EDF
ENVIRONMENTAL DEFENSE FUND™
Finding the ways that work

# Smart Innovation

## THE OPPORTUNITY FOR SAFER PRESERVATIVES

## ABOUT ENVIRONMENTAL DEFENSE FUND

The goal of the health program at Environmental Defense Fund (EDF) is to improve human and ecological health through reductions in exposure to harmful chemicals and pollution. EDF's health program uses the dual levers of public policy and corporate leadership to phase harmful substances and practices out of the market and introduce safer products and practices into mainstream use. We encourage and support innovations that work toward this end.

## ABOUT THIS REPORT

The Preservative Innovation Project (PIP) offers a framework to direct innovation for specific functional classes of chemicals (e.g., preservatives) in order to drive safer chemicals and products into the marketplace. The primary output of the framework is a uniformly-developed, baseline set of toxicological information for a representative set of chemicals in a functional class. Such baseline toxicological information can be used to inform design criteria for new chemical research and development (R&D); provide a basis of toxicological comparison for new chemicals entering the market; and direct additional chemical testing and research where data are lacking or insufficient. The PIP was led by Environmental Defense Fund, with input from several companies including Active Micro Technologies, Beautycounter, Clariant, and Seventh Generation as well as the Green Chemistry and Commerce Council. However, EDF is the sole author of this report. Organizations that provided input into its development should not be interpreted as endorsers of the content.

This report describes the PIP framework, and the findings and conclusions drawn from the toxicological evaluation of a subset of commercially available preservatives.

## ACKNOWLEDGEMENTS

EDF would like to thank ToxServices **(www.toxservices.com)** for its contribution to this report, including conducting GreenScreen® for Safer Chemicals assessments, providing project management support, and helping compile this report.

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# Executive Summary

More and more consumers, commercial purchasers, and retailers are seeking products that are responsibly and sustainably produced (Headwaters, 2016), and as part of this movement, are increasingly attentive to the potential health and environmental hazards of product ingredients. Recent reports show that the health impacts of products are a number one priority for consumers (Headwaters, 2016; UL, 2013). Finding ways to innovate safer ingredients and products is proving to be good for consumers and the environment, and for business growth. By using safer chemicals in products, retailers and manufacturers stay ahead of regulatory developments, better manage brand and financial risk, and demonstrate that they are responsive to consumer demand.

Some of the most important chemicals in consumer products today are preservatives. Preservatives play an important role in preventing microbial growth in products such as personal care products. However, certain preservatives have come under regulatory and market pressure for human health and environmental concerns (see Appendix A). Given these realities and the ubiquity of preservatives in products, the development of safer, effective preservatives is crucial and offers a prime opportunity for innovation.

## Did you know?

66%

of consumers worldwide are **willing to pay more** for sustainable products.

87%

of consumers globally say "uses no harsh chemicals or toxins" is a major driver when buying beauty and personal care products.

Many major retailers, including Walmart and Target, are creating or expanding upon chemical policies that ban or limit the use of toxic chemicals in the products they sell.

The lack of comprehensive, structured, transparent, and comparable toxicological information across different functional classes (e.g., preservatives) is a major obstacle to safer chemical innovation. Such baseline information is invaluable for setting safer chemical design criteria that chemical and product developers can use in their efforts to design or select safer chemicals.

EDF launched the Preservative Innovation Project (PIP) in 2015 to show the utility of generating baseline sets of toxicological information to guide chemical innovation efforts.

Focusing on preservatives used in personal care products, EDF assembled a small group of leading preservative suppliers and product manufacturers (PIP working group) to identify a set of 16 commercially available preservatives (PIP preservatives) on which to conduct a toxicological evaluation. Specifically, PIP preservatives were evaluated using the GreenScreen® for Safer Chemicals Method (GreenScreen®) — a comprehensive chemical hazard assessment method that has been used by government, public interest groups, researchers, and businesses alike to evaluate and characterize the potential hazards of chemicals.

## Meaningful baseline toxicological information should be the following:

### COMPREHENSIVE

An extensive set of human and ecological toxicity endpoints are evaluated.

### STRUCTURED

Data collection, assessment, and integration is accomplished in a consistent manner for all chemicals evaluated. Hazard characterizations are assigned according to pre-specified criteria.

### TRANSPARENT

The approach used to research hazard characterizations including how data are identified, collected, and integrated is clear, documented, and made available. Similarly, full chemical hazard assessments are made available.

### COMPARABLE

Hazard characterizations across all endpoints are presented in a consistent, accessible manner that allows for easy comparison.

# GreenScreen® for Safer Chemicals Method

In the GreenScreen® method, a licensed GreenScreen® assessor evaluates chemicals across 18 human health, environmental, and physical hazard endpoints and assigns a hazard score for each endpoint using prescribed criteria.

An indication of the degree of confidence in the assignment of a hazards score, based on the quality of the available data, is also provided. Where data are insufficient to assign a hazard score, the assessor will assign the endpoint as a Data Gap.

Finally, an overall toxicity 'Benchmark' score that integrates hazard scores and data gaps across all 18 endpoints is determined using a specified algorithm (CPA, 2011).

*CPA, 2011, 2012a, 2013 See Appendix C for a fuller description of GreenScreen®*

GreenScreen® is strictly a hazard assessment method, developed to rigorously evaluate the intrinsic hazard of chemicals. GreenScreen® does not assess how much exposure there may be to a given chemical, an important aspect in the evaluation of the overall risk a chemical may present to an individual or ecosystem. Often product manufacturers will manage chemical risk by limiting the amount of a chemical in a product, in other words, by managing the extent of exposure to the chemical. However, identification and use of ingredients with lower intrinsic hazard is an important and effective way to reduce overall potential health concerns. Individuals are often exposed to mixtures of chemicals presenting similar hazards, and certain subpopulations can be more susceptible than others to these exposures. Innovation efforts focused on creating inherently safer chemicals complement important restrictions on the amount of chemicals presenting hazard permitted in products—together reducing overall impacts to human health and the environment.

# Key Findings

## GreenScreen® evaluations of the 16 PIP preservatives yielded the following key findings:

- Several PIP preservatives scored Moderate to Very High for skin sensitization, skin irritation, eye irritation, and acute and chronic aquatic toxicity.
- Only one PIP preservative, DMDM hydantoin, received a High hazard score for a GreenScreen® Group I human health endpoint. Specifically, DMDM hydantoin scored High for carcinogenicity, as a result of its release of formaldehyde, a known human carcinogen. GreenScreen® Group I human health endpoints represent hazards that lead to chronic or life-threatening health effects that may result from low dose exposures and include carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, and endocrine activity (see Appendix C).
- Confidence in the assignment of hazard scores varied widely across the PIP preservatives. For any given preservative, endpoints assigned scores with high confidence ranged from two (caprylohydroxamic acid, Lactobacillus ferment, sorbitan caprylate) to 14 (methylisothiazolinone and piroctone olamine), with an average of ten endpoints assigned scores with high confidence.
- All PIP preservatives had data gaps for at least two hazard endpoints. The number of data gaps ranged from two (IPBC, methylisothiazolinone, propylparaben, and sorbic acid) to 13 (Lactobacillus ferment), and the average number of data gaps across the preservatives was four.
- Data gaps were consistently encountered in the assessment of endocrine activity, neurotoxicity, and respiratory sensitization.

*Endpoints often scored as Moderate to Very High*

| PIP PRESERVATIVE | HAZARD ENDPOINT | | | |
|---|---|---|---|---|
| | Skin sensitization | Skin irritation | Eye irritation | Acute and/or chronic aquatic toxicity |
| Benzyl alcohol | ● | | ● | |
| Caprylohydroxamic acid | | | ● | ● |
| Caprylyl glycol | | | ● | ● |
| DMDM Hydantoin | ● | ● | | ● |
| EDTA | | ● | ● | ● |
| Ethylhexylglycerin | ● | | ● | ● |
| Gluconolactone | | | | |
| IPBC | ● | | ● | ● |
| Lactobacillus ferment | | | | |
| Methylisothiazolinone | ● | ● | ● | ● |
| Phenoxyethanol | | | ● | |
| Piroctone olamine | | ● | ● | ● |
| Propylparaben | ● | ● | | ● |
| Sorbic acid | ● | ● | ● | ● |
| Sorbitan caprylate | | | | ● |
| Undecylenic acid | ● | ● | ● | ● |
| **TOTAL** | **8** | **7** | **11** | **12** |

## Overall GreenScreen® Benchmark (BM) scores for the PIP preservatives were as follows:

| | | |
|---|---|---|
| BENCHMARK 4 | Safer chemical | • None |
| BENCHMARK 3 | Use but still opportunity for improvement | • Caprylyl glycol<br>• Sorbitan caprylate |
| BENCHMARK 3DG | [Data gaps exist] Use but still opportunity for improvement[1] | • Gluconolactone |
| BENCHMARK 2 | Use but search for safer alternatives | • Benzyl alcohol • EDTA • Ethylhexylglycerin • IPBC<br>• Methylisothiazolinone • Phenoxyethanol • Piroctone olamine<br>• Propylparaben • Sorbic acid • Undecylenic acid |
| BENCHMARK 1 | Avoid - Chemical of high concern | • DMDM Hydantoin |
| BENCHMARK U | Unspecified due to insufficient data | • Caprylohydroxamic acid<br>• Lactobacillus ferment |

1 A Benchmark score of 3DG means that the chemical meets the hazard classification requirements of a Benchmark 4 but does not meet the data gap requirements; however, it does meet the data gap requirements for a Benchmark 3

The EDF Preservative Innovation Project was successful in identifying human and ecological hazard hotspots among the preservatives evaluated, such as skin sensitization and aquatic toxicity as well as identifying endpoints for which data were frequently lacking or insufficient, such as endocrine activity and neurotoxicity. The baseline information generated through the PIP can be used to set design criteria and define data needs for safer preservative R&D, as well as provide a basis of toxicological comparison for new preservatives entering the market.

One element not pursued in the PIP was a measure of performance—that is how well a particular chemistry provides the function of interest, in this case product preservation. Performance is key to evaluate when comparing safer alternative options. For example, a product manufacturer typically needs to prevent the growth of a broad spectrum of pathogenic microorganisms including certain bacteria, yeast, and molds. Because preservatives can be effective against some microorganisms and not others, a product manufacturer needs to consider preservative performance or efficacy alongside potential toxicity. Indeed, product manufacturers often use blends of preservative chemicals in their products to achieve broad spectrum preservation. Similarly, alternative preservative chemicals may be effective against the same microorganism but under different formulation conditions or at different concentrations, which in turn can impact product cost and toxicological risk. EDF was ultimately unable to pursue performance testing of the PIP preservatives due to funding and time constraints.

Full GreenScreen® reports are available **online.**

# Recommendations

## MAKE HAZARD A PRIORITY INNOVATION CRITERION.

Certain preservatives are under increased scrutiny by regulators, consumers, and the marketplace due to concerns around impacts to human health or the environment. Though safety is considered in the development of new chemicals, it is not often touted as the major benefit or driving force of innovation. EDF maintains that the development of inherently safer chemicals should be recognized as just as significant and innovative as the development of chemicals with improved performance. Innovation efforts focused on creating inherently safer chemicals complement important restrictions on the amount of potentially hazardous chemicals permitted in products—together reducing overall impacts to human health and the environment.

## TACKLE HAZARD HOTSPOTS.

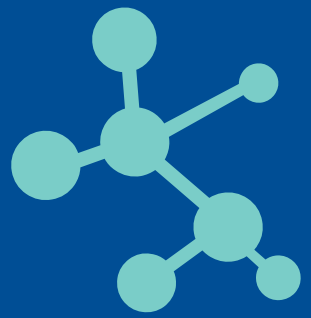
Preservative innovation efforts should focus on tackling identified hazard hotspots (i.e., endpoints that received the highest hazard scores in this assessment): skin sensitization, skin irritation, eye irritation, acute aquatic toxicity, and chronic aquatic toxicity.

## AVOID TRADING OFF HAZARDS.

While certain hazard endpoints were not identified as hazard hotspots for the preservatives evaluated in the PIP, as a general practice, chemical innovators should continue to consider all potential hazards in the development of new preservatives. This is to avoid the introduction of a new hazard while tackling another.

## Did you know?

The inherent hazard of a chemical is a critical component in evaluating its relative safety. The reduction of hazard is a defining element in the Twelve Principles of Green Chemistry and leading alternatives assessment methodologies.



**FOR MORE INFORMATION SEE:**

- National Academy of Sciences - A Framework to Guide Selection of Chemical Alternatives
- BizNGO - The Commons Principles for Alternatives Assessment
- Interstate Chemicals Clearinghouse - Alternatives Assessment Guide, Version 1.1
- U.S. Environmental Protection Agency - Design for the Environment (DfE) Alternatives Assessments

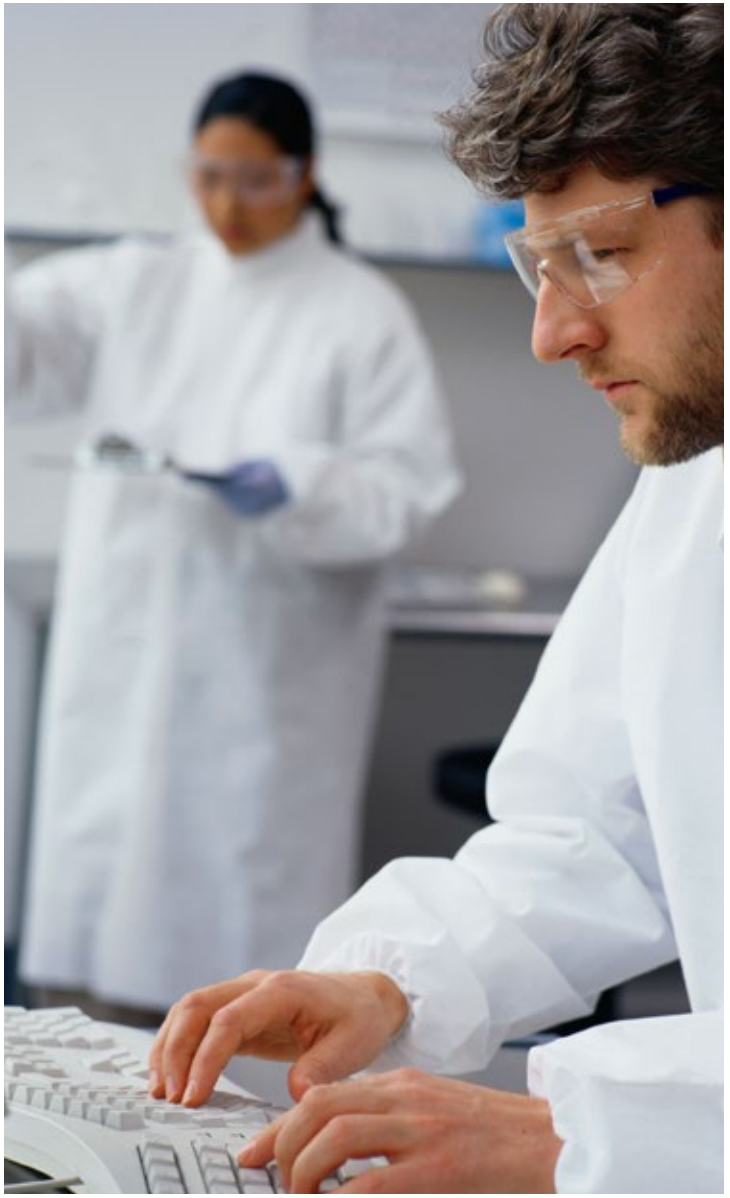
# Recommendations

## CREATE A CHEMICALS ASSESSMENT CLEARINGHOUSE.

EDF calls for the creation of an independent chemicals assessment clearinghouse that would provide comprehensive, structured, transparent, and comparable health and safety assessments of chemicals in a centralized, web-accessible repository. Operational standards would be established for qualifying assessors to develop and contribute assessments to the clearinghouse, ensuring quality assurance, and updating assessments to reflect the most current science—all with an eye toward producing assessments that are meaningful, actionable, and credible to actors along the supply chain. Such a clearinghouse would serve as a significant resource to various stakeholders looking to move the dial on safer chemistry, whether as a chemical innovator looking for information to inform design criteria or to show how a new chemistry represents an improvement over the status quo; as a product manufacturer searching for safer product formulation and fabrication options; or as a retailer interested in understanding what alternatives may be available for chemicals they are looking to move away from. Assessments from the clearinghouse would also indicate where toxicity data are lacking or insufficient, and thus where more chemical testing is needed. Finally, an independent chemical assessment clearinghouse holds the potential for participating parties to share the cost burden of producing objective, mutually desired and beneficial toxicological assessments of chemicals.

In sum, the framework employed in the EDF PIP provides valuable baseline toxicological information for preservative innovation, and can be similarly applied to other chemical functional classes.

Additional evaluation lenses, for example performance, could be included in future similar efforts so long as these evaluations are also conducted in a consistent and transparent manner. Ultimately an independent chemical assessment clearinghouse is needed to replicate the work of the PIP at scale across multiple chemical functional classes.



# Introduction

Recent reports show that the health impacts of products are a high priority for consumers (Headwaters, 2016; UL, 2013). At the same time market research shows increasing market growth opportunities in safer chemistry (ASBC, 2015). Finding ways to innovate safer chemicals and products is proving to be good for consumers and the environment, and for business growth. By using safer chemicals in products, retailers and manufacturers can get ahead of regulatory developments, better manage brand and financial risk, and demonstrate that they are responsive to consumer demand.

One major obstacle facing chemical innovation is the lack of widely-available baseline sets of toxicological information across different chemical functional classes that are comprehensive, structured, transparent, and comparable. Such baseline toxicological information can be used to develop data-driven criteria or benchmarks for safer chemical design, or selection, during chemical and product R&D respectively.

## Meaningful baseline toxicological information should be the following:

- ✓ COMPREHENSIVE
- ✓ STRUCTURED
- ✓ TRANSPARENT
- ✓ COMPARABLE

“Although the investment in safer chemistry is nascent and difficult to quantify, there are signs that it is growing. The rise in patents for more sustainable chemistry based on a search of US Patent and Trademark Office records shows increasing momentum and evolving industry capacity. Interest by investors of various types in advanced materials and technological innovation further underscores how capital could flow toward safer chemistry in the future.”

(ASBC, 2015, pg. 9)

**CHECK OUT THESE CASE STUDIES** of leading companies that have found opportunity in safer chemistry:

- AkzoNobel
- Seventh Generation
- Panera Bread

## In 2015, EDF launched the Preservative Innovation Project (PIP) to pilot a framework to address this need. The core steps of the framework are:

- Identify a chemical functional class (e.g., preservatives) and corresponding use scenario (e.g., personal care products) for which innovation is desired owing to human health or ecological concerns
- Conduct chemical hazard assessments (e.g., GreenScreen® for Safer Chemicals method) on a representative subset of chemicals in the identified chemical functional class

## The results of chemical hazard assessments provide:

- Input into the development of design criteria for safer chemical innovation through the identification of hazard hotspots
- A basis of toxicological comparison for evaluating new chemicals entering the market
- Information that innovators and product manufacturers can use to demonstrate how a particular innovation is an improvement over existing options with regard to toxicity
- Identification of hazard data gaps for which additional information or testing is needed in order to provide a more complete picture of potential toxicity concerns

Importantly, the EDF PIP did not attempt to tackle every aspect of what is involved in taking chemical innovations to market including performance testing, examination of production scalability, and cost. These are all important considerations in chemical innovation beyond the scope of this particular effort.

## WHY A FOCUS ON PRESERVATIVES?

EDF chose to focus on preservatives in personal care products given consumer, marketplace, and regulatory pressures on certain commonly used preservatives (see Appendix A). As a functional class, preservatives present an interesting innovation challenge. Personal care products can become contaminated through contaminated raw materials, poor manufacturing conditions, inadequate packaging, or consumer use. Product preservation is important for protecting consumers from pathogenic microorganisms that can cause skin infections, eye infections, and in the most severe cases, illness or death (Brannan, 1997). Since some degree of biocidal activity is required for preservative efficacy, many preservatives on the market today typically carry some degree of inherent hazard.

## Did you know?

A preservative is a chemical agent that may be added to food, cosmetics, pharmaceuticals, and other products to prevent the growth of microorganisms or slow down or prevent decomposition through oxidation.

Preservatives extend the shelf life of products.

Preservatives can be synthetic, like parabens, or naturally occurring, like salt.

In the 1960s and early 1970s, cosmetic contamination with certain microorganisms was a large problem. Cases of skin infections, rashes, eye infections, and even blindness resulted from use of contaminated cosmetics.

Chemical preservatives are widely used in cosmetics to prevent the growth of microorganisms, like bacteria and fungi, some of which are pathogenic and can be hazardous to human health.

Manufacturers are faced with the challenge of identifying preservative systems that sufficiently protect consumers against pathogenic microbial contamination while minimizing any potential hazards of the preservatives themselves.

EDF believes that dedicated innovation effort on preservatives will yield new, promising chemical or other solutions that achieve product preservation with far less human health and ecological hazard concerns than those of certain preservatives currently in use in the market today.

Additionally, a number of public-private initiatives have emerged to advance preservative innovation including the UC Berkeley Greener Solutions project and the Green Chemistry and Commerce Council (GC3) Preservative Project (UC Berkeley, 2016; GC3, 2016). The UC Berkeley Greener Solutions project involved a student-led literature search of naturally-occurring compounds with antimicrobial properties, in collaboration with Beautycounter and Seventh Generation; while the GC3 project is pursuing a **crowdsourcing challenge** to surface promising safe and effective preservation options and involves several businesses and a handful of state and environmental groups.

These efforts focus primarily on identifying new preservation solutions, while the EDF PIP focused on providing baseline information that can be used to:

1. inform safer preservative design criteria, and
2. serve as a basis against which to evaluate new preservatives options with regard to hazard.

We hope that the work conducted through the PIP will serve as a resource in solution-seeking preservative innovation efforts.

## EDF CONVENED A GROUP OF ORGANIZATIONS TO PROVIDE INPUT INTO THE PIP, INCLUDING:

- ACTIVE MICRO TECHNOLOGIES
- BEAUTYCOUNTER
- CLARIANT
- GREEN CHEMISTRY AND COMMERCE COUNCIL
- SEVENTH GENERATION
- TOXSERVICES

These organizations represent businesses in the personal care product arena that either use or supply preservatives; experts skilled in chemical assessment; or individuals with expertise in public-private collaborations focused on green chemistry. However, EDF is the sole author of the PIP report and fully responsible for the final content.

# Selection of PIP Preservatives

EDF conducted a market scan of preservatives used in personal care products, followed by consultation with and consensus by the PIP Working Group to select preservatives to evaluate in the PIP.

EDF's market scan included an online examination of preservatives used in over 40 personal care product brands. In particular, EDF looked at skin lotion products since these products are applied directly to the body, intended for prolonged exposure, and require the use of preservatives to prevent microbial contamination (Poulsen and Strandesen, 2011; Kabara and Orth, 1996).

Preservatives used in skin lotions were identified using two approaches: 1) reading online product ingredient lists for chemicals explicitly identified as preservatives, and 2) cross-referencing lotion product ingredient lists against chemicals classified as preservatives by various cosmetic ingredient resources, including the Cosmetic Ingredient Review (CIR) compendium (CIR, 2014a), Preservatives for Cosmetics, 3rd edition, by David Steinberg (Steinberg, 2012), and chemical supplier data sheets. While the compiled candidate list was extensive, it was not exhaustive; there are a large number of personal care product brands and not all brands post product ingredient information online.

The PIP working group then reviewed the candidate list of preservatives using criteria for inclusion developed by the group. Chemicals were excluded or proposed by the group, and through a consensus process a final set of 16 preservatives were identified for evaluation (see Table 1). Additional information on each preservative can be found in Appendix B.

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Through a consensus process a final set of 16 preservatives were identified for evaluation.

## Table 1: Preservatives selected for PIP

| PRESERVATIVE | Microbial Activity |
|---|---|
| **Benzyl alcohol** 100-51-6 | Most active against gram-positive bacteria, moderately active against gram-negative bacteria and yeast/mold (Siegert, 2014) |
| **Caprylohydroxamic acid** [2] 7377-03-9 | Most active against mold; also active against gram-positive and negative bacteria and yeast (Hase et al., 1971; Ammendola et al., 2009; Bravo and Lazo, 1993; Steinberg, 2012). |
| **Caprylyl glycol** 1117-86-8 | Active against gram-positive and gram-negative bacteria; moderate activity for yeasts/molds (Dr. Straetmans, 2008); also able to improve the effectiveness of other preservatives at concentrations lower than their typical use level. |
| **DMDM Hydantoin** 6440-58-0 | Good activity for gram-positive and gram-negative bacteria; moderately active against yeasts and molds (Siegert, 2014). |
| **Ethylenediaminietetraacetic Acid (EDTA)** 60-00-4 | Reduces availability of iron for microbial growth; not active against gram-positive bacteria; enhances activities of antibacterial agents particularly against drug-resistant gram-negative microbes by increasing the permeability of cellular membranes; prevents growth of yeast and molds in zinc-dependent fashion (Brul et al., 1997; CIR, 2002). |
| **Ethylhexylglycerin** 70445-33-9 | Most active against gram positive bacteria; boosts the efficacy of traditional preservatives and acts as an antimicrobial stabilizer (Steinberg, 2012; Leschke and Siegert, 2008). |
| **Gluconolactone** 90-80-2 | The active agent, gluconic acid, is able to control microbial growth by reducing pH to a level that inhibits putrefactive and toxigenic bacteria growth (Lemay et al., 2000). |
| **Iodopropynyl Butylcarbamate (IPBC)** 55406-53-6 | Very active against yeast and mold, inadequate activity against bacteria (Steinberg, 2012). |
| **Lactobacillus ferment** 1686112-36-6 | Active against gram-positive and gram-negative bacteria; moderate activity for yeasts and molds (Active Micro, 2014). |
| **Methylisothiazolinone (MIT)** 2682-20-4 | Good to moderate activity for gram-positive and gram-negative bacteria, yeasts, and molds (Siegert, 2014). |
| **Phenoxyethanol** 122-99-6 | Most active against gram-negative bacteria; moderate activity for gram-positive bacteria and yeasts/molds (Siegert, 2014). |
| **Piroctone olamine** 68890-66-4 | Good activity against gram-positive bacteria, yeasts and molds; moderate activity for gram-negative bacteria (Clariant, 2004; Siegert, 2014). |
| **Propylparaben** 94-13-3 | Good activity against gram-positive bacteria, yeasts and molds; moderate activity against gram-negative bacteria (Seigert, 2014). |
| **Sorbic acid** 110-44-1 | Most active against yeast and mold and poorly active against bacteria (CIR, 2012). |
| **Sorbitan caprylate** [2] 60177-36-8 | Demonstrates efficacy against gram-positive bacteria; not active against gram-negative bacteria and undetermined for yeasts/molds (Clariant, 2012; Wagh et al., 2012). |
| **Undecylenic acid** 112-38-9 | Active against fungi (Spectrum, 2015a); no activity against bacteria (Siegert, 2014). |

2 The vast majority of the PIP preservatives are considered traditional preservative compounds; however, caprylohydroxamic acid and sorbitan caprylate, which may be considered non-traditional preservatives or preservative boosters, were also selected for this project because of their increased use in consumer products and a recommendation for inclusion by the PIP working group

# Hazard Assessment Method

EDF selected the GreenScreen® for Safer Chemicals (GreenScreen®) method for the hazard evaluation of the PIP preservatives (CPA, 2011; CPA, 2012a; CPA, 2013). The GreenScreen® method was chosen as the preferred method because of its structured, comprehensive design; the thorough documentation of data considered and results; and its record of application by both public and private sector entities. EDF contracted with ToxServices, an environmental consultancy with extensive experience performing chemical hazard and risk assessments, to perform the hazard evaluations. ToxServices is a highly experienced, licensed user of GreenScreen® tools.

## WHY GREENSCREEN® IS USEFUL TO COMPANIES

Consumer product companies are under pressure to to develop products with less toxic chemicals. Many have programs which ban or restrict the use of highly toxic chemicals in the products that they manufacture or sell. They use tools like GreenScreen® to help meet these increasing demands. GreenScreen® can be used to evaluate current product formulations to identify problematic chemicals and help select safer alternatives to those chemicals. GreenScreen® can also be used during product development to select less toxic chemicals from the start of product design, avoiding chemical substitutions down the road, which can be costly and time consuming. A growing number of professionals in companies like GOJO Industries and Hewlett Packard have become Authorized GreenScreen® Practitioners.

# GreenScreen® for Safer Chemicals

The GreenScreen® for Safer Chemicals is a comparative hazard assessment method designed to evaluate substances across a broad set of human and environmental toxicity endpoints. The method has been used by companies, advocacy groups, and state chemicals regulatory programs. It is also recognized as a hazard assessment platform for several standards and ecolabels, including the U.S. Green Building Council's LEED certification and the Cradle to Cradle Certified Product Standard™ and material health certificate.

The GreenScreen® method is publically available and includes evaluation of 18 human health, environmental, and physical hazard endpoints.

*Groupings of GreenScreen Hazard Endpoints*

| **Human Heath Group I** | **Human Heath Group II** | **Human Heath Group II*** | **Environmental Toxicity & Fate[3]** | **Physical Hazards** |
|---|---|---|---|---|
| Carcinogenicity | Acute Mammalian Toxicity | Systemic Toxicity & Organ Effects (repeated dose) | Acute Aquatic Toxicity | Reactivity |
| Mutagenicity & Genotoxicity | Systemic Toxicity & Organ Effects (single dose) | Neurotoxicty (repeated dose) | Chronic Aquatic Toxicity | Flammability |
| Reproductive Toxicity | Neurotoxicity (single dose) | Skin Sensitization | Persistence | |
| Developmental Toxicity including Neurodevelopmental Toxicity | Skin Irritation | Respiratory Sensitization | Bioaccumulation | |
| Endocrine Activity | Eye Irritation | | Other Ecotoxicity studies when available | |

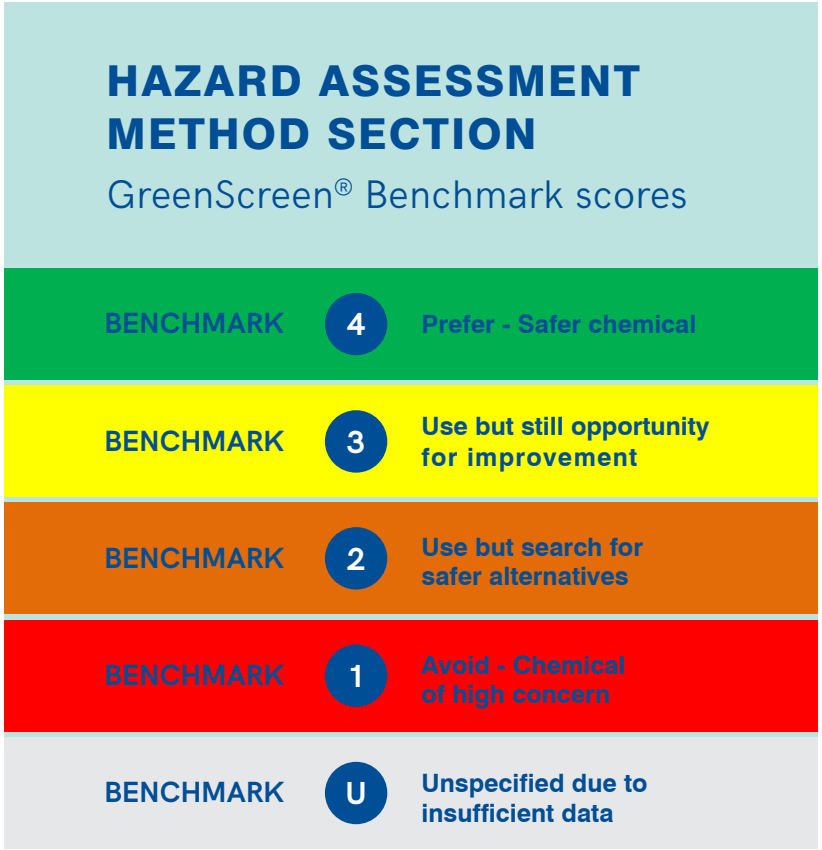
Evaluation of a chemical across each of the hazard endpoints includes a review of specified authoritative lists,[3] primary studies, and other available data. A hazard score—Very Low, Low, Moderate, High, or Very High—is assigned to each endpoint along with a confidence level (low or high) to indicate the quality and robustness of the dataset used to assign the hazard score. If insufficient or no data exist for a particular endpoint, Data Gap is assigned as the score. Finally, an overall GreenScreen® Benchmark™ score is assigned, ranging from 1 ("Avoid-Chemical of High Concern") to 4 ("Prefer-Safer Chemical"). A fuller description of the GreenScreen® for Safer Chemicals method can be found in Appendix C.

## GreenScreen® List Translator

The GreenScreen® List Translator is an abbreviated version of the full GreenScreen® method that involves screening chemicals against specified authoritative lists and not a review of primary studies (CPA, 2012b).

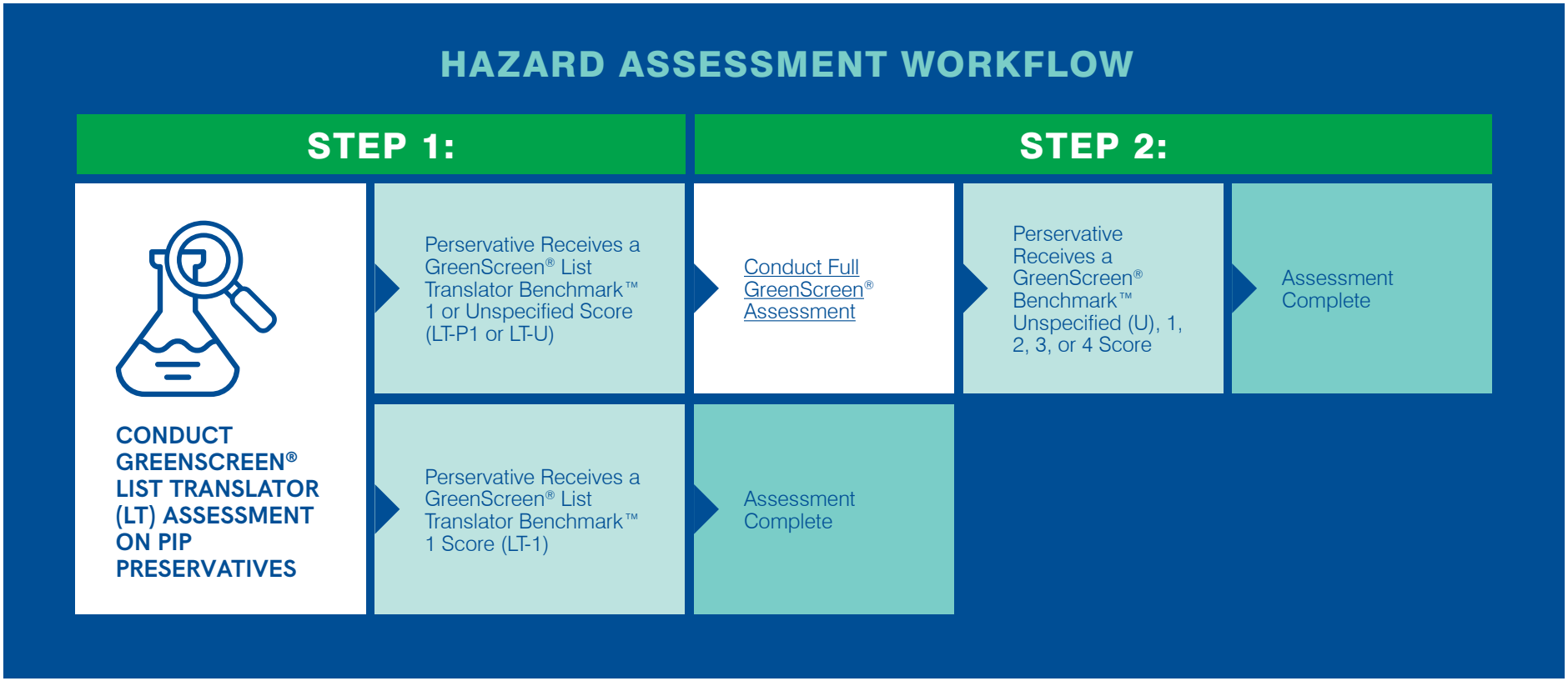
The List Translator approach involves a review of specified authoritative lists to identify chemicals that can be classified as LT-1, which is equivalent to a GreenScreen® Benchmark 1 ("Avoid-Chemical of High Concern"), or an LT-P1, which may be equivalent to a Benchmark 1 following a further review of data. LT-1 chemicals have been identified by authoritative bodies as carcinogens, mutagens, reproductive or developmental toxicants, endocrine active compounds, or persistent, bioaccumulative, and toxic (PBT) compounds. An LT-U score means that there is insufficient information from the screening of authoritative lists alone to assign a Benchmark LT-1 or LT-P1 score, and a full GreenScreen® must be performed to assign a Benchmark score. Additional information on GreenScreen® List Translator can be found **here.**

3 GreenScreen® specified authoritative lists can be found at http://www.greenscreenchemicals.org/



# Hazard Assessment Workflow

EDF and ToxServices used the following two-step hazard screening and assessment approach for the PIP:



## STEP 1

### GreenScreen® List Translator Screening

For the GreenScreen® List Translator screening, ToxServices used the Pharos Chemical and Materials Library online tool that automates the GreenScreen® authoritative list search and benchmark equivalency scoring (Pharos, 2015). As none of the selected preservatives were identified as LT-1 chemicals, each proceeded to the full GreenScreen® hazard assessment.

## STEP 2

### GreenScreen® for Safer Chemicals Assessment

ToxServices performed a full GreenScreen® hazard assessment on all PIP preservatives (**available online here**). In addition to the review of specified GreenScreen® authoritative lists, ToxServices evaluated existing, publically available data that at a minimum included a search of the data sources listed to the right.

ToxServices also requested that PIP working group members provide any data not available in the public domain to facilitate as comprehensive of hazard assessments as possible. ToxServices offered participants the opportunity to share such data under a non-disclosure agreement (NDA). One supplier provided additional data to ToxServices and granted explicit permission to include the data in the GreenScreen® assessments included in the current report.

## DATA RESOURCES

**COSMETIC INGREDIENT REVIEW (CIR)**

CIR Compendium

**EUROPEAN CHEMICALS AGENCY (ECHA)**

International Uniform Chemical Information Database (IUCLID)

Information on Chemicals

**HUMAN AND ENVIRONMENTAL RISK ASSESSMENT (HERA)**

HERA on ingredients of household cleaning products

**WORLD HEALTH ORGANIZATION (WHO)**

International Agency for Research on Cancer (IARC)

**OTHER**

ToxPlanet

EU Scientific Committee on Consumer Safety (SCCS) Opinions

**INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY (IPCS)**

INCHEM

**NATIONAL INSTITUTES OF HEALTH (NIH)**

ChemIDplus

Hazardous Substances Data Bank (HSD)

National Toxicology Program (NTP)

Toxline

**NATURAL MEDICINES**

Database of natural medicines

**ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD)**

OECD Existing Chemicals Database

**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (US EPA)**

High Production Volume Information System (HPVIS)

In the absence of sufficient data and where possible, ToxServices identified and evaluated a structurally similar chemical or class of chemicals for which data were available. ToxServices toxicologists identified appropriate structural analogs using the resources listed below.

Analogs were selected according to guidance in the U.S. Environmental Protection Agency's procedure for identifying analogs (USEPA, 2010), ECHA's read across assessment framework (ECHA, 2015), and OECD's guidance on grouping of chemicals (OECD, 2014).

In cases where suitable analogs could not be identified, ToxServices used modeling software to assess hazards as appropriate for a given preservative and the domain of the model.

Once all data were collected, a hazard score (i.e., high or low) and accompanying confidence level in that score (i.e., high confidence in bold, reduced confidence in italics) was assigned for each of the 18 GreenScreen® hazard endpoints according to the method. In instances where no data were available, no suitable analogs were identified, and modeling was not possible, a data gap (DG) was assigned for that hazard endpoint.

ToxServices also performed a GreenScreen® List Translator evaluation on known transformation products of PIP preservatives, such as biodegradation or hydrolysis products that are likely to occur across the chemical's lifecycle, and are likely to persist and be encountered in the environment (CPA, 2013). Considering the Benchmark score of the parent compound and transformation products, a final Benchmark™ score was assigned to the evaluated preservative, applying the more conservatwive of the two scores.

## RESOURCES TO IDENTIFY STRUCTURAL ANALOGS

### NIH

ChemIDplus structural similarity search

### OECD

OECD Toolbox

### U.S. EPA

Analog Identification Methodology (AIM)

Chemical Assessment Clustering Engine (ChemACE)

## MODELING SOFTWARE RESOURCES

### ORGANISATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD)

ChemIDplus structural similarity search

### TOXTREE

Toxic Hazard Estimation by Decision Tree Approach

### UNITED STATES ENVIRONMENTAL PROTECTION AGENCY (USEPA)

Ecological Structure Activity Relationships (ECOSAR) Predictive Modeling

EPI (Estimation Program Interface) Suite™

OncoLogic™ - A computer system to evaluate the carcinogenic potential of chemicals

### VEGA

Vega Predictive model for skin sensitization

# Results of GreenScreen® for Safer Chemical Assessments

The results of the GreenScreen® List Translator[4] and full GreenScreen® hazard assessments are presented below in Table 2 and on page 23, in Table 3.

TABLE 2

## GREENSCREEN® LIST TRANSLATOR RESULTS FOR PIP CHEMICALS

| LIST TRANSLATOR SCORE | *Chemicals* | |
|---|---|---|
| **LT-U** | • Benzyl alcohol<br>• Caprylohydroxamic acid<br>• DMDM Hydantoin<br>• Ethylhexylglycerin<br>• Gluconolactone | • Lactobacillus ferment<br>• Phenoxyethanol<br>• Sorbic acid<br>• Sorbitan caprylate<br>• Undecylenic acid |
| **LT-P1** | • Caprylyl glycol<br>• EDTA<br>• IPBC | • Methylisothiazolinone<br>• Piroctone olamine<br>• Propylparaben |

4 Definitions and explanations of the List Translator scores can be found in the GreenScreen® List Translator subsection of the Hazard Assessment Method section

# TABLE 3 GreenScreen® Hazard Assessments

| CHEMICAL NAME & CAS# | Group I Human Health | | | | | Group II and II* Human Health | | | | | | | | | Ecotox | | Fate | | Physical | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Carcinogenicity | Mutagenicity | Reproductive Toxicity | Developmental Toxicity | Endocrine Activity | Acute Toxicity | Systemic Toxicity | | Neurotoxicity | | Skin Sensitization* | Respiratory Sensitization* | Skin Irritation | Eye Irritation | Acute Aquatic Toxicity | Chronic Aquatic Toxicity | Persistence | Bioaccumulation | Reactivity | Flammability | |
| | | | | | | | s | r* | s | r* | | | | | | | | | | | |
| **Benzyl alcohol** 100-51-6 | L | L | L | *M* | DG | M | DG | L | *M* | *H* | H | DG | L | H | L | L | vL | vL | *L* | L | 2 |
| **Caprylohydroxamic acid** 7377-03-9 | DG | *L* | DG | *L* | DG | *L* | DG | *M* | DG | DG | *L* | DG | L | *H* | *H* | *H* | vL | *vL* | *L* | *L* | U |
| **Caprylyl glycol** 1117-86-8 | *L* | L | *L* | L | DG | L | DG | L | M | L | L | DG | L | H | *H* | *M* | vL | vL | *L* | L | 3 |
| **DMDM Hydantoin** 6440-58-0 | *H* | M | L | L | DG | L | *M* | L | DG | DG | M | *M* | *M* | L | H | M | vL | vL | *L* | L | 1 |
| **EDTA** 60-00-4 | L | L | L | M | DG | *L* | *M* | H | DG | DG | L | DG | *M* | H | H | H | *M* | vL | *L* | L | 2 |
| **Ethylhexylglycerin** 70445-33-9 | *L* | *L* | *M* | *L* | DG | M | M | *M* | DG | *L* | *M* | DG | L | vH | M | M | *M* | vL | *L* | L | 2 |
| **Gluconolactone** 90-80-2 | *L* | *L* | *L* | L | DG | L | L | L | DG | DG | *L* | DG | *L* | *L* | L | *L* | vL | *vL* | *L* | L | $3_{DG}$ |
| **IPBC** 55406-53-6 | L | L | *M* | *M* | *M* | H | DG | H | *M* | *L* | H | DG | L | vH | vH | vH | L | vL | L | *L* | 2 |
| **Lactobacillus ferment** 1686112-36-6 | DG | DG | DG | DG | DG | DG | DG | DG | DG | DG | L | DG | L | *L* | *L* | DG | *vL* | DG | *L* | *L* | U |
| **Methylisothiazolinone** 2682-20-4 | *L* | L | L | L | DG | vH | M | *M* | M | DG | H | *L* | vH | vH | vH | vH | L | vL | *L* | L | 2 |
| **Phenoxyethanol** 122-99-6 | L | L | *L* | M | DG | M | DG | *L* | M | L | L | DG | L | H | L | *L* | vL | vL | *L* | L | 2 |
| **Piroctone olamine** 68890-66-4 | *L* | L | L | *M* | DG | L | M | L | M | DG | L | DG | H | vH | vH | H | *vL* | L | L | L | 2 |
| **Propylparaben** 94-13-3 | *L* | L | L | *L* | *M* | L | L | L | DG | L | M | DG | *M* | L | H | H | vL | vL | *L* | L | 2 |
| **Sorbic acid** 110-44-1 | L | L | L | *M* | *M* | L | *M* | L | DG | L | M | DG | *H* | H | M | M | vL | vL | *L* | L | 2 |
| **Sorbitan caprylate** 60177-36-8 | *L* | *L* | *L* | *L* | DG | *L* | *L* | *L* | DG | *L* | *L* | DG | *L* | *L* | *M* | *M* | *vL* | vL | *L* | L | 3 |
| **Undecylenic acid** 112-38-9 | *L* | L | *L* | L | DG | *L* | L | L | DG | DG | *M* | DG | *H* | H | vH | *vH* | *vL* | *L* | *L* | L | 2 |

## KEY:

**vL** = Very Low

**L** = Low

**M** = Moderate

**H** = High

**vH** = Very High

*italics* indicates hazard scores assigned with low confidence

**bold** indicates hazard scores assigned with high confidence

**s** indicates single exposure

**r** indicates repeated exposure

***** indicates Group II health hazards evaluated based on repeated exposures to a chemical

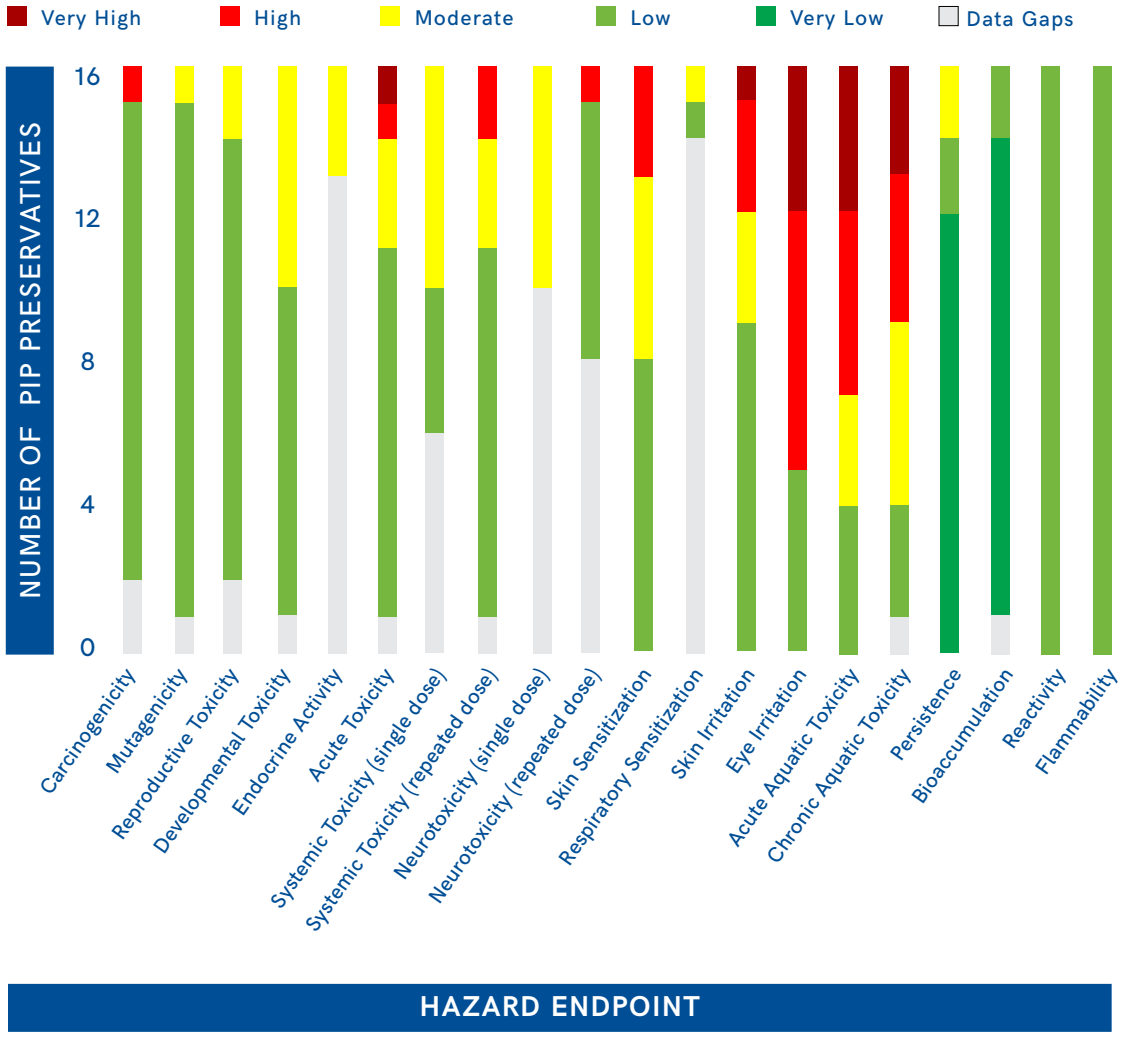
# Discussion of Results

A review of the GreenScreen® chemical hazard assessments reveals certain trends across the hazard profiles of the PIP preservatives including shared hazard endpoints of concern, a lack of toxicity across other hazard endpoints, and hazard endpoints for which toxicity could not be assessed due to a consistent lack of data. Full GreenScreen® assessments of PIP preservatives are **provided online**.

While the assessments developed in this project provide valuable, baseline data for preservative innovators, it is important to acknowledge that a larger review of additional preservatives could reveal new trends or refine those discussed below. Similarly, toxicological analyses of PIP preservatives were limited to publically available data which varied in quality and breadth across chemicals and endpoints. That the EDF PIP identified certain hazard hotspots among the PIP preservatives, as discussed below, does not mean that other endpoints should be ignored during new preservative research and development. Innovators should continuously assess the full scope of potential toxicity of their solutions.

## PIP PRESERVATIVE HAZARD SCORES BY HAZARD ENDPOINT

The stacked bar chart depicts the number of PIP preservatives assigned to distinct GreenScreen® hazard scores (Very Low, Low, Moderate, High, Very High, or Data Gap) within each hazard endpoint.



# Hazard Trends

## SKIN SENSITIZATION

Skin sensitization concerns were identified for eight of the 16 preservatives evaluated: five preservatives received a Moderate hazard score based on low to moderate potency and/or frequency of occurrence of sensitization responses, and three received a High hazard score for skin sensitization based on high potency and/or frequency of occurrence. Most (six of eight) of these Moderate and High hazard scores were assigned with high confidence as the hazard classifications were based on experimental data in laboratory animals, patch tests in humans, and human case reports that support a skin sensitization effect.

Skin sensitization is of particular relevance for ingredients in personal care products like lotions where normal use of the product results in prolonged and repeated contact with skin. Such use conditions provide increased opportunity for induction of sensitization to occur. Because an individual, once sensitized, is typically sensitized for life, he or she will be susceptible to allergic responses upon all subsequent exposures.

These results indicate that skin sensitization is a priority area for innovation. Preservative innovation efforts should focus on developing preservatives with lower skin sensitization potential, and broadening the palette of available preservatives to minimize repeated and high aggregate exposures to individual or classes of skin sensitizing chemicals that may lead to cross-sensitization reactions.

## SKIN AND EYE IRRITATION

Nearly half (seven of 16) of the preservatives were found to be skin irritants and the majority (11 of 16) were found to be eye irritants. Of the skin irritants, three received a score of Moderate, three received a score of High, and one received a score of Very High. Of the eye irritants, seven received a score of High and four received a score of Very High.

A score of Very High for skin or eye irritation means that the undiluted preservative can irreversibly damage the skin or eyes. Although individuals are unlikely to be exposed to undiluted preservatives through use of consumer products, skin and eye irritation remain important areas for preservative innovation given the extent and degree of irritation identified, and in consideration of potential occupational exposures.

**SKIN ALLERGIES**

Skin sensitization is of particular relevance for ingredients in personal care products like lotion where normal use of the product results in prolonged and repeated contact with skin.

# Hazard Trends

## TOXICITY TO AQUATIC ORGANISMS AND ENVIRONMENTAL FATE

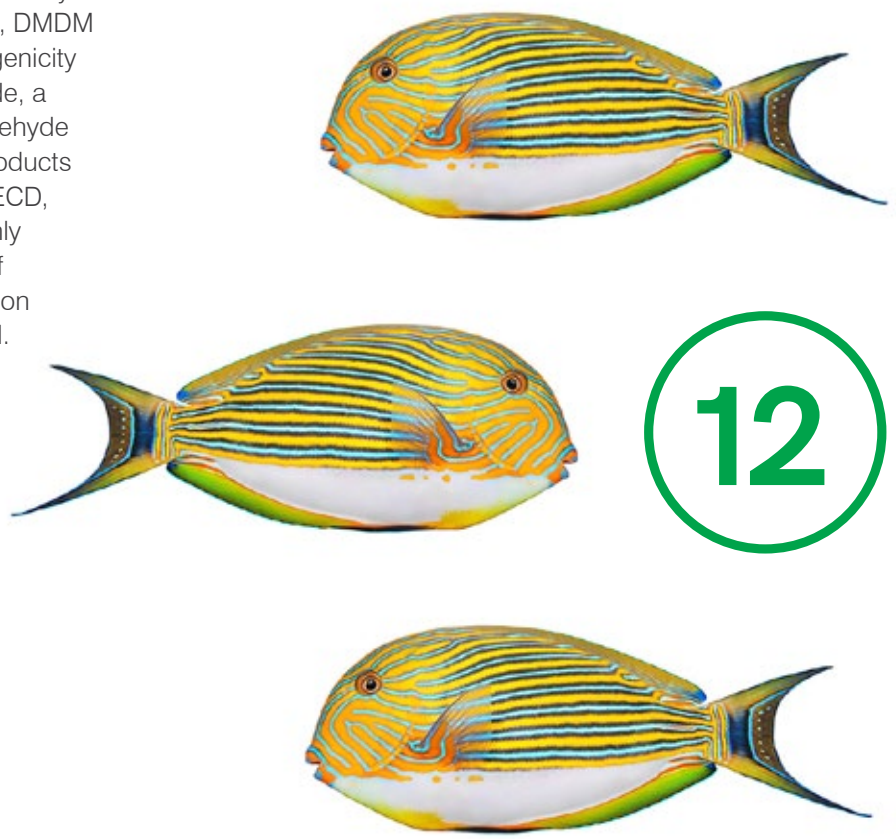
Toxicity to aquatic organisms was a frequent hazard across the PIP preservatives. Of the 16 preservatives evaluated, 12 received scores of Moderate or above for acute aquatic toxicity, with nine receiving scores of High or Very High. These same 12 preservatives also received scores of Moderate or above for chronic aquatic toxicity, with seven receiving scores of High or Very High. Additionally, two of these 12 preservatives were shown or predicted to be Moderately persistent with the remainder expected to be readily or rapidly biodegradable (i.e., not persistent). None of the preservatives are expected to be bioaccumulative based on experimental data, physicochemical properties, and/or modeled data.

While the Low scores for persistence and bioaccumulation may help to limit ecological impacts, the development of preservatives with lower intrinsic hazards to aquatic organisms is an area for innovation given the widespread use of these compounds and their potential for direct release into the environment (Northcott et al., 2013; Santos et al., 2016; Zhang et al., 2015; Bledzak et al., 2014).

## CARCINOGENICITY AND MUTAGENICITY

The GreenScreen® hazard assessments did not indicate any trends for carcinogenicity or mutagenicity. Only one preservative, DMDM hydantoin, scored High for carcinogenicity based on its release of formaldehyde, a known human carcinogen. Formaldehyde release, via hydrolysis, occurs in products and may also occur in the body (OECD, 2016). DMDM hydantoin was the only chemical that displayed evidence of genotoxicity sufficient for classification following the GreenScreen® method.

Of the 16 preservatives evaluated, 12 received scores of Moderate or above for acute aquatic toxicity, with nine receiving scores of High or Very High.



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# Hazard Trends

## REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Most of the preservatives did not show evidence of reproductive toxicity (12 of 14) or developmental toxicity (nine of 14) sufficient for classification based on the data available and following the GreenScreen® method. Due to a lack of data, caprylohydroxamic acid and Lactobacillus ferment, could not be evaluated for reproductive toxicity; further, Lactobacillus ferment could not be evaluated for developmental toxicity.

Seven preservatives showed evidence of reproductive toxicity and/or developmental toxicity and received Moderate toxicity scores for those endpoints. Both moderate scores for reproductive toxicity and four of six Moderate scores for developmental toxicity were reported with reduced confidence as they are based on equivocal or mixed results, effects of uncertain toxicological significance, or poorly reported studies.

In sum, based on the available data, the 16 preservatives examined did not indicate reproductive or developmental toxicity as priority focus areas for targeted innovation. It is important to note however that reproductive and developmental toxicity are complex endpoints and that traditional guideline studies—which represent the vast majority of the available studies for the PIP—have been critiqued with regard to their ability to sufficiently capture reproductive and developmental effects, particularly as they relate to endocrine disruption (Vandenberg, 2014; Endocrine Society, 2015).

## ACUTE AND SYSTEMIC TOXICITY

The GreenScreen® hazard assessments did not reveal any specific trends for acute toxicity or systemic toxicity but did identify some preservatives with hazards for these endpoints.

Of the preservatives with acute toxicity data available (15 of 16), three received a score of Moderate, one received a score of High, and one received a score of Very High.

Although six of 10 preservatives with single dose systemic toxicity data available received scores of Moderate, per the GreenScreen® method these scores were assigned based on evidence of respiratory tract irritation, which is a localized effect rather than a true systemic effect. The remainder of chemicals with available data for single dose systemic toxicity were all assigned a score of Low. Repeated dose systemic toxicity data were available for 15 of the 16 preservatives. The majority, 10 of 15, received a score of Low for this endpoint, while three of 15 received a score of Moderate and two of 15 received a score of High. A review of the data for chemicals that received toxicity scores of Moderate or High for repeated dose systemic toxicity did not reveal any specific trends regarding shared target organs/systems.

# Hazard Endpoints Often Scored as Data Gaps

Data gaps were frequently encountered for certain hazard endpoints, including endocrine activity, respiratory sensitization, and neurotoxicity.

## ENDOCRINE ACTIVITY

Only three out of 16 of the preservatives assessed in this report had data adequate to assess and assign hazard scores for endocrine activity: IPBC, propylparaben, and sorbic acid. All three of these preservatives received Moderate hazard scores for endocrine activity and these scores were assigned with low confidence.

The lack of available endocrine activity data is not a unique challenge to preservatives. Few endocrine activity-explicit endpoints are evaluated in guideline toxicology studies typically used by industry, and which represent the majority of the available data for the PIP (also see reproductive and developmental toxicity above). There are some in vitro and in vivo assays designed to include an evaluation of endocrine activity and disruption, such as those incorporated into U.S. EPA's Endocrine Disruption Screening Program (USEPA, 2017a; USEPA, 2017b), but they are not routinely conducted, and while useful do not yet comprehensively examine effects on the endocrine system.

New predictive toxicity testing approaches continue to be developed and have the potential to provide more information for the evaluation of endocrine activity. Strengthening and employing these new methods should be a focal point of chemical innovation efforts broadly.

## RESPIRATORY SENSITIZATION

The majority of the preservatives (14 of 16) were assigned a Data Gap for respiratory sensitization. For the two preservatives assigned scores—methylisothiazolinone, Low and DMDM hydantoin, Moderate—both scores were assigned with low confidence. The scarcity of data for this endpoint in part stems from the lack of agreed upon in vitro or animal models for the testing of respiratory sensitization in guideline studies.

Typically, respiratory sensitizers are identified through case reports, especially in occupationally exposed individuals. Historically, chemicals are presumed to be a low hazard for respiratory sensitization if there is a lack of case reports over a long history of use. However, this is a very limited approach and further, such a history of use is not likely available for more recently developed preservatives. Consideration of respiratory sensitization becomes extremely important for those exposed occupationally and for consumers if there is inhalation potential.

As approaches for assessing respiratory sensitization continue to be developed and refined, a more in depth assessment of the respiratory sensitization potential of preservatives should be pursued.


Data gaps were frequently encountered for certain hazard endpoints, including endocrine activity, respiratory sensitization, and neurotoxicity.

## NEUROTOXICITY

The evaluated preservatives are not well studied with regard to their potential for neurotoxicity (i.e., adverse changes to the structure and/or function of the nervous system). GreenScreen® separately evaluates neurotoxicity data from studies that administer single doses or repeated doses. Of the 16 PIP preservatives, six chemicals were evaluated in single-dose studies and eight chemicals were evaluated in repeated-dose studies.

In the single-dose studies, which evaluated the neurological effects of a single, high dose of each chemical preservative, all six chemicals produced reversible neurological effects. These six chemicals, therefore, received a GreenScreen® score of Moderate for neurotoxicity. In studies evaluating neurological effects of repeated doses of chemical preservatives, only one chemical, benzyl alcohol, received a GreenScreen® score of High, as it was shown to produce irreversible neurotoxicity in humans. However, these effects were observed in infants exposed intravenously and therefore the relevance to oral, dermal, and inhalation exposures expected through use as a preservative in a personal care product is uncertain. The other seven preservatives with repeated dose toxicity data were scored as Low hazard.

Insufficient data were available to assess potential single- or repeated- dose neurotoxicity of six preservatives (i.e. chemicals had data gaps for single- and repeated-dose studies), highlighting the need for data development such as predictive toxicity testing approaches, targeted histopathological evaluations of the brain, functional observational batteries, and specialized behavioral tests.

# Variability in Data Gaps and Confidence Assigned to Hazard Scores

A review across all of the GreenScreen® hazard assessments reveals variability in both the quantity and quality of available data for evaluating individual preservatives. This variability is manifest by differences in the number of hazard endpoint scores assigned as Data Gaps, and the extent to which hazard endpoint scores were assigned with low or high confidence.

For any given preservative, the number of hazard endpoint scores assigned as Data Gaps ranged from two (IPBC, methylisothiazolinone, propylparaben, and sorbic acid) to 13 (Lactobacillus ferment). The average number of Data Gap scores across all preservatives was four.

There was also a large range in the number of hazard endpoint scores assigned with high confidence for any given preservative. In accordance with the GreenScreen® method, endpoints were assigned a toxicity score with high confidence when relatively complete datasets were available for that endpoint (e.g., measured data was available on the actual preservative under consideration and not a surrogate). Other endpoints were assigned a toxicity score with low confidence because they relied on weak surrogates, modeled data, studies of limited reliability due to methodological and/or reporting deficiencies, or studies producing mixed results. For any given preservative, endpoints assigned scores with high confidence ranged from two (capyrylohydroxamic acid, Lactobacillus ferment, sorbitan caprylate) to 14 (methylisothiazolinone and piroctone olamine). All of the evaluated preservatives had at least three hazard endpoint scores assigned with low confidence.

# Hazard Analysis Summary

The GreenScreen® chemical hazard assessments provided a consistent evaluation of the human health and environmental toxicity and fate of 16 preservatives currently in use in personal care products. Key findings include:

- Several PIP preservatives scored Moderate to Very High for skin sensitization, skin irritation, eye irritation, and acute and chronic aquatic toxicity (see table to the right).
- Only one PIP preservative, DMDM hydantoin, received a High hazard score for a GreenScreen® Group I human health endpoint. Specifically, DMDM hydantoin scored High for carcinogenicity, as a result of its release of formaldehyde, a known human carcinogen. GreenScreen® Group I human health endpoints represent hazards that lead to chronic or life-threatening health effects that may result from low dose exposures and include carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, and endocrine activity (see Appendix C).
- Confidence in the assignment of hazard scores varied widely across the PIP preservatives. For any given preservative, endpoints assigned scores with high confidence ranged from two (capyrylohydroxamic acid, Lactobacillus ferment, sorbitan caprylate) to 14 (methylisothiazolinone and piroctone olamine), with an average of ten endpoints assigned scores with high confidence.

*Endpoints often scored as Moderate to Very High*

| | HAZARD ENDPOINT | | | |
|---|---|---|---|---|
| **PIP PRESERVATIVE** | **Skin sensitization** | **Skin irritation** | **Eye irritation** | **Acute and/ or chronic aquatic toxicity** |
| Benzyl alcohol | ● | | ● | |
| Capyrylohydroxamic acid | | | ● | ● |
| Caprylyl glycol | | | ● | ● |
| DMDM Hydantoin | ● | ● | | ● |
| EDTA | | ● | ● | ● |
| Ethylhexylglycerin | ● | | ● | ● |
| Gluconolactone | | | | |
| IPBC | ● | | ● | ● |
| Lactobacillus ferment | | | | |
| Methylisothiazolinone | ● | ● | ● | ● |
| Phenoxyethanol | | | ● | |
| Piroctone olamine | | ● | ● | ● |
| Propylparaben | ● | ● | | ● |
| Sorbic acid | ● | ● | ● | ● |
| Sorbitan caprylate | | | | ● |
| Undecylenic acid | ● | ● | ● | ● |
| **TOTAL** | **8** | **7** | **11** | **12** |

- All PIP preservatives had data gaps for at least two hazard endpoints. The number of data gaps ranged from two (IPBC, methylisothiazolinone, propylparaben, and sorbic acid) to 13 (Lactobacillus ferment), and the average number of data gaps across the preservatives was four.
- Data gaps were consistently encountered in the assessment of endocrine activity, neurotoxicity, and respiratory sensitization.
- Overall GreenScreen® Benchmark (BM) scores across the PIP preservatives were as follows:

| | |
|---|---|
| **BENCHMARK 4 Safer chemical** | • None |
| **BENCHMARK 3 Use but still opportunity for improvement** | • Caprylyl glycol<br>• Sorbitan caprylate |
| **BENCHMARK 3DG [Data gaps exist] Use but still opportunity for improvement*** | • Gluconolactone |
| **BENCHMARK 2 Use but search for safer alternatives** | • Benzyl alcohol • EDTA • Ethylhexylglycerin • IPBC<br>• Methylisothiazolinone • Phenoxyethanol • Piroctone olamine<br>• Propylparaben • Sorbic acid • Undecylenic acid |
| **BENCHMARK 1 Avoid - Chemical of high concern** | • DMDM Hydantoin |
| **BENCHMARK U Unspecified due to insufficient data** | • Caprylohydroxamic acid<br>• Lactobacillus ferment |

* A Benchmark score of 3DG means that the chemical meets the hazard classification requirements of a Benchmark 4 but does not meet the data gap requirements; however, it does meet the data gap requirements for a Benchmark 3

# Conclusion and Recommendations

With the PIP, EDF and its collaborators set out to provide a resource for chemical innovators and product manufacturers looking to create or discover new, safer chemical options for product preservation.

Specifically, the PIP sought to develop comprehensive toxicological profiles for a representative set of commercially available preservatives in a structured, transparent, and comparable manner using the GreenScreen® for Safer Chemicals method.

Based on the results of the PIP, EDF recommends the following for those pursuing preservative innovation:

## MAKE HAZARD A PRIORITY INNOVATION CRITERION.

Certain preservatives are under increased scrutiny by regulators, consumers, and the marketplace due to concerns around impacts to human health or the environment. Though safety is considered in the development of new chemicals, it is not often touted as the major benefit or driving force of innovation. EDF maintains that the development of inherently safer chemicals should be recognized as just as significant and innovative as the development of chemicals with improved performance. Innovation efforts focused on creating inherently safer chemicals complement important restrictions on the amount of potentially hazardous chemicals permitted in products—together reducing overall impacts to human health and the environment.

## TACKLE HAZARD HOTSPOTS.

Preservative innovation efforts should focus on tackling identified hazard hotspots (i.e., endpoints that received the highest hazard scores in this assessment): skin sensitization, skin irritation, eye irritation, acute aquatic toxicity, and chronic aquatic toxicity.

## AVOID TRADING OFF HAZARDS.

While certain hazard endpoints were not identified as hazard hotspots for the preservatives evaluated in the PIP, as a general practice, chemical innovators should continue to consider all potential hazards in the development of new preservatives. This is to avoid the introduction of a new hazard while tackling another.

## CREATE A CHEMICALS ASSESSMENT CLEARINGHOUSE.

EDF calls for the creation of an independent chemicals assessment clearinghouse that would provide comprehensive, structured, transparent, and comparable health and safety assessments of chemicals in a centralized, web-accessible repository. Operational standards would be established for qualifying assessors to develop and contribute assessments to the clearinghouse, ensuring quality assurance, and updating assessments to reflect the most current science—all with an eye toward producing assessments that are meaningful, actionable, and credible to actors along the supply chain. Such a clearinghouse would serve as a significant resource to various stakeholders looking to move the dial on safer chemistry, whether as a chemical innovator looking for information to inform design criteria or to show how a new chemistry represents an improvement over the status quo; as a product manufacturer searching for safer product formulation and fabrication options; or as a retailer interested in understanding what alternatives may be available for chemicals they are looking to move away from. Assessments from the clearinghouse would also indicate where toxicity data are lacking or insufficient, and thus where more chemical testing is needed. Finally, an independent chemical assessment clearinghouse holds the potential for participating parties to share the cost burden of producing objective, mutually desired and beneficial toxicological assessments of chemicals.

## Market demand for safer chemicals is significant and growing. Interests center on driving harmful chemicals out of commerce and ushering in safer solutions that, together, work to protect public health and the environment.

From a business perspective, investments in safer chemicals means getting ahead of regulatory demands, expanding market potential, and mitigating against future business risk, such as market deselection of a chemical of concern and legal fines imposed from the mismanagement of hazardous waste.

Innovators play a crucial role in developing safer solutions -- from using less toxic chemicals to making engineering changes that reduce or eliminate the need for a chemical of concern. Access to data-driven, uniformly-developed toxicological profiles of the sort developed in the PIP is invaluable for defining robust criteria to push safer chemical R&D.

Ideally, the PIP framework could be replicated across other functional classes of chemicals and product types. However, replication of the PIP framework is contingent, among other things, on the availability of robust data for chemical assessments. Greater public access to chemical health and safety information enables comprehensive assessments of chemicals, strengthening the type of evaluation undertaken in the PIP, and identification of true data gaps that would benefit from additional research.

EDF calls for the creation of an independent chemicals assessment clearinghouse to replicate the PIP framework at scale for multiple chemical functional classes. Such a clearinghouse would provide a significant resource to those looking to move the dial on safer chemistry by facilitating credible, data-driven decision-making that moves us all toward a more sustainable, healthy world.

# APPENDIX A

# Preservative Regulatory and Market Action Landscape

Regulatory and market forces paired with a growing body of scientific research have driven the market to seek alternatives to certain traditional preservatives as product formulators face the challenge of balancing product preservation and regulatory requirements with competing consumer interests and health concerns. We summarize below some of the key regulatory and market activities focused on the use of preservatives in personal care products.

## Regulatory Landscape UNITED STATES (NATIONAL)

### Food and Drug Administration (FDA)

Under the Federal Food, Drug, and Cosmetic Act (FDCA), personal care products are primarily regulated as cosmetics, drugs, or both cosmetics and drugs (FDA, 2015a). Under the FDCA, formulators are prohibited from marketing "adulterated" products, which includes any product that has been contaminated or decomposed, rendering "it injurious to users under the conditions of use prescribed in the labeling thereof" (FDA, 2014). Products that are contaminated by microbial growth are considered adulterated per the FDCA definition.

As a general matter, FDA does not approve cosmetic products or ingredients before they enter the market with the exception of color additives that are not coal-tar hair dyes. The FDA may choose to review products or ingredients. There are a few cosmetic ingredients that are prohibited by regulation (FDA, 2015b). The FDA has regulated the following ingredients with antimicrobial properties for use in personal care products (some of which were previously used as preservatives) (Steinberg, 2012):[5]

- Hexachlorophene (21 CFR 250.250)
- Mercury compounds (21 CFR 700.13)
- Bithional (21 CFR 700.11)
- Halogenated salicylanides (21 CFR 700.15)

It is the legal responsibility of companies who make or sell personal care products to ensure the safety of their products and ingredients including that the product is adequately preserved.

A manufacturer may use a particular ingredient in a product if that ingredient and product are safe under the conditions of use as determined by the manufacturer; the product is compliant with labeling requirements; and the ingredient and product are not otherwise adulterated (FDA, 2014). This requires that a product does not contain pathogenic microorganisms and has a low density of non-pathogenic microorganisms (Steinberg, 2012). The FDA can take action if products are not in compliance with the law.

The FDA has the authority to perform post-market testing or analysis of ingredients and products during cosmetic facility inspections and inspections of imported cosmetic products. The FDA may also respond to complaints regarding adulterated products and investigates concerns about the safety of specific preservative ingredients.

All told the personal care product sector is largely self-regulating in the U.S.

### Cosmetic Ingredient Review

The Cosmetic Ingredient Review (CIR)[6], a U.S.-based and industry-funded organization convenes an Expert Panel of scientists and medical experts to review cosmetic ingredient safety and recommend any potential restrictions. Expert Panel ingredient assessments are based on available literature and industry-submitted data. Assessments are provided in a compendium for purchase and freely on CIR's webpages.

5 For a list of other cosmetic ingredients that the FDA has prohibited or restricted, current as of November 2011, see here: http://www.cir-safety.org/sites/default/files/prohibitedrestrictedbyFDA%2011-30-2011.pdf

6 http://www.cir-safety.org/

# Regulatory Landscape UNITED STATES (STATE)

## Minnesota Statutes Section 325F.176-325F.178

Minnesota Statutes Section 325F.176 – 325F.178 bans formaldehyde and chemicals that release formaldehyde (formaldehyde releasers such as DMDM hydantoin) in certain children's products sold in the state of Minnesota.[7] Beginning in 2014, product manufacturers and wholesalers were prohibited from selling any applicable children's products that intentionally contain formaldehyde or chemicals that will degrade under "normal conditions of temperature and pressure" to release formaldehyde at levels greater than 0.05%. Beginning in 2015 the same prohibition applied to retailers. The statute also requires that product manufacturers not replace formaldehyde or formaldehyde-releasers in applicable children's products with known or suspected with a high degree of probability to cause developmental toxicity, cancer, reproductive toxicity, endocrine disruption, or systemic toxicity as determined by authoritative bodies.

## Washington State Children's Safe Product Act

The Washington State Children's Safe Product Act (CSPA) and accompanying reporting rule establish reporting requirements for children's products that contain one or more chemicals found on the Washington state list of Chemicals of High Concern to Children (CHCC). Chemicals included on the CHCC list meet specified criteria related to hazard and exposure concerns for a child or developing fetus.[8] The CHCC includes chemicals that may be used as preservatives in children's products, such as formaldehyde and several parabens (WA DoH, 2011a,b). Product manufacturers are required to report, by product category, the amount and function of a CHCC chemical present in a product or component of a product. The product categories covered by the reporting rule are based on the definition of children's products established in the CSPA (WSDE, 2013). Reported data are published, updated, and searchable on the Washington Department of Ecology website.[9]

7 https://www.revisor.mn.gov/statutes/?id=325F (see 325F.176 - 325F.178)

8 http://apps.leg.wa.gov/RCW/default.aspx?cite=70.240.030

9 http://www.ecy.wa.gov/programs/hwtr/RTT/cspa/

# Regulatory Landscape INTERNATIONAL

## European Union

The safety of personal care products like soap, shampoo, and makeup, is the responsibility of the product manufacturer under EU Cosmetics Regulation 1223/2009[10] ("Cosmetics Regulation"), which came into force on July 11, 2013. All such products must be registered through the Cosmetic Products Notification Portal (CPNP) before entering the market in the EU. The product manufacturer must ensure that the product has undergone a safety assessment following the requirements identified in Annex I of the Cosmetics Regulation prior to placing the product on the market.

The additional Annexes to the Cosmetics Regulation set forth specific lists of permissible, restricted, or prohibited chemicals and classes of chemicals: chemicals that are prohibited in cosmetic products (Annex II), chemicals that are allowed for use with certain restrictions (Annex III), colorants allowed or allowed provisionally in products (Annex IV), permitted preservatives (Annex V), and UV filters which cosmetic products may contain (Annex VI).

The Cosmetics Regulation defines preservatives as "substances which are exclusively or mainly intended to inhibit the development of microorganisms in the cosmetic product" (EC, 2009). Currently, Annex V includes 57 permitted preservatives for cosmetic products, though the

10 http://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A32009R1223

# Regulatory Landscape INTERNATIONAL

actual number of individual preservative chemicals in Annex V is much greater as many entries include multi salts or esters of substances.[11] Annex V also stipulates conditions of use that include maximum concentration of use; specific concentration limitations based on product type and/or body parts on which a product is applied; prohibitions on use in specific product types (e.g., use in children's products) and other considerations, such as purity criteria. Annex I requires that the party responsible for the safety of the product submit a qualitative and quantitative description of the composition of the cosmetic product, including the identity and intended function of all chemicals comprising the product formulation. Only chemicals included on Annex V are allowed as active preservative ingredients. However, opportunities to circumvent the use of only permitted preservatives per the Cosmetics Regulation can result from the use of multifunctional chemicals where the primary function of these ingredients is not to inhibit the growth of microorganisms yet they still exhibit biostatic properties. This has enabled some companies to claim their products as "preservative-free" (Schulke, 2015).

The European Commission Scientific Committee on Consumer Safety (SCCS) is responsible for the safety evaluation of chemicals to be added to the Annexes, including preservatives (EC, 2015a). The chemical manufacturer must submit a toxicological dossier to the SCCS, which then performs a hazard identification, dose-response assessment, exposure assessment, and risk characterization of the submitted chemical.[12] The SCCS issues scientific opinions on the chemicals in question. These opinions are considered and recommendations are often followed, but the adoption of a recommendation is not required by law. In particular, these opinions inform decisions by the European Commission for chemical listing on Annexes and other decisions related to risk management and hazard communication.

## Canada

The safety of cosmetic products in Canada is regulated under the Food and Drugs Act (R.S.C., 1985, c. F-27) and the Cosmetic Regulations (C.R.C., c. 869). The "Cosmetic Ingredient Hotlist" (Hotlist) identifies substances that are restricted (e.g., concentration limits, product-type exclusions, and labeling requirements) or prohibited for use in cosmetic products, pulling from stipulations laid out in both the Food and Drugs Act and Cosmetics Regulation (HC, 2014). Health Canada is the entity responsible for maintaining this list. In addition to its own reviews, Health Canada consults ingredient assessments and decisions made by other authoritative bodies, for example, the Scientific Committee on Consumer Safety (SCCS) in the EU. Additions and updates to the Hotlist occur via a formal consultation process that allows for stakeholder input. Notably, Health Canada has also set specific conditions and limitations for making "free of" ingredient claims on products including for preservatives (Steinberg, 2012).

## Japan

In Japan, personal care products and ingredients, including preservatives, are regulated by the Ministry of Health, Labour, and Welfare (MHLW) under the Pharmaceutical Affairs Law (Rannou, 2015). Under the Pharmaceutical Affairs Law, product manufactures and importers are responsible for ensuring the safety of their products which in part requires product testing by MHLW-designated laboratories. A Japanese regulation pursuant to the Pharmaceuticals Affairs Law, the Standard for Cosmetics, defines ingredients that are prohibited or restricted for use in products, as well as cosmetic ingredients that are permitted for use within particular functional classes (e.g., preservatives) (Rannou, 2015). The Standard for Cosmetics list of restrictions and permitted substances set stricter standards than other authorities in many cases. Also under the Standard, product manufacturers and importers must submit specific notifications to specified state authorities prior to introducing the cosmetic product to the market (ChemLinked, 2015). As part of this notification process, submitters must include testing results that verify a product does not contain prohibited ingredients and that permitted ingredients are in compliance with relevant restrictions.

11 For a full list of preservatives in Annex V, see: http://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.results&annex_v2=V&search

12 http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf

# Market-Based Activities

In addition to the regulatory activities directed at the use of preservatives in personal care products, a variety of consumer campaigns and market actions have prompted market deselection of certain preservative ingredients and a push for safer, effective alternatives. A handful of market campaigns are described below.

The Campaign for Safe Cosmetics, a coalition organized by the Breast Cancer Prevention Partners, pursues a number of initiatives including public education, policy advocacy, and corporate engagement, to urge the personal care industry to stop the use of certain chemicals and ultimately, drive safer products. The Campaign has created *Red Lists* of ingredients to avoid in personal care products. These *Red Lists* include commonly used preservatives, such as parabens and formaldehyde releasers (Campaign for Safe Cosmetics Undated). The Campaign for Safe Cosmetics launched the "Cosmetics Without Cancer" Campaign in early 2015, for consumers to petition select product manufacturers to remove chemicals linked to cancer from their cosmetic products. Formaldehyde-releasing preservatives were among the targeted compounds. The Campaign for Safe Cosmetics reports that several companies targeted by the Campaign have responded to the petition and proceeded with reformulations of their products to address consumer concerns (Campaign for Safe Cosmetics, 2014).

The Mind the Store campaign, launched by the Safer Chemicals, Healthy Families coalition, has generated a list of slightly over 100 chemicals of concern, the *Hazardous Hundred List*, based on U.S. and international authoritative listings of chemicals that have been determined to present hazard and/or risk. Mind the Store advocates for retailers to remove the *Hazardous Hundred List* chemicals from the products they sell. The *List* includes parabens for their endocrine disrupting activity (Safer Chemicals, undated).

International market campaigns have also focused on personal care products ingredients. For example, Environmental Defence is a Canadian environmental action organization focused on a variety of sustainability issues including reducing exposures to harmful chemicals. Environmental Defence's "Just Beautiful Pledge" features a toxic 10 list of harmful ingredients for consumers to avoid and includes preservatives, i.e., formaldehyde-releasing agents, parabens, BHA & BHT, and triclosan (Environmental Defence, 2016).

In addition to advocacy led market-based activities, certain product manufacturers and retailers are increasingly pursing initiatives to reduce and eliminate toxic chemicals from their products and shelves respectively. Certain preservatives have been among the targets of such initiatives. Notably, Walmart's 2016 progress report on its Sustainable Chemistry Policy identified eight high priority chemicals, four of which are preservatives: butylparaben, propylparaben, formaldehyde, and triclosan (Walmart, 2016). Target's 2017 chemicals policy identified a handful of chemicals for elimination by 2020 in its beauty, baby care, personal care and household cleaning product categories including the preservatives propylparaben, butylparaben, and formaldehyde-donors (Target, 2017).

# APPENDIX B

# PIP Preservative Profiles

Brief profiles of the 16 selected PIP preservatives are provided. The profiles include information regarding the preservatives' function in products (including and in addition to preservation), product use, microbial activity, formulation considerations, and regulatory and related information.

To compile regulatory and related information, the EU Cosmetics Regulation, Health Canada's Cosmetic Ingredient Hotlist and Japan Standard for Cosmetics were consulted. If a chemical is listed on the EU Cosmetics regulation Annex V "List of Preservatives Allowed in Cosmetics," it is permitted as a preservative ingredient in cosmetic products in the EU and is noted in the profile. If a ban or restriction exists for a specific chemical in the EU, the chemical is found on Annex II or III, respectively, and this is provided as well. Absence of a listing on EU Annex V indicates that a chemical is not permitted to be used as a preservative; absence of a listing on Annex II or III indicates a chemical is not otherwise banned or restricted in personal care products. Applicable activities from the following state departments were also searched: WSDE (2011); CA OEHHA (2015); ME DEP (2012); MN DH (2013); CA DPH (2015); and CA DTSC (2015). Finally, synopses of Cosmetic Ingredient Review (CIR) Expert Panel opinions are provided. Regulatory and related information from these sources is noted in each chemical profile where available.[13]

13 Not including the regulatory information, the following primary resources were searched to compile the preservative profiles unless noted otherwise: Steinberg (2012), EC (2015b), chemical supplier information provided exclusively via UL Prospector (https://www.ulprospector.com/en/na/PersonalCare), and the NIH hazardous substances data bank (https://www.nlm.nih.gov/pubs/factsheets/hsdbfs.html). The profile information is accurate as of January 2016, however resources used to compile the profiles change and information may be outdated. Note the information presented here does not reflect the view of Environmental Defense Fund and is strictly a digest of what is reported in the referenced resources.

## BENZYL ALCOHOL (CAS# 100-51-6)

### Overview

- Functions: Fragrance component, preservative, solvent, viscosity-controlling (EC, 2015b); flavoring component, plasticizer, degreasing agent (HSDB, 2009).
- Microbial Activity: Most active against gram-positive bacteria, moderately active against gram-negative bacteria and yeast/mold (Siegert, 2014).
- Product Uses: Cosmetics[14], food, over the counter drugs, inks and paint (Steinberg, 2012).
- Formulation Considerations (Steinberg, 2012):
  - Most effective below pH 7;
  - Inactivated by nonionics;
  - Soluble in water;
  - Will oxidize to benzaldehyde, which has a strong odor, therefore antioxidants are co-incorporated into formulations.

14 The FDA defines "cosmetics" by their intended use, as "articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body...for cleansing, beautifying, promoting attractiveness, or altering the appearance" [FD&C Act, sec. 201(i)]. The EU Cosmetics Regulation stipulates that the determination of a product as a "cosmetic" is done on a case-by-case basis; section (7) of the Cosmetics Regulation provides a list of possible products (EC, 2009). The CIR defines "cosmetics" as "(1) articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance, and (2) articles intended for use as a component of any such articles, except that it shall not include soap" (CIR, 2010).

# BENZYL ALCOHOL (CAS# 100-51-6)

## Regulatory and Related Information

- Listed in Section 34 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Maximum concentration in ready for use preparation: 1.0%.
- Listed in Section 45 of EC Cosmetics Regulation No. 1223/2009Annex III: Substances which cosmetic products must not contain except subject to the restrictions laid down:
  - May be used for uses other than as a preservative in certain product types (i.e., as a solvent or fragrance); the purpose has to be apparent from the presentation of the product;
  - Requirements due to identification as EU Fragrance Allergen (SCCS, 2012): The presence of the substance must be indicated in the list of ingredients when its concentration exceeds: 0.001% in leave-on products and 0.01% in rinse-off products;
- Reviewed by CIR Expert Panel, as amended (CIR, 2011c):
  - Safe in current practices of use and concentration[15] (S);[16]
  - Use concentrations for S conclusion: 0.000006 – 10%.

15 The CIR Expert Panel bases its safety determinations on the expected use of each ingredient in cosmetics. The Panel determines expected use, including use concentrations, based on data received from the FDA through its Voluntary Cosmetic Registration Program (VCRP) as well as by industry submissions in response to a survey conducted by the Personal Care Products Council (PCPC) on the maximum reported use concentrations by product category (CIR, 2010).

16 The CIR Expert Panel determines, for each cosmetic ingredient, whether it is: safe in the present practices of use and concentration (S), safe for use in cosmetics with qualifications (SQ), the available data are insufficient to support safety (I), the available data are insufficient to support safety but the ingredient is not in current use (Z), the ingredient is unsafe for use in cosmetics (U), the available data are insufficient and the ingredients use in cosmetics is not supported (UNS).

# CAPRYLHYDROXAMIC ACID (CAS# 7377-03-9)

## Overview

- Functions: Chelant[18] (EC, 2015b) (chelates with $Fe2^{+}$ and $Fe3^{+}$ ions); preservative (Steinberg, 2012).
- Product Uses: Cosmetics (Inolex, 2013a).
- Microbial Activity: Most active against mold; also active against gram-positive and negative bacteria and yeast (Hase et al. 1971; Ammendola et al., 2009; Bravo and Lazo, 1993; Steinberg, 2012).
- Formulation considerations (Inolex, 2013a):
  - Suitable for pH 2-8;
  - May interact with residual iron found in certain clay-type compounds which can result in a very mild orange color or color shift and decreased preservative activity in products.

## Regulatory and Related Information: None available in searched sources.

17 "Reacts and forms complexes with metal ions which could affect the stability and/or appearance of cosmetics" (EC, 2015b)

# CAPRYLYL GLYCOL (CAS# 1117-86-8)

## Overview

- Functions: Emollient[18], hair-conditioning agent[19], humectant[20], skin-conditioning agent[21] (EC, 2015b); viscosity agent, preservative (CIR, 2011b).
- Product Uses: Cosmetics (Steinberg, 2012).
- Microbial Activity: Active against gram-positive and gram-negative bacteria; moderate activity for yeasts/molds (Dr. Straetmans, 2008); also able to improve the effectiveness of other preservatives at concentrations lower than their typical use level.
- Formulation Considerations (Steinberg, 2012):
  - Active in broad pH range;
  - Inactivated by dilution;
  - Insoluble in water;
  - Poorly active in surfactant systems;
  - May affect the viscosity and stability of certain emulsions as it is a secondary emulsifier.

## Regulatory and Related Information

- Reviewed by CIR Expert Panel (CIR, 2011b):
  - Safe in the current practices of use and concentration (S);
  - Use concentration for S conclusion: 0.00003 - 5% for dermal contact personal care products;
  - Potential skin penetration enhancers.

18 "Softens and smooths the skin" (EC, 2015b)

19 "Leaves the hair easy to comb, supple, soft and shiny and/or imparts volume, lightness, gloss, etc." (EC, 2015b)

20 "Holds and retains moisture" (EC, 2015b)

21 "Maintains the skin in good condition" (EC, 2015b)

# DMDM HYDANTOIN (CAS# 6440-58-0)

## Overview

- Functions: Preservative (EC, 2015b).
- Microbial Activity: Good activity for gram positive and gram negative bacteria; moderately active against yeasts and molds (Siegert, 2014).
- Product Uses: Personal care products, paints, coatings and household products, adhesives, polymer solutions, metal working products and clay slurries (Steinberg, 2012).
- Formulation considerations (Steinberg, 2012):
  - Active at pH 3-9;
  - Water soluble, low oil solubility

Commercially available for cosmetics in aqueous solution, oil solution, or as an anhydrous powder.

## Regulations and Related Information

- Listed in Section 33 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Substance name: 1,3-Bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione:
  - Maximum concentration in ready for use preparation: 0.6%;
  - If the concentration of free formaldehyde exceeds 0.05% in the finished product, the product must be labeled “contains formaldehyde”.
- Minnesota Ban on Formaldehyde Releasers in Children’s Product (also see Appendix A).
- Reviewed by CIR Expert Panel (CIR, 1988):
  - Safe in current practices of use and concentration (S);
  - Use concentration for S conclusion: Up to 1% for dermal contact cosmetics.

# ETHYLENEDIAMINIETETRAACETIC ACID (EDTA) (CAS# 60-00-4)

## Overview

- Functions: Chelant (EC, 2015b); antioxidant, detergent, bleaching agent, etching agent (HSDB, 2012).
- Microbial Activity: Reduces availability of iron for microbial growth; not active against gram-positive bacteria; enhances activities of antibacterial agents particularly against drug-resistant gram-negative microbes by increasing the permeability of cellular membranes; prevents growth of yeast and molds in zinc-dependent fashion (Brul et al., 1997).
- Product Uses: Cosmetics, food, medicine, cleaning (Steinberg, 2012).
- Formulation Considerations (Steinberg, 2012):
  - EDTA is mostly insoluble in water, preferred incorporation through its salts (Disodium EDTA, Trisodium EDTA, and Tetrasodium EDTA);
  - Aqueous solution of EDTA contains by-products of formalin and sodium cyanide, however, the purified and dried form of aqueous EDTA forms the salts which have had the impurities removed.

## Regulatory and Related Information

- Reviewed by CIR Expert Panel (CIR, 2002):
  - Safe in current practices of use and concentration (S);
  - Use concentration for S conclusion: Up to 2%.

# ETHYLHEXYLGLYCERIN (CAS# 70445-33-9)

## Overview

- Functions: Skin-conditioning agent (EC, 2015b); Solvent and enhancer for other preservatives (Steinberg, 2012).
- Product Uses: Personal care products (emulsions only) (Inolex, 2013a).
- Microbial Activity: Most active against gram positive bacteria; boosts the efficacy of traditional preservatives and acts as an antimicrobial stabilizer (Steinberg, 2012; Leschke and Siegert, 2008).
- Formulation Considerations (Steinberg, 2012):
  - Active over broad pH range;
  - No published inactivators;
  - Poorly soluble in water.

## Regulatory and Related Information

- Reviewed by CIR Expert Panel (CIR, 2011a; 2013):
  - Safe in the current practices of use and concentration (S).
  - No use concentration identified for S conclusion, but used in products at concentrations up to 8% (as of 2011).

# GLUCONOLACTONE (CAS# 90-80-2)

## Overview

- Functions: Chelant; skin-conditioning agent (EC, 2015b); flavoring ingredient (Spectrum, 2015a).
- Microbial Activity: The active agent, gluconic acid, is able to control microbial growth by reducing pH to a level that inhibits putrefactive and toxigenic bacteria growth (Lemay et al., 2000).
- Product Uses: Cosmetics (EC, 2015b); food (Spectrum, 2015b).
- Formulation considerations: No information available in searched sources.

Regulatory and Related Information: None available in searched sources.

# IODOPROPYNYL BUTYLCARBAMATE (IPBC) (CAS# 55406-53-6)

## Overview

- Functions: Preservative (EC, 2015b); fungicide (Steinberg, 2012).
- Microbial Activity: Very active against yeast and mold, inadequate activity against bacteria (Steinberg, 2012).
- Product Uses: Personal care products, industrial applications (Steinberg, 2012)
- Formulation Considerations (Steinberg, 2012):
  - Active at pH 2-9, slowly hydrolyzes at alkaline pH;
  - Inactivated by strong reducing agents, acids, and bases;
  - Low water solubility, soluble in propylene glycol.

## Regulatory and Related Information

- Listed in Section 56 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics with the following restrictions:
  - Maximum concentration in ready for use preparation:
    - Rinse-off products: 0.02%; not to be used in rinse-off products for children under the age of 3 except in bath products, shower gels, and shampoos;
    - Leave-on products: 0.01%; not to be used in body lotion and body cream; not be used in leave-on product for children under the age of 3;
    - Deodorants/antiperspirants: 0.0075%;
    - Not to be used in oral and lip products.
  - Warning labels required. Wording of warnings:
    - For rinse off products other than bath products/ shower gels and shampoo, which might be used for children under 3 years of age: “Not to be used for children under 3 years of age”;
    - For leave on products and deodorants/anti-perspirants which might be used on children under 3 years of age: “Not to be used for children under 3 years of age”.
- Reviewed by CIR Expert Panel (CIR, 1998):
  - Safe for use in cosmetics with qualifications (SQ): Safe for use at 0.1%; should not be used in products intended to be aerosolized;
  - Generally used at less than 0.0125%.
- Additional Regulatory Information:
  - Allowed in Japan in cosmetics up to 0.02%.

# LACTOBACILLUS FERMENT (CAS# 1686112-36-6)

## Overview

- Functions: Skin-conditioning agent (EC, 2015b); skin and hair conditioning agent, preservative (Active Micro, 2014).
- Microbial Activity: Active against gram positive and gram negative bacteria, moderate activity for yeasts and molds (Active Micro, 2014).
- Product Uses: Cosmetics.
- Formulation Considerations (Active Micro, 2014):
  - Active at pH 3-8;
  - No identified inactivators;
  - Water soluble.

Regulatory and Related Information: None available in searched sources.

# METHYLISOTHIAZOLINONE (MIT) (CAS# 2682-20-4)

## Overview

- Functions: Preservative (EC, 2015b).
- Microbial Activity: Good to moderate activity for gram positive and gram negative bacteria, yeasts, and molds (Siegert, 2014).[22]
- Product Uses: Personal care products, cleaning products, industrial applications (Ashland, undated).
- Formulation Considerations (Steinberg, 2012):
  - Active at pH 2-10;
  - Reacts and loses activity with: bisulfites, secondary amines, strong nucleophiles;
  - Soluble in water.

## Regulatory and Related Information

- Listed in Section 57 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Maximum concentration in ready for use preparation: 0.01%; however, a ban on MIT in leave-on applications is set to go into effect in 2017;
  - Maximum concentration in mixture of Methylchloroisothiazolinone (MCI) and Methylisothiazolinone in ready for use preparations: 0.0015% (of a 3:1 mixture of MCI:MIT);
  - SCCS (2015): Use of MIT in rinse-off applications should be lowered to 0.0015% due to sensitizing effects.
- Reviewed by CIR Expert Panel (CIR, 2014a):
  - Safe for use in cosmetics with qualifications (SQ): Safe at concentrations up to 100 ppm (0.01%) in rinse-off products and in leave-on products when formulated to be non-sensitizing, which may be determined based on quantitative risk assessment (QRA).
- Additional regulatory information:
  - Allowed preservative in Japan at concentrations equal or less than 0.01%; not allowed in any products applied to mucosa;
  - Restricted in Health Canada's Cosmetic Ingredient Hotlist:
    - MIT by itself is allowed for use as a preservative in concentrations equal to or less than 0.01%;
    - MCI may only be used when in combination with MIT. The mixture is banned in leave on products and restricted to 0.0015% in rinse off products.

22 Siegert (2014) notes that the 100 ppm restriction on MIT will render it unable to protect cosmetics

# PHENOXYETHANOL (CAS# 122-99-6)

## Overview

- Functions: Preservative (EC, 2015b); perfume fixative (CIR, 2014a); solvent, insect repellent (Steinberg, 2012).
- Microbial Activity: Most active against gram-negative bacteria; moderate activity for gram-positive bacteria and yeasts/molds (Siegert, 2014).
- Product Uses: Cosmetics, fragrances, insect repellent, paint strippers, drug products, adhesives (Steinberg, 2012; CIR, 2014a).
- Formulation Considerations (Steinberg, 2012):
  - Active over pH range 3-10;
  - Inactivated by highly ethoxylated compounds;
  - Soluble in water, propylene glycol, and glycerin;
  - Purity level of ingredient activity can vary in commercial products, with several different impurities possible. In particular, the level of the impurity free phenol, which is an irritant, is important to consider;
  - Phenoxyethanol may increase bacterial load in anionic surfactant solutions if the water is not saturated with phenoxyethanol, as a low level of the compound can serve as a nutrient for bacteria.

## Regulatory and Related Information

- Listed in Section 29 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Maximum concentration in ready for use preparations: 1%.
- Reviewed by CIR Expert Panel (CIR, 2014a):
  - Safe in the current practices of use and concentrations (S);
  - Use concentration for S conclusion: 0.0002 to 1%.
- Additional regulatory information:
  - Japan has approved for use at a maximum concentration of 1% without restrictions for all personal care products.

# PIROCTONE OLAMINE (CAS# 68890-66-4)

## Overview

- Functions: Preservative (EC, 2015b); anti-dandruff agent (Clariant, 2004).
- Microbial Activity: Good activity against gram-positive bacteria, yeasts and molds; moderate activity for gram negative bacteria (Clariant, 2004;
  Siegert, 2014).
- Product Uses: Cosmetics, over-the-counter drugs (anti-dandruff hair products) (Clariant, 2004).
- Formulation Considerations: No information available in searched sources.

## Regulations and Related Information

- Listed in Section 35 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Substance group: 1-Hydroxy-4-methyl-6-(2,4,4-trimethylpentyl)-2 pyridon and its monoethanolamine salt;
  - Maximum concentration in ready for use preparation for rinse-off products: 1.0%;
  - Maximum concentration in ready for use preparation for other products: 0.5%.
- Listed in Section 61 of EC Cosmetics Regulation No. 1223/2009 Annex III: Substances which cosmetic products must not contain except subject to the restrictions laid down:
  - Substance group: Monoalkylamines, monoalkanolamines and their salts;
  - Maximum concentration in ready for use preparation: Maximum secondary amine content: 0.5%;
  - Other:
    - Do not use with nitrosating systems;
    - Minimum purity: 99%;
    - Maximum secondary amine content: 0.5% (applies to raw materials);
    - Maximum nitrosamine content: 50 microgram/kg;
    - Keep in nitrite-free containers.

# PROPYLPARABEN (94-13-3)

## Overview

- Functions: Preservative (EC, 2015b).
- Microbial Activity: Good activity against gram-positive bacteria, yeasts and molds; moderate activity against gram-negative bacteria (Seigert, 2014).
- Product Uses: Cosmetics, food (HSDB, 2007).
- Formulation Considerations (Steinberg, 2012):
  - No activity above pH 6 as it is in inactive salt form;
  - Inactivated by raising the pH; the method of addition of the paraben to formulations will affect inactivation;
  - Water soluble;
  - Only active in the water phase, not active in the oil phase.

### Regulatory and Related Information

- Listed in Section 12 of EC Cosmetics Regulation 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Listed in substance group: Butyl 4-hydroxybenzoate and its salts, Propyl 4-hydroxybenzoate and its salts;
  - Maximum concentration in ready for use preparation:
    - 0.14% (as acid);
    - Aggregate concentration of butyl- and propylparaben and their salts cannot exceed 0.14%;
    - Aggregate concentration of substances in substance group[23] cannot exceed 0.8% (as acid).
  - Additional conditions:
    - Not to be used in leave-on products designed for application on the nappy area of children under three years of age;
    - Required wording of warning labels for conditions of use for leave-on products designed for children under three years of age: "Do not use on the nappy area".
- Maine Chemical of High Concern (ME DEP, 2012).
- Minnesota Chemical of High Concern (MN DH, 2013).
- Washington State Department of Ecology Chemical of High Concern to Children (WSDE, 2011).
- CA DTSC Informational List of Candidate Chemicals (CA DTSC, 2015).

23 The substance group includes all substances listed in entries 12 and 12a in Annex V, which includes: butylparaben, propylparaben, sodium propylparaben, sodium butylparaben, potassium butylparaben, potassium propylparaben, 4-hydroxybenzoicacid, methylparaben, potassium ethylparaben, potassium paraben, sodium methylparaben, sodium ethylparaben, ethylparaben, sodium paraben, potassium methylparaben, and calcium paraben.

- Reviewed by CIR Expert Panel (CIR, 2008):
  - Safe in the current practices of use and concentrations (S);
  - Use concentration for S conclusion: Up to 0.4% if used alone; maximum aggregate concentration of parabens in a product is 0.8%.

## SORBIC ACID (CAS# 110-44-1)

### Overview

- Functions: Preservative (EC, 2015b).
- Microbial Activity: Most active against yeast and mold (fungistatic) and poorly active against bacteria (CIR, 2012).
- Product Uses: Cosmetics, food, pharmaceuticals (Steinberg, 2012); Animal feeds, tobacco (HSDB, 2002).
- Formulation Considerations (CIR, 2012; Steinberg, 2012):
  - Active at pH values up to 6.5;
  - Inactivated by raising the pH;
  - Poorly soluble in water;
  - Subject to oxidation.

### Regulatory and Related Information

- Listed in Section 4 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetics:
  - Listed in substance group: Hexa-2,4-dienoic acid and its salts;
  - Maximum concentration in ready for use preparation: 0.6% (acid).
- Reviewed by CIR Expert Panel (CIR, 1988):
  - Safe in the current practices of use and concentration (S);
  - Use concentration for S conclusion: up to 5% for dermal contact personal care products.
- Permitted in Japan in all applications up to 0.5%.

## SORBITAN CAPRYLATE (CAS# 60177-36-8)

### Overview

- Functions: Emulsifier (EC, 2015b); viscosity controlling agent, assists efficacy of preservatives (Clariant, 2012).
- Microbial Activity: Demonstrates efficacy against gram-positive bacteria; not active against gram-negative bacteria and undetermined for yeasts/molds (Clariant, 2012; Wagh et al., 2012).
- Product Uses: Personal care products (Clariant, 2012).
- Formulation Considerations (Clariant, 2012):
  - Active at pH 4-8;
  - No identified inactivator;
  - Poor solubility in water.

### Regulatory and Related Information

- Reviewed by CIR Expert Panel (CIR, 2014b):
  - Safe in current practices of use and concentration (S);
  - Use concentration for S conclusion: up to 5% for dermal contact personal care products.

# UNDECYLENIC ACID (CAS# 112-38-9)

## Overview

- Functions: Cleansing[24], emulsifier, preservative, surfactant[25] (EC, 2015b); modifying agent, fungistat (Bingham and Cohrssen, 2012).
- Microbial Activity: Active against fungi (Spectrum, 2015b); no activity against bacteria (Siegert, 2014).
- Product Uses: Cosmetics, pharmaceuticals (over-the-counter drugs) (Spectrum 2015ba); plasticizer and lubricant additive (Bingham and Cohrssen, 2012).
- Formulation considerations: No information available in searched sources.

## Regulations and Related Information

- Listed in Section 18 of EC Cosmetics Regulation No. 1223/2009 Annex V: Preservatives allowed for use in cosmetic products:
  - Substance group: Undec-10-enoic acid and its salts;
  - Maximum concentration in ready for use preparations: 0.2% (as acid).
- Following CIR procedure, CIR deferred evaluation because the safety of this ingredient has been assessed by the FDA (Cosmetics Info, undated).
- Additional regulatory information:
  - Approved by the FDA as an antifungal ingredient in topical antimicrobial drug products for over-the-counter human use, provided that the total concentration of undecylenate in formulation is 10 – 25% (FDA, 2002).

24 "Helps to keep the body surface clean" (EC, 2015b)

25 "Lowers the surface tension of cosmetics as well as aids the even distribution of the product when used" (EC, 2015b)

# APPENDIX C Overview of GreenScreen® for Safer Chemicals Method

GreenScreen® for Safer Chemicals is a comparative hazard assessment method designed to efficiently and consistently characterize hazards for human health and environmental fate and toxicity endpoints using a robust literature search approach that builds from authoritative and screening sources (CPA, 2015). The GreenScreen® method has been used by many companies as well as advocacy groups to evaluate and make decisions around the use of chemicals in a variety of product types such as electronics, building materials, and textiles (Eisenberg, 2013; GC3, 2013; Heine, 2013; Material IQ, 2016). It has also been used as a hazard assessment method for alternative assessments by several state regulatory programs (WA DoH, 2008; MN DEP 2012), and is recognized as the hazard assessment platform for several standards and ecolabels (USGBC, 2008; ZDHC, 2013; CPA, 2015).

The GreenScreen® hazard assessment method is publically available and involves an evaluation of 18 human health, environmental and physical hazard endpoints (CPA, 2011; 2012; 2013). The human health endpoints are subdivided into 1) Group I Human Health hazards (carcinogenicity, mutagenicity, reproductive toxicity, developmental toxicity, and endocrine activity), which according to the developers, represent hazards that lead to chronic or life-threatening health effects that may result from low dose exposures, and 2) Group II Human Health hazards (acute toxicity, systemic toxicity-single dose, neurotoxicity-single dose, skin irritation, and eye irritation) and II* (systemic toxicity-repeated dose, neurotoxicity-repeated dose, skin sensitization, and respiratory sensitization). The environmental endpoints include ecotoxicity (acute aquatic and chronic aquatic) and environmental fate (persistence and bioaccumulation), while the physical hazard endpoints include reactivity and flammability (CPA, 2013).

Figure C1: Sample GreenScreen® Hazard Assessment Table

| Group I Human Health | | | | | Group II and II* Human Health | | | | | | | | 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 | M | DG | L | *M* | *H* | H | DG | L | H | L | L | vL | vL | *L* | L |

Evaluation of a chemical across each of the hazard endpoints involves both a review of authoritative lists[26] and available data.[27] Following the compilation and review of data, a hazard score is assigned (i.e., Very Low (vL), Low (L), Moderate (M), High (H), or Very High (vH)) to each endpoint according to the GreenScreen® method, which is largely based on criteria outlined in the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UN, 2015; CPA, 2012). In addition, a confidence level (low or high) is assigned to the hazard score to indicate the quality and robustness of the dataset leading to the score. The confidence level of the score is assigned based on the quantity, quality (both in terms of experimental design and reporting), and type (e.g., experimental or modeled, in vitro or in vivo) of available data and overall ability of the dataset to support the hazard classification. Scores assigned with high confidence are reported in bold, while score assigned with reduced confidence are reported in italics. A Data Gap (DG) is assigned when data are lacking or insufficient to assign an endpoint hazard score.

26 GreenScreen® specified authoritative lists can be found at http://www.greenscreenchemicals.org/

27 Data considered in the evaluation include experimental data for the target chemical and surrogates as well as modeled and estimated data

Finally, an overall GreenScreen® Benchmark™ score ranging from 1 (Avoid—Chemical of High Concern) to 4 (Prefer—Safer Chemical) is assigned based on the individual hazard endpoint scores as outlined in the GreenScreen® method (CPA, 2011). The Benchmark™ score is intended to serve as a high-level indicator of hazard, while the individual hazard scores and data summaries for each endpoint provide a deeper level of hazard characterization for comparison and decision-making.

## GreenScreen® for Safer Chemicals v1.3
## GreenScreen Benchmarks™

**ABBREVIATIONS**
- **P** Persistence
- **B** Bioaccumulation
- **T** Human Toxicity and Ecotoxicity

GS BENCHMARK 4

**GREENSCREEN BENCHMARK–4**

Low P* + Low B + Low T (Ecotoxicity, Group I, II and II* Human) + Low Physical Hazards (Flammability and Reactivity) + Low (additional ecotoxicity endpoints when available)

**Prefer—Safer Chemical**

**GREENSCREEN BENCHMARK–3**

a. Moderate P or Moderate B
b. Moderate Ecotoxicity
c. Moderate T (Group II or II* Human)
d. Moderate Flammability or Moderate Reactivity

**Use but Still Opportunity for Improvement**

**GREENSCREEN BENCHMARK–2**

a. Moderate P + Moderate B + Moderate T (Ecotoxicity or Group I, II, or II* Human)
b. High P + High B
c. High P + Moderate T (Ecotoxicity or Group I, II, or II* Human)
d. High B + Moderate T (Ecotoxicity or Group I, II, or II* Human)
e. Moderate T (Group I Human)
f. Very High T (Ecotoxicity or Group II Human) or High T (Group II* Human)
g. High Flammability or High Reactivity

**Use but Search for Safer Substitutes**

**GREENSCREEN BENCHMARK–1**

a. PBT = High P + High B + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]
b. vPvB = very High P + very High B
c. vPT = very High P + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]
d. vBT = very High B + [very High T (Ecotoxicity or Group II Human) or High T (Group I or II* Human)]
e. High T (Group I Human)

**Avoid—Chemical of High Concern**

GREENSCREEN® FOR SAFER CHEMICALS

**GREENSCREEN BENCHMARK–U**
Unspecified Due to Insufficient Data



**See Guidance** (GreenScreen for Safer Chemicals Hazard Assessment Guidance) at http://greenscreenchemicals.org/method/method-documents for instructions.

**Group I Human** includes Carcinogenicity, Mutagenicity/Genotoxicity, Reproductive Toxicity, Developmental Toxicity (incl. Developmental Neurotoxicity), and Endocrine Activity. **Group II Human** includes Acute Mammalian Toxicity, Systemic Toxicity/Organ Effects-Single Exposure, Neurotoxicity-Single Exposure, Eye Irritation and Skin Irritation. **Group II* Human** includes Systemic Toxicity/Organ Effects-Repeated Exposure, Neurotoxicity-Repeated Exposure, Respiratory Sensitization, and Skin Sensitization. Immune System Effects are included in Systemic Toxicity/Organ Effects. **Ecotoxicity** includes Acute Aquatic Toxicity and Chronic Aquatic Toxicity.

* For inorganic chemicals, Persistence alone will not be deemed problematic. See Section 13.4 in this Guidance.

# References


Active Micro Technologies. 2014. Leucidal® Liquid PT Technical Data Sheet. Available: **http://activemicrotechnologies.com/product/leucidal-liquid-pt/**

American Sustainable Business Council (ASBC). 2015. Making the Business & Economic Case for Safer Chemistry. Report for the American Sustainable Business Council and Green Chemistry & Commerce Council. April 24. Available: **http://asbcouncil.org/sites/default/files/asbcsaferchemicalsreportpresred.pdf**

Ammendola, S., A. Lembo, A. Battistoni, P. Tagliatesta, C. Ghisalberti, and A. Desideri. 2009. 10-Undecanhydroxamic acid, a hydroxamate derivative of the undecanoic acid, has strong antimicrobial activity through a mechanism that limits iron availability. FEMS Microbial Letters. 294:61-67.

Ashland. Undated. Optiphen® MIT Datasheet.

Bingham, E., and Cohrssen, B., eds. 2012. Patty's Toxicology. Sixth Edition. Volume 3. John Wiley & Sons, Inc., Hoboken, New Jersey. pgs. 550-551.

Bledzka D, Gromadzinska J, Wasowicz W. 2014. Parabens. From environmental studies to human health. Environ Int. Jun; 67:27-42.

Brannan, D.K. 1997. Cosmetic Microbiology: A Practical Handbook. CRC Press, New York.

Bravo, H.R., and W. Lazo. 1993. Antimicrobial activity of cereal hydroxamic acids and related compounds. Phytochemistry. 33(3):569-571.

Brul, S., M. Stratford, J.M. van der Vaart, S.K. Dielbandhoesing, H. Steels, F.M. Klis, and C.T. Verrips. 1997. The antifungal action of 1,10-o-phenanthroline and EDTA is mediated through zinc chelation and involves cell wall function. Food Technol. Biotechnol. 35(4):267-274.

California Department of Public Health (CA DPH). 2015. California Safe Cosmetics Program: Reportable Ingredient List. Occupational Health Branch. Available: **https://safecosmetics.cdph.ca.gov/search/**

California Department of Toxic Substances Control (CA DTSC). 2015. Safer Consumer Products Act: Informational list of candidate chemicals and chemical groups. Available: **https://www.dtsc.ca.gov/SCP/CandidateChemicals.cfm**.

California Environmental Protection Agency Office of Environmental Health Hazard Assessment (CA OEHHA). 2015. Chemicals known to the state to cause cancer or reproductive toxicity. State of California, Environmental Protection. Agency. Dated: November 20, 2015. Available: **https://oehha.ca.gov/proposition-65/proposition-65-list**

Campaign for Safe Cosmetics. Undated. Chemicals of Concern. **http://www.safecosmetics.org/get-the-facts/chemicals-of-concern/**

Campaign for Safe Cosmetics. 2014. Revlon eliminating toxic chemicals from cosmetics: press release. Available: **http://www.safecosmetics.org/about-us/media/press-releases/revlon-eliminating-toxic-chemicals-from-cosmetics/**

ChemLinked. 2015. Japan Cosmetics Regulation. Last updated: October 15, 2015. REACH24H Consulting Group, A. Hu (ed.). Available: **https://cosmetic.chemlinked.com/chempedia/japan-cosmetics-regulation**

Clariant Corporation. 2004. Safety and effectiveness information for piroctone olamine. FDA Docket No. 2004N-0050. Submitted pursuant to 21 C.F.R 330.14(f) and 330.10(a)(2). Available: **http://www.fda.gov/ohrms/dockets/dailys/04/oct04/101904/04n-0050-rpt0001-02-SEI-vol3.pdf**

Clariant Corporation. 2012. Material Safety Data Sheet for Velsan SC. Available: **http://www.essentialingredients.com/msds/Velsan%20SC.pdf**

Clean Production Action (CPA). 2011. The GreenScreen® for Safer Chemicals Version 1.2 Benchmarks. Dated October 2011. Available: **http://www.greenscreenchemicals.org/**

Clean Production Action (CPA). 2012a.The GreenScreen® for Safer Chemicals Version 1.2 Criteria. Dated: November 2012. Available: **http://www.greenscreenchemicals.org/**

Clean Production Action (CPA). 2012b. List Translator. Dated: February 2012. Available at: **http://www.greenscreenchemicals.org/**

Clean Production Action (CPA). 2013. The GreenScreen® for Safer Chemicals Chemical Hazard Assessment Procedure. Version 1.2 Guidance. Dated August 31, 2013. Available: **http://www.greenscreenchemicals.org/**

Clean Production Action (CPA). 2015. GreenScreen® For Safer Chemicals. Available: **http://www.greenscreenchemicals.org/**

Cosmetic Ingredient Review (CIR). 1988. Final Report on the Safety Assessment of DMDM Hydantoin. J Am College of Toxicology. 7(3): 245-277. Available: **http://www.cir-safety.org/sites/default/files/Supplement%20Book%202.pdf**

Cosmetic Ingredient Review (CIR). 1988. Final Report on the Safety Assessment of DMDM Hydantoin. J Am College of Toxicology. 7(3): 245-277.

Cosmetic Ingredient Review (CIR). 2002. Final report on the safety assessment of EDTA, calcium disodium EDTA, diammonium EDTA, dipotassium EDTA, disodium EDTA, TEA-EDTA, tetrasodium EDTA, tripotassium EDTA, trisodium EDTA, HEDTA, and trisodium HEDTA.

Cosmetic Ingredient Review (CIR). 2008. Final amended report on the safety assessment of methylparaben, ethylparaben, propylparaben, isopropylparaben, butylparaben, isobutylparaben, and benzylparaben as used in cosmetic products. Available: **http://www.cir-safety.org/sites/default/files/PR427.pdf**

Cosmetic Ingredient Review (CIR). 2010. Cosmetic Ingredient Review Procedures. Available: **http://www.cir-safety.org/sites/default/files/pdf1.pdf**

Cosmetic Ingredient Review (CIR). 2011a. Final Safety Assessment of Alkyl Glyceryl Ethers as Used in Cosmetics. December 19, 2011. Available: **http://www.cir-safety.org/sites/default/files/ethylh122011finalx.pdf**

Cosmetic Ingredient Review (CIR). 2011b. Final report on the safety assessment of 1,2-gycols. Available: **http://www.alegesanatos.ro/dbimg/files/1,2-Glycols.pdf**

Cosmetic Ingredient Review (CIR). 2011c. Benzyl alcohol, benzoic acid, and its salts and ester. CIR Expert Panel Meeting December 2011. Available: **http://www.cir-safety.org/sites/default/files/115_buff2_rr.pdf**

Cosmetic Ingredient Review (CIR). 2012. Dicarboxylic Acids and Their Salts as Used in Cosmetics Esters of Dicarboxylic Acids as Used in Cosmetics. Re-review. Available: **http://www.cir-safety.org/sites/default/files/Supplement%20Book%202.pdf**

Cosmetic Ingredient Review (CIR). 2013. Safety Assessment of Alkyl Glyceryl Ethers as Used in Cosmetics. International Journal of Toxicology. 32(S3):5S-21S.

Cosmetic Ingredient Review (CIR). 2014a. CIR Compendium: Containing abstracts, discussions, and conclusions of CIR cosmetic ingredient safety assessments. Washington, DC: Cosmetic Ingredient Review.

Cosmetic Ingredient Review (CIR). 2014b. CIR Expert Panel Report on the Safety Assessment of Sorbitan Esters as Used in Cosmetics. Washington, D.C.: Cosmetic Ingredient Review. Available: **http://www.cir-safety.org/sites/default/files/sorbes092014TAR.pdf**

Cosmetics Info. Undated. Ingredient: Undecylenic Acid. Available: **http://www.cosmeticsinfo.org/ingredient/undecylenic-acid**

Dr. Straetmans. 2008. Dermosoft® Octiol Product Information.

Eisenberg, A., M. Yu, C.W. Lam, O.A. Ogunseitan, and J.M. Schoenung. 2013. Comparative alternative materials assessment to screen toxicity hazards in the life cycle of CIGS thin film photovoltaics. J Hazard Mater 260: 534-542.

Endocrine Society. 2015. Endocrine-Disrupting Chemicals in the European Union. Position Statement. June.

Environmental Defence. 2016. The Just Beautiful Personal care Products Pocket Shopping Guide. Available: **http://environmentaldefence.ca/reports-guides/report-the-just-beautiful-personal-care-products-pocket-shopping-guide/**

European Chemicals Agency (ECHA). 2015. Read-Across Assessment Framework (RAAF). Available: **http://echa.europa.eu/documents/10162/13628/raaf_en.pdf**

European Commission (EC). 2009. Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Available: **http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:02009R1223-20150416&from=EN**

European Commission (EC). 2015a. "Scientific Committee on Consumer Safety (SCCS): About." Available: **http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm**

European Commission (EC). 2015b. CosIng Database. Available at: **http://ec.europa.eu/growth/tools-databases/cosing**

Food and Drug Administration (FDA). 2002. CFR Title 21, Volume 5, Subchapter D, Part 333, Subpart C, Sec. 333.210: Antifungal active ingredients. Amended February 8, 2002. Available: **http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=333.210&SearchTerm=undecylenic%20acid**

FDA. 2006. Parabens. Updated October 31, 2007. Available: **http://www.fda.gov/Cosmetics/ProductsIngredients/Ingredients/ucm128042.htm#Does_FDA_regulate**

FDA. 2014. FDA authority over cosmetics. Updated March 20, 2014. Available: **https://www.fda.gov/Cosmetics/GuidanceRegulation/LawsRegulations/ucm074162.htm**

FDA. 2015a. Cosmetics safety Q&A: Personal care products. Updated March 24, 2015. Available: **http://www.fda.gov/Cosmetics/ResourcesForYou/Consumers/ucm136560.htm**

FDA. 2015b. 21 C.F.R. Part 700. Available: **https://www.ecfr.gov/cgi-bin/text-idx?SID=25a3c592e74803338e92275737cf5e64&mc=true&node=pt21.7.700&rgn=div5**

Green Chemistry and Commerce Council (GC3). 2013. Chemical Hazard Assessments of Alternative Plasticizers for Wire & Cable Applications. Available: **http://greenchemistryandcommerce.org/documents/PilotProjectFullReportOct2-final_000rev.pdf**

Green Chemistry and Commerce Council (GC3). 2016. Preservatives Project. Available: **http://www.greenchemistryandcommerce.org/projects/preservatives-project**

Hase, J., K. Kobashi, N. Kawaguchi, and K. Sakamoto. 1971. Antimicrobial activity of hydroxamic acids. Chemical and Pharmaceutical Bulletin. 19(2):363-368.

Hazardous Substances Data Bank (HSDB). 2002. Entry for Sorbic Acid (CAS# 110-44-1). United States National Library of Medicine. Available: **http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+590**

Hazardous Substances Databank (HSDB). 2007. Propylparaben (CAS# 94-13-3). Available: **http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+203**

Hazardous Substances Data Bank (HSDB). 2009. Entry for Benzyl Alcohol (CAS #100-51-6). HSDB Number 46. Last revision date April 20, 2009. United States National Library of Medicine. Available: **http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+46**

Hazardous Substances Data Bank (HSDB). 2012. Entry for Ethylenediamine Tetraacetic Acid (CAS #60-00-4). HSDB Number 809. Last revision date April 26, 2012. United States National Library of Medicine. Available: **http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/r?dbs+hsdb:@term+@DOCNO+809**

Headwaters. 2016. LOHAS Lifestyles of Health and Sustainability Goes Mainstream. Headwaters MB. Available at: **https://www.eticanews.it/wp-content/uploads/2016/10/LOHAS-Summer_2016.pdf**

Health Canada (HC). 2014. Cosmetic ingredient hotlist. Available: **http://www.hc-sc.gc.ca/cps-spc/alt_formats/pdf/cosmet-person/hot-list-critique/hotlist-liste-eng.pdf**

Heine, L. and S. A. Franjevic. 2013. Chemical Hazard Assessment and the GreenScreen® for Safer Chemicals. In Chemical Alternatives Assessments pp 129-156. Eds. R.e. Hester and R.M. Harrison. RSC Publishing.

Inolex. 2013a. Lexgard® E Product Bulletin. **http://inolex.com/pc/Products/Alternative-Preservation/Lexgard-Series/Lexgard-E**

Kabara & Orth, 1996. Preservative-free and self-preserving cosmetics and drugs: principles and practice. Editedby Kabara JJ, Orth DS. Cosmetic Science and Technology Series/Volume 16, 1996.

Lemay, M-J., N. Rodrigue, C. Gariepy and L. Saucier. 2000. Adaption of Lactobacillus alimentarius to environmental stresses. Int. J. Food Microbiol. 55:249-253.

Leschke, M., and W. Siegert. 2008. Boosting efficacy of preservatives. Preservatives: Reprinted from Personal Care Europe. 1-4.

Maine Department of Environmental Protection (ME DEP). 2012. Safer Chemicals in Children's Products: Chemicals of High Concern Available: **http://www.maine.gov/dep/safechem/highconcern/**

Material IQ. 2016. Material IQ: The Profile. Available: **http://www.materialiq.com/profile.html**

Minnesota Department of Health (MN DH). 2013. Chemicals of High Concern List. Available: **http://www.health.state.mn.us/divs/eh/hazardous/topics/toxfreekids/highconcern.html**

Northcott, M.; Gaw, S; Tremblay, L. 2016. An updated on emerging organic contaminants of concern for New Zealand with guidance on monitoring approaches for councils. Auckland Technical Report. March.

Organisation for Economic Co-operation and Development (OECD). 2014. Guidance on Grouping of Chemicals, Second Edition. Series on Testing and Assessment No. 194. Available: **http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en**

Organisation for Economic Co-operation and Development (OECD). 2016. OECD QSAR Toolbox for Grouping Chemicals into Categories Version 3.4.0.17. Available at: **http://toolbox.oasis-lmc.org/?section=download&version=latest)ofr**

Pharos. 2015. Pharos Chemical and Material Library. Available: **http://www.pharosproject.net/**

Poulsen, PB; Strandesen, M. 2011. Survey and health assessment of cosmetic products marketed as "non-preserved." Danish Ministry of the Environment, Environmental Protection Agency. By of FORCE Technology. Products No. 111 2011 **http://www2.mst.dk/udgiv/publications/2011/04/978-87-92708-67-0.pdf**

Rannou, E. 2015. Guidebook for Exporting/Importing Cosmetics to Japan. EU-Japan Centre for Industrial Cooperation. Tokyo. Available: **http://www.eu-japan.eu/sites/default/files/publications/docs/cosmetics-japan.pdf**

Safer Chemicals, Healthy Families (Safer Chemicals). Undated. "Parabens". Available: **http://saferchemicals.org/chemicals/parabens/**

Santos, MM; Brehm, FA; Knapik, HG; Azevedo JCR. 2016. Occurrence and risk assessment of parabens and triclosan in surface waters of southern Brail: a problem of emerging compounds in an emerging country. RBRH vol. 21 no.3, July/September. **http://www.scielo.br/scielo.php?script=sci_arttext&pid=S2318-03312016000300603**

Schulke. 2015. How to formulate preservative free cosmetics?

Scientific Committee on Consumer Safety (SCCS). 2012. Opinion on fragrance allergens in cosmetic products. Available: **http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf**

Scientific Committee on Consumer Safety (SCCS). 2015. Opinion on methylisothiazolinone (MI) (P94). Submission III (Sensitisation only). SCCS/1557/15 Final Opinion December 2015. Available: **http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_178.pdf**

Siegert, W. 2014. Approved Preservatives for Cosmetics: A Review of Actives Listed in Regulation (EC) No 1223/2009 on Cosmetic Products – Annex V. Berlin: Shulke & Mayr GmbH.

Spectrum Chemical Manufacturing Corporation. 2015a. Undecylenic acid: Safety data sheet.

Spectrum Chemical Manufacturing Corporation. 2015b. Gluconolactone: Safety data sheet.

Steinberg, D.C. 2012. Preservatives for Cosmetics, Third Edition. Allured Business Media: Carol Stream, IL.

Target Corporation. 2017. Target Announces New Chemical Strategy including Policy and Goals for its Products and Operations. January 25. Available: **https://corporate.target.com/article/2017/01/chemical-policy-and-goals**

Underwriters Laboratories (UL). 2013. The Product Mindset 2013 Country Reports. Available: **http://productmindset.ul.com/**

United Nations (UN). 2015. Globally Harmonized System of Classification and Labelling of Chemicals (GHS). Sixth revised edition. Available: **http://www.unece.org/trans/danger/publi/ghs/ghs_rev06/06files_e.html**

United States Environmental Protection Agency (USEPA). 2010. The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program.

United States Environmental Protection Agency (USEPA). 2017a. Series 890 – Endocrine Disruptor Screening Program Test Guidelines. Available: **https://www.epa.gov/test-guidelines-pesticides-and-toxic-substances/series-890-endocrine-disruptor-screening-program**

United States Environmental Protection Agency (USEPA). 2017b. Use of High Throughput Assays and Computational Tools in the Endocrine Disruptor Screening Program. Available: **https://www.epa.gov/endocrine-disruption/use-high-throughput-assays-and-computational-tools-endocrine-disruptor**

United States Green Building Council (USGBC). 2008. Material ingredient optimization. Available: **http://www.usgbc.org/**

University of California, Berkeley (UC Berkeley). 2016. Berkeley Center for Green Chemistry, Greener Solutions. Available: **https://bcgc.berkeley.edu/greener-solutions/**

Vandenberg, LN. 2014. Non-Monotonic Dose Responses in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study. Dose Response. May; 12(2): 259-276.

Wagh, A., S. Shen, F.A. Shen, C.D. Miller, and M.K. Walsh. 2012. Effect of lactose monolaurate on pathogenic and nonpathogenic bacteria. Applied and Environmental Microbiology. 78(9):3465-3468.

Walmart. 2016. Sustainable Chemistry Policy. **http://www.walmartsustainabilityhub.com/sustainable-chemistry**

Washington State Department of Ecology (WSDE). 2011. Children's Safe Product Act: The Reporting List of Chemicals of High Concern to Children (CHCC). Updated August 31, 2014. Available: **http://www.ecy.wa.gov/programs/hwtr/RTT/cspa/chcc.html**

Washington State Department of Ecology (WSDE). 2013. Children's Safe Product Act – reporting rule – WAC 173-334, reporting guidance – product categories and scope. Available: **http://www.ecy.wa.gov/programs/hwtr/rtt/cspa/pdf/cspaguide_category.pdf**

Washington State Department of Health (WA DoH). 2011a. Rationale for reporting list of chemicals of high concern to children: formaldehyde. Available: **http://www.ecy.wa.gov/programs/hwtr/rtt/cspa/pdf/50000.pdf**

Washington State Department of Health (WA DoH). 2011b. Rationale for reporting list of chemicals of high concern to children: propylparaben, butyl paraben, methyl paraben, ethyl, para-hydroxybenzoic paraben. Available: **http://www.ecy.wa.gov/programs/hwtr/rtt/cspa/pdf/parabens.pdf**

Washington State Department of Health (WA DoH). 2008. Alternatives to Deca-BDE in Televisions and Computers and Residential Upholstered Furniture. Final Report. Available: **https://fortress.wa.gov/ecy/publications/documents/0907041.pdf**

Zero Discharge of Hazardous Chemicals. 2013. Framework for the Prioritisation of Hazardous Chemicals. Joint Roadmap. Available: **http://www.roadmaptozero.com/fileadmin/layout/media/downloads/en/FrameworkPrioritisationReportRev1.pdf**

Zhang, Nai-Shen, Liu, You-sheng, Van den Brink, Paul J., Price, Oliver R., Ying, Guang-Guo. 2015. Ecological risks of home and personal care products in the riverine environment of a rural region in South China without domestic wastewater treatment facilities. Ecotoxicology and Environmental Safety. 122:417-425. September.