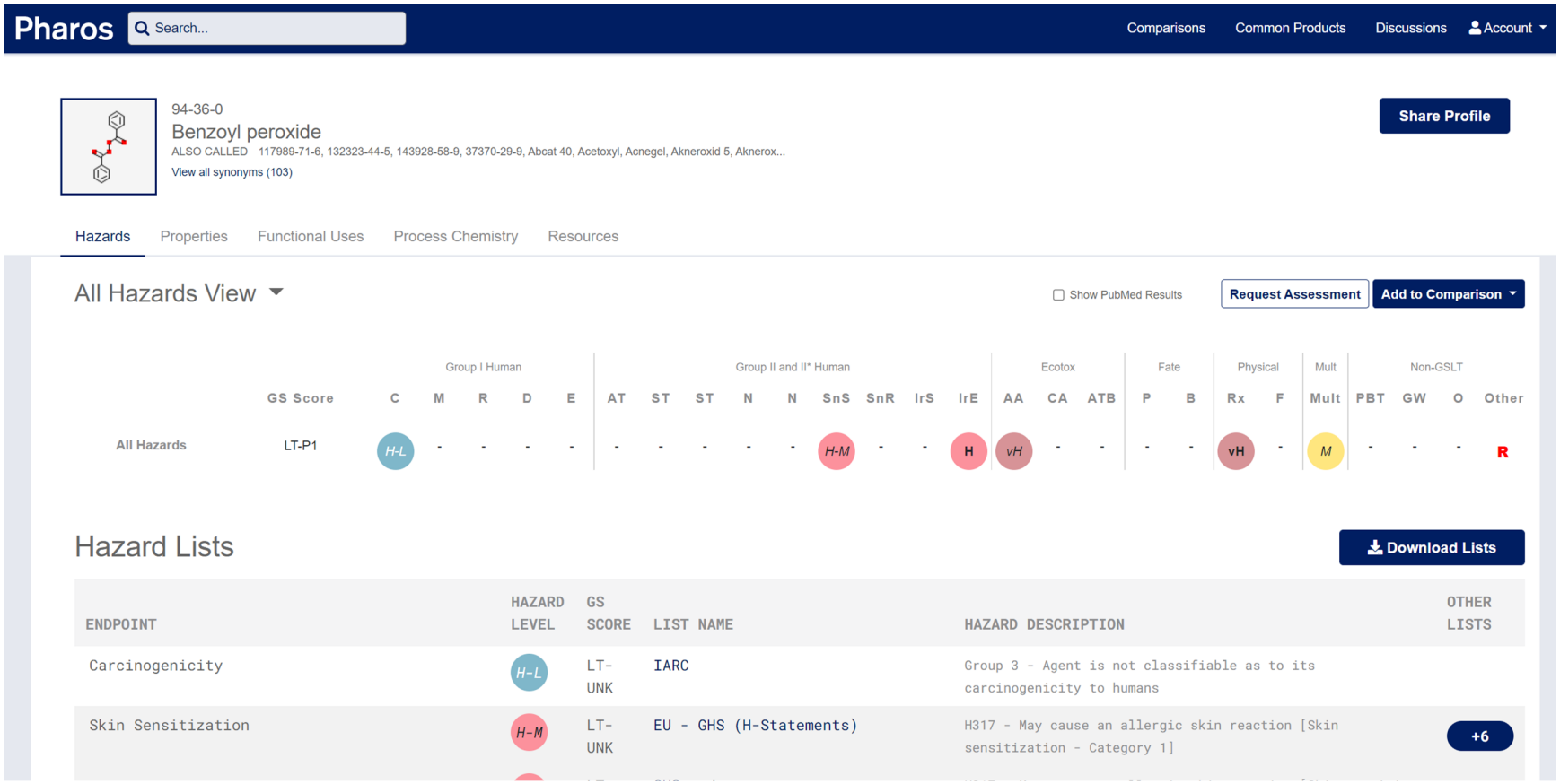
Chemical Name	Final GreenScreen® Benchmark Score
Benzoyl peroxide	2

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 Benzoyl Peroxide (CAS #94-36-0)



	H	LT-UNK	GHS - Japan	H317 - May cause an allergic skin reaction [Skin sensitizer - Category 1]	
	H	LT-UNK	GHS - Korea	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	H	LT-UNK	GHS - New Zealand	6.5B (contact) - Contact sensitisers (Cat. 1)	
	H-M	LT-UNK	GHS - Australia	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	H-M	LT-UNK	GHS - Malaysia	H317 - May cause an allergic skin reaction [Skin sensitization - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H317 - May cause an allergic skin reaction (unverified) [Skin sensitization - Category 1]	
Eye Irritation/Corrosivity	H	LT-UNK	EU - GHS (H-Statements)	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	+5
	H	LT-UNK	GHS - Australia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - Malaysia	H319 - Causes serious eye irritation [Serious eye damage/eye irritation - Category 2A]	
	H	LT-UNK	GHS - New Zealand	6.4A - Irritating to the eye (Cat. 2A)	
	H-M	LT-UNK	GHS - Japan	H319 - Causes serious eye irritation [Serious eye damage / eye irritation - Category 2]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H319 - Causes serious eye irritation (unverified) [Serious eye damage/eye irritation - Category 2A]	

Acute Aquatic Toxicity	vH	LT-UNK	GHS - Japan	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	+2
	vH	LT-UNK	GHS - Korea	H400 - Very toxic to aquatic life [Hazardous to the aquatic environment (acute) - Category 1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H400 - Very toxic to aquatic life (unverified) [Hazardous to the aquatic environment (acute) - Category 1]	
Reactivity	vH	LT-UNK	EU - GHS (H-Statements)	H241 - Heating may cause a fire or explosion [Self-reactive substances and mixtures; and Organic peroxides - Type or B]	+10
	vH	LT-UNK	GHS - Australia	H241 - Heating may cause a fire or explosion [Self-reactive substances and mixtures; and Organic peroxides - Type or B]	
	vH	LT-UNK	GHS - Japan	H241 - Heating may cause a fire or explosion [Organic peroxides - Type B]	
	vH	LT-UNK	GHS - Malaysia	H241 - Heating may cause a fire or explosion [Self-reactive substances and mixtures; and Organic peroxides - Type or B]	
	vH	LT-UNK	GHS - New Zealand	5.2B - Organic peroxides: type B	
	H	LT-UNK	GHS - New Zealand	5.2C - Organic peroxides: type C	
	vH-M	LT-UNK	Québec CSST - WHMIS 1988	Class C - Oxidizing materials	
	vH-M	LT-UNK	Québec CSST - WHMIS 1988	Class F - Dangerously reactive materials	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H201 - Explosive; mass explosion hazard (unverified) [Explosives - Division 1.1]	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H241 - Heating may cause a fire or explosion (unverified) [Self-reactive substances and mixtures; and Organic	

	pC	NoGS	EU - Manufacturer REACH hazard submissions	H242 - Heating may cause a fire (unverified) [Self-reactive substances and mixtures; and Organic peroxides - Types C or D or E or F]	
Human and/or Aquatic toxicity and/or Persistence and/or Bioaccumulation	U	LT-P1	German FEA - Substances Hazardous to Waters	Class 2 - Hazard to Waters	
Carcinogenicity,Mutagenicity/Genotoxicity Reproductive Toxicity, Developmental Toxicity, Acute Mammalian Toxicity, or System Toxicity/Organ Effects.	U	LT-UNK	Québec CSST - WHMIS 1988	Class D2B - Toxic material causing other toxic effects	
T & P and/or B [(Chronic Aquatic Toxicity and Persistence) or (Acute Aquatic Toxicity and Persistence and/or Bioaccumulation)]	U	LT-UNK	GHS - New Zealand	9.1D (algal) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	+3
	U	LT-UNK	GHS - New Zealand	9.1D (crustacean) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
	U	LT-UNK	GHS - New Zealand	9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action	
	pC	NoGS	EU - Manufacturer REACH hazard submissions	H410 - Very toxic to aquatic life with long lasting effects (unverified) [Hazardous to the aquatic environment (chronic) - Category 1]	
Systemic Toxicity/Organ Effects [Single Exposure] and/or Neurotoxicity [Single Exposure]	M	LT-UNK	GHS - Japan	H335 or H336 [Specific target organs/systemic toxicity following single exposure - Category 3]	
Acute aquatic toxicity; Chronic aquatic toxicity	U	LT-UNK	EC - CEPA DSL	Inherently Toxic in the Environment (iTE)	

Restricted Substance Lists (5)

- Cradle to Cradle Certified Products Standard Version 4.0 Restricted Substances List (RSL) - Effective July 1, 2021: Cosmetics & Personal Care Products
- EU - Cosmetics Regulation: Annex III - Restricted Substances
- EU - PACT-RMOA Substances: Substances selected for RMOA or hazard assessment
- Health Canada - Cosmetic Ingredient Hotlist: Ingredients that are Restricted for Use in Cosmetic Products
- MA Toxics Use Reduction Act (TURA) listed substances: Reportable Chemicals

APPENDIX D: Danish QSAR Predictions Output for Benzoyl Peroxide (CAS #94-36-0)

Endocrine and Molecular Endpoints

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Estrogen Receptor α Binding, Full training set (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Binding, Balanced Training Set (Human *in vitro*)		NEG_IN	NEG_OUT	NEG_IN	NEG_IN
Estrogen Receptor α Activation (Human *in vitro*)		NEG_OUT	NEG_OUT	NEG_IN	INC_OUT
Estrogen Receptor Activation, CERAPP data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition (Human *in vitro*)		NEG_IN	NEG_IN	NEG_IN	NEG_IN
Androgen Receptor Binding, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Inhibition, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Androgen Receptor Activation, CoMPARA data (*in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroperoxidase (TPO) inhibition QSAR1 (Rat *in vitro*)		N/A	N/A	NEG_OUT	N/A
Thyroperoxidase (TPO) inhibition QSAR2 (Rat *in vitro*)		N/A	N/A	NEG_IN	N/A
Thyroid Receptor α Binding (Human *in vitro*)					
- mg/L			38746.09	3373.944	15.17148
- µM			159955.8	13928.68	62.63254
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Thyroid Receptor β Binding (Human *in vitro*)					
- mg/L			7838.413	44.22297	9.62117
- µM			32359.38	182.566	39.71915
- Positive for IC_{50} ≤ 10 µM					
- Positive for IC_{50} ≤ 100 µM					
- Domain		OUT	OUT	OUT	OUT
Arylhydrocarbon (AhR) Activation – Rational final model (Human *in vitro*)		N/A	N/A	NEG_IN	N/A
Arylhydrocarbon (AhR) Activation –		N/A	N/A	NEG_IN	N/A

	Exp	Battery	CASE Ultra	Leadscope	SciQSAR
Random final model (Human *in vitro*)					
Pregnane X Receptor (PXR) Binding (Human *in vitro*)	N/A	INC_OUT	NEG_OUT	NEG_OUT	NEG_OUT
Pregnane X Receptor (PXR) Binding (Human *in vitro*) NEW	NEG	N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Pregnane X Receptor (PXR) Activation (Rat *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Activation at max. 50 µM (*in vitro*)	NEG	N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 20 µM (*in vitro*)		N/A	N/A	NEG_IN	N/A
Constitutive Androstane Receptor (CAR) Inhibition at max. 50 µM (*in vitro*)		N/A	N/A	NEG_OUT	N/A
CYP3A4 Induction (Human *in vitro*)	NEG	N/A	N/A	NEG_IN	N/A

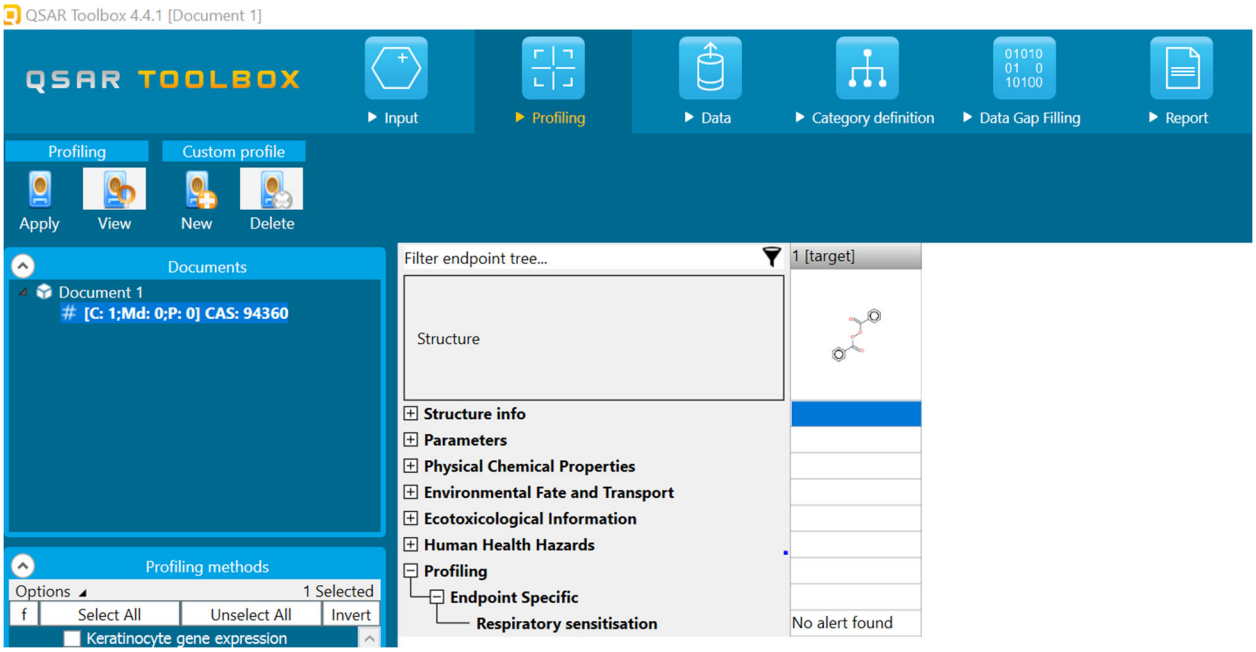
DTU-developed models

Estrogen Receptor Binding, alerts in:	
- parent only	Non binder, without OH or NH2 group
- metabolites from *in vivo* Rat metabolism simulator only	Non binder, without OH or NH2 group
- metabolites from Rat liver S9 metabolism simulator only	Non binder, without OH or NH2 group
rtER Expert System - USEPA, alerts in:	
- parent only	No alert found
- metabolites from *in vivo* Rat metabolism simulator only	No alert found
- metabolites from Rat liver S9 metabolism simulator only	No alert found

OECD QSAR Toolbox v.4.2 profilers

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

APPENDIX E: OECD Toolbox Respiratory Sensitization Results for Benzoyl Peroxide (CAS #94-36-0)



APPENDIX F: EPI Suite™ Modeling Results for Benzoyl Peroxide (CAS #94-36-0)

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

CAS Number: 94-36-0
SMILES : O=C(OOC(=O)c(cccc1)c1)c(cccc2)c2
CHEM : Peroxide, dibenzoyl
MOL FOR: C14 H10 O4
MOL WT : 242.23
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.30
Boiling Point (deg C) : ------
Melting Point (deg C) : 103.00
Vapor Pressure (mm Hg) : ------
Water Solubility (mg/L): ------
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.69 estimate) = 3.43
Log Kow (Exper. database match) = 3.46
Exper. Ref: SANGSTER (1993)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 328.57 (Adapted Stein & Brown method)
Melting Pt (deg C): -2.07 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 7.32E-005 (Modified Grain method)
VP (Pa, 25 deg C) : 0.00976 (Modified Grain method)
MP (exp database): 105 deg C
Subcooled liquid VP: 0.000423 mm Hg (25 deg C, Mod-Grain method)
: 0.0563 Pa (25 deg C, Mod-Grain method)

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 246
log Kow used: 2.30 (user entered)
melt pt used: 103.00 deg C
Water Sol (Exper. database match) = 9.1 mg/L (25 deg C)
Exper. Ref: CHEMICALS INSPECTION AND TESTING INSTITU (1992)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 394.52 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 3.54E-006 atm-m3/mole (3.59E-001 Pa-m3/mole)
Group Method: Incomplete

For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 9.484E-008 atm-m3/mole (9.610E-003 Pa-m3/mole)
VP: 7.32E-005 mm Hg (source: MPBPVP)
WS: 246 mg/L (source: WSKOWWIN)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.30 (user entered)
Log Kaw used: -3.839 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 6.139
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.8884
Biowin2 (Non-Linear Model) : 0.9596
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.7079 (weeks-months)
Biowin4 (Primary Survey Model) : 3.5080 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.1764
Biowin6 (MITI Non-Linear Model): 0.1010
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.3181
Ready Biodegradability Prediction: NO

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

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 0.0564 Pa (0.000423 mm Hg)
Log Koa (Koawin est): 6.139
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 5.32E-005
Octanol/air (Koa) model: 3.38E-007
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 0.00192
Mackay model : 0.00424
Octanol/air (Koa) model: 2.7E-005

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 3.5549 E-12 cm3/molecule-sec
Half-Life = 3.009 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 36.105 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
0.00308 (Junge-Pankow, Mackay avg)

2.7E-005 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 91.77 L/kg (MCI method)
Log Koc: 1.963 (MCI method)
Koc : 54.79 L/kg (Kow method)
Log Koc: 1.739 (Kow method)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Total Kb for pH > 8 at 25 deg C : 5.433E+004 L/mol-sec
Kb Half-Life at pH 8: 12.758 seconds
Kb Half-Life at pH 7: 2.126 minutes
(Total Kb applies only to esters, carbmates, alkyl halides)

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.185 (BCF = 15.29 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.8494 days (HL = 0.1414 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.172 (BCF = 14.84)
Log BAF Arnot-Gobas method (upper trophic) = 1.172 (BAF = 14.84)
log Kow used: 2.30 (user entered)

Volatilization from Water:
Henry LC: 3.54E-006 atm-m3/mole (estimated by Bond SAR Method)
Half-Life from Model River: 259 hours (10.79 days)
Half-Life from Model Lake : 2956 hours (123.2 days)

Removal In Wastewater Treatment:
Total removal: 2.83 percent
Total biodegradation: 0.10 percent
Total sludge adsorption: 2.54 percent
Total to Air: 0.20 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model: (MCI Method)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	**1.85**	**72.2**	**1000**
Water	**24.6**	**900**	**1000**
Soil	**73.4**	**1.8e+003**	**1000**
Sediment	**0.155**	**8.1e+003**	**0**

Persistence Time: 925 hr

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

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.85	72.2	1000
Water	24.6	900	1000
water	(24.6)		

biota (0.000245)
suspended sediment (0.00339)
Soil 73.4 1.8e+003 1000
Sediment 0.155 8.1e+003 0
Persistence Time: 925 hr

Level III Fugacity Model: (EQC Default)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	1.89	72.2	1000
Water	25.3	900	1000
water	(25.3)		
biota	(0.000252)		
suspended sediment	(0.00311)		
Soil	72.7	1.8e+003	1000
Sediment	0.148	8.1e+003	0

Persistence Time: 910 hr

APPENDIX G: Change in Benchmark Score

Table 6 provides a summary of changes to the GreenScreen® Benchmark™ for benzoyl peroxide. This GreenScreen® has undergone one round of update and the benchmark score remains the same.

Table 6: Change in GreenScreen® Benchmark™ for Benzoyl Peroxide

Date	GreenScreen® Benchmark™	GreenScreen® Version	Comment
August 17, 2021	BM-2	v. 1.4	New assessment
November 15, 2021	BM-2	v. 1.4	Minor updates without changing scores for any hazard endpoints.

Licensed GreenScreen® Profilers

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