Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics

Status:	Revised Draft Report for Panel Review
Release Date:	May 19, 2023
Panel Meeting Date:	June 12 – 13, 2023

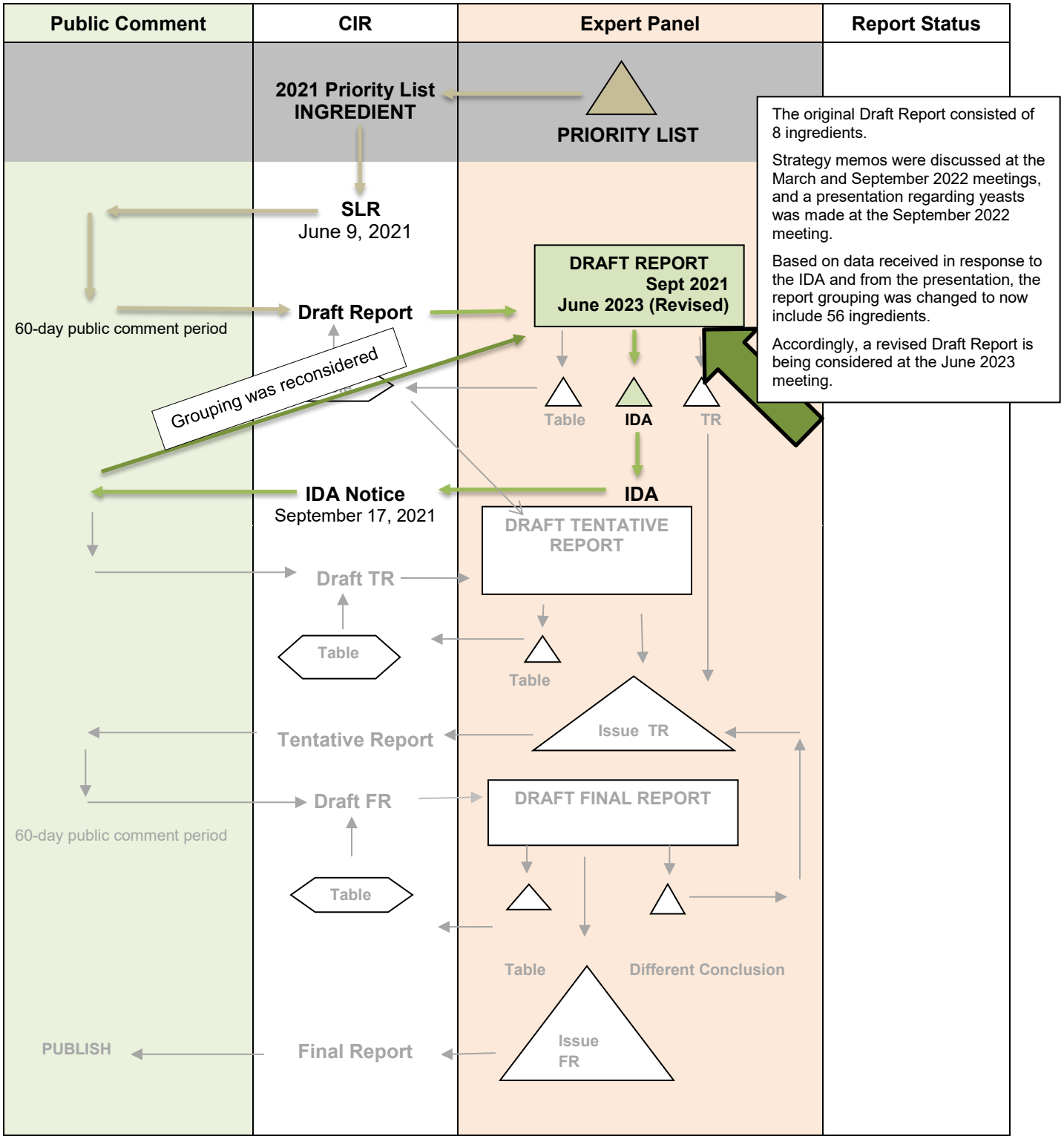
Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◇ Washington, DC 20036-4702 ◇ ph 202.331.0651
cirinfo@cir-safety.org

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Yeast-derived ingredients

MEETING June 2023



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 19, 2023
Subject: Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics

At the September 2021 meeting, the Panel reviewed the Draft Report on the following 8 yeast-derived ingredients:

Hydrolyzed Yeast
Hydrolyzed Yeast Extract
Hydrolyzed Yeast Protein
Yeast
Yeast Beta-Glucan
Yeast Extract
Yeast Polysaccharides
Saccharomyces Cerevisiae Extract

As the definition of Yeast given in the *International Cosmetic Ingredient Dictionary and Handbook* is extremely broad, the Panel issued an Insufficient Data Announcement (IDA) for this ingredient group and requested clarification on the species of yeast used in the manufacturing of these ingredients for use cosmetics. At the time the IDA was issued and until February 2022, *Saccharomyces cerevisiae* was thought to be the predominant species used in the preparation of these yeast-derived ingredients. However, on February 7, 2022, summary information on Yeast Extract derived from several other species of yeast belonging to the Saccharomycetes class (e.g., *Pichia anomala*) was received from Council. Because of this new information, at the March 2022 meeting, a strategy memo was issued asking the Panel for guidance as to whether the report should review only *Saccharomyces cerevisiae*-derived ingredients, or, if ingredients derived from other species of yeast under the class Saccharomycetes class (e.g., Pichia Anomala Extract) should also be reviewed. The Panel suggested the preparation of another strategy memo, including all yeast ingredients currently listed in the *Dictionary*, along with notations of whether or not these ingredients (or their corresponding species) are used in foods, and their frequency of use in cosmetics. The Panel also requested the guidance of an expert with knowledge regarding the classification and general biology of yeasts, and again requested verification from industry on which yeast species are used in the manufacturing of the generic yeast ingredients (e.g., Yeast Extract).

At the September 2022 meeting, an expert presented on the manufacturing, general characteristics, and classification of yeast-derived cosmetic ingredients. (This presentation can be found in the packet as *presentation_Yeast_062023.*) The Panel reviewed the list of all yeast-derived ingredients present in the wINCI *Dictionary* and determined that a Revised Draft Report should be prepared on all ingredients (regardless of frequency of use).

Accordingly, the Revised Draft Report (*report_Yeast_062023*) on 56 yeast-derived ingredients is submitted for review. Unfortunately, no verification has been provided by industry regarding all the species of yeast that can be used in the production of the generic yeast ingredients. However, three data submissions (described below) were received on Yeast Extract, and the genus and species of yeasts (there were several) that were used to derive the Yeast Extract named as the test article in each submission were identified. Based on personal communication with the Council, even though Yeast Extract was identified as the INCI name, it was determined that those data should be associated with the specific ingredients derived from the genus and species named in those submissions. (For example, sensitization data on Yeast Extract derived from *Pichia anomala* are summarized in the report as a study on Pichia Anomala Extract.)

The following are the data that were received:

- Dermal and ocular irritation data on a mixture containing 1.25% Yeast Extract derived from *Saccharomyces cerevisiae* (identified as Saccharomyces Cerevisiae Extract in the report) (*data1_Yeast_062023*)

- Dermal irritation data on a mixture containing 4.5% Yeast Extract derived from *Saccharomyces cerevisiae* (identified as Saccharomyces Cerevisiae Extract in the report) (*data1_Yeast_062023*)
- Summary manufacturing data and chemical properties information on Yeast Extract derived from *Saccharomyces cerevisiae* (identified as Saccharomyces Cerevisiae Extract in the report) (*data2_Yeast_062023*)
- Summary manufacturing, composition, impurities, and toxicological data on Yeast Extracts derived from several species (in the report, each is associated with the corresponding ingredients based on the genus and species) (*data3_Yeast_062023*)

Additionally, in many instances, data were found on the species of yeast (e.g., *Yarrowia lipolytica*), but not on specific ingredients that are reviewed in this report (e.g., Yarrowia Lipolytica Ferment Lysate). Because of the lack of definitive data on the *cosmetic ingredient*, each section of this report is primarily organized by species names, rather than ingredient names.

Furthermore, the data profile (*dataprofile_Yeast_062023*) included herein is composed of two tables. Table 1 of the data profile includes all ingredients derived from a known yeast genus and species. The first column contains the names of the known genus/species used to derive the ingredients, and in the second column, the related ingredients are identified (e.g., column 1: *Phaffia rhodozyma*; column 2: Phaffia Rhodozyma Extract, Phaffia Rhodozyma Ferment Extract). If data were found on the cosmetic ingredient itself (e.g., Phaffia Rhodozyma Extract), or an ingredient derived from that genus and species with unknown cosmetic use (e.g., a *Phaffia rhodozyma extract*), a notation of available data will be present in the ingredient-specific (i.e., Phaffia Rhodozyma Extract) row.

Also, if data were identified as Yeast Extract derived from a known yeast species, but the extract was not identical to the cosmetic ingredient (e.g., data were present for *Metschnikowia reukaufii* extract (not a wINCI ingredient), but not for Hydrolyzed Metschnikowia Reukaufii Extract (the cosmetic ingredient)), a notation of available data will be present in the species only row (i.e., *Metschnikowia reukaufii*) row.

Also in the first table, the "Food Use" and "Dermal Sensitization" columns are highlighted in blue. If a strategy similar to the algae reports is used, ingredients with these types of use and information can be easily identified.

Table 2 of the data profile document lists the generic yeast-derived ingredients. This includes ingredients that, according to the *Dictionary*, do not have a reported genus and species (e.g., Yeast Extract), or, ingredients that have reported genus but no reported species (e.g., Hydrolyzed Saccharomyces Cell Wall). As many species of yeast may be used in the preparation of these generic ingredients, proper searches could not be performed. However, if data were available on a generic ingredient derived from a specific yeast species (e.g., Yeast Extract derived from *Pichia anomala*), in addition to this being noted in Table 1, a notation was also made in this table indicating available data for that ingredient (e.g., Yeast Extract). Although this information is captured for the generic ingredient, it is unknown whether these data are completely representative for that ingredient since it is demonstrated that various species are used in the manufacture of these generic ingredients. Of note, a column to identify food use is not included in this table due to the generic nature of these ingredients.

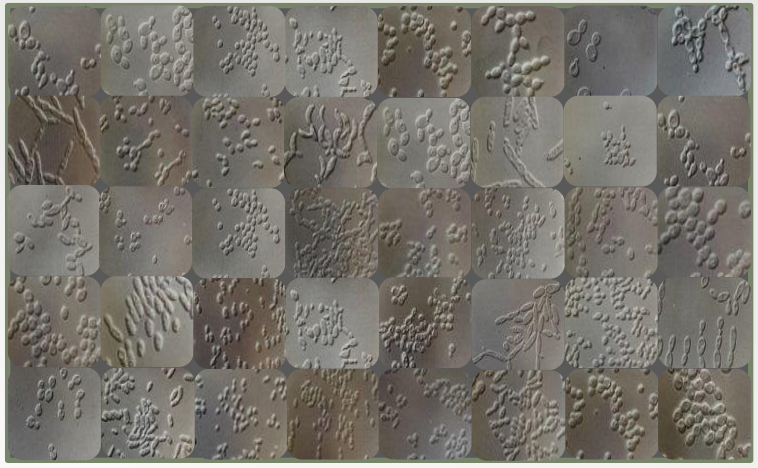
Also included in this packet are transcripts from the previous reviews of this report, including those meetings at which the strategy memos were discussed (*transcripts_Yeast_062023*), the 2021/2022, search strategy (*search_Yeast_062023*), and the flow chart (*flow_Yeast_062023*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, unsafe, or split conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue a second IDA, specifying the data needs therein.

Yeast-derived Cosmetic Ingredients

September 26 – 27th, 2022

Audrey POKRZYWA
Sylvain MAZALREY
(SILAB)



YEASTS : characteristics & identification (third edition)

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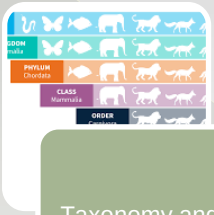
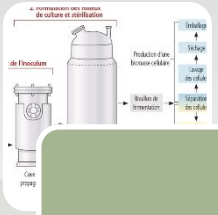
Safety measures and Identification

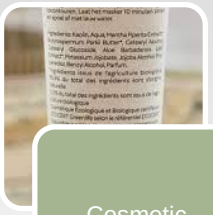


Taxonomy and INCI names



Process

Characterization
Toxicological data

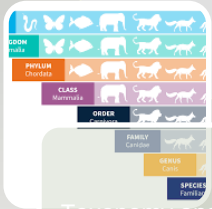


Cosmetic ingredient

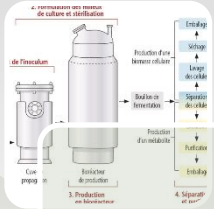
Sourcing

Sourcing

Safety measures and Identification



Taxonomy and INCI names



Process

Characterization

Toxicological data

Cosmetic ingredient

Origin of the strain

- The strains can be sourced from :
  - **Official collection** : ATCC (American Type Culture Collection), CBS (Westerdijk Fungal Bio Diversity Institute) , DSMZ (German Collection of Microorganisms and Cell Cultures), MUCL (Belgian Coordinated Collections of Microorganisms),…

ATCC

WESTERDIJK FUNGAL BIO DIVERSITY INSTITUTE

DSMZ Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH

BCCM BELGIAN COORDINATED COLLECTIONS OF MICROORGANISMS

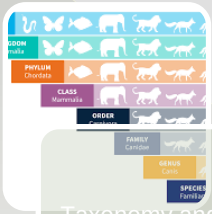
  - **Custom collection** : partnerships with International Centers for Microbial Resources, for example : CIRM dedicated to yeasts in Montpellier (France)

Cirm

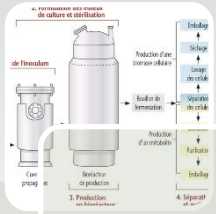
Safety measures, Identification

Sourcing

Safety measures and Identification



Taxonomy and INCI names



Process

Characterization
Toxicological data

Cosmetic ingredient

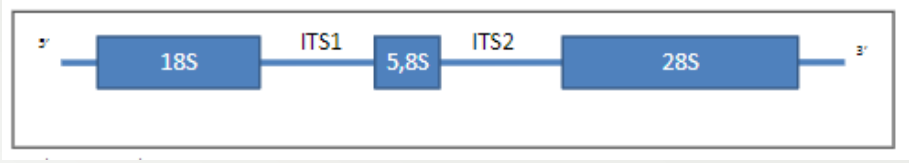
Strain identification

- To be sure to work on the right strain, it is imperative to confirm its taxonomic identification

The best way is by r-28S DNA sequencing and ITS

Principle: Amplification and sequencing of a portion of 28S rRNA encoding the 60S ribosomal subunit. The Internal Transcribed Space (ITS) is a region located on the genomic DNA of eukaryotes between the 28S rRNA and 18S rRNA coding genes. It is composed of three sub-regions: ITS1, ITS2 and the 5.8S gene.

The variability of the ITS seems to favour the identification of the genus and species of fungal populations.

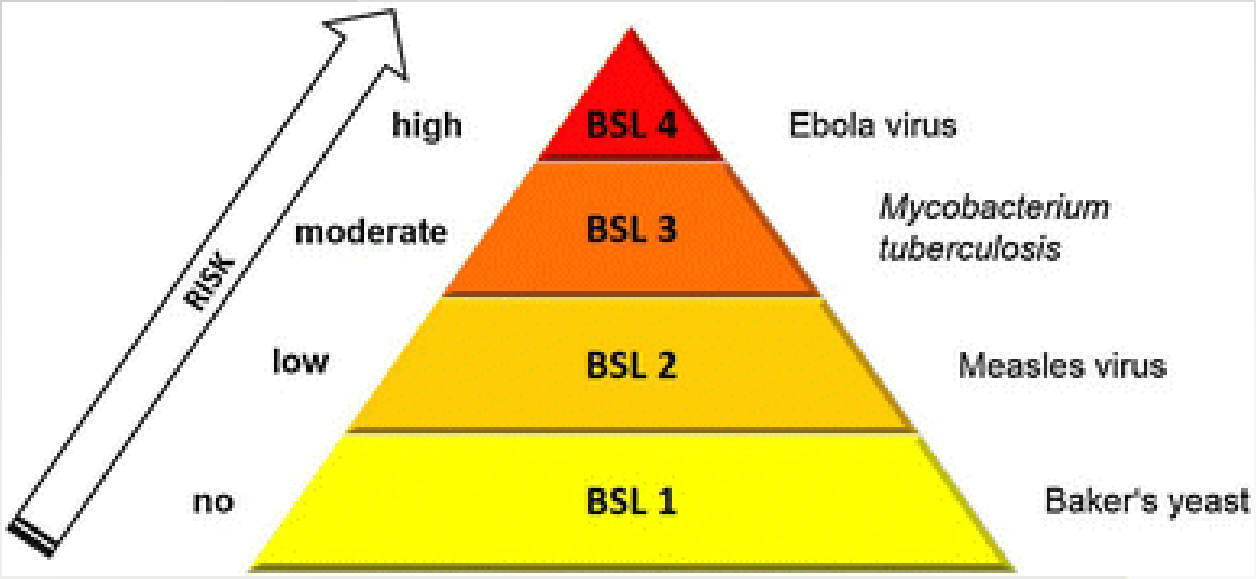


Strain Identification

Biosafety Level	BSL-1	BSL-2	BSL-3	BSL-4
Description	· No Containment · Defined organisms · Unlikely to cause disease	· Containment · Moderate Risk · Disease of varying severity	· High Containment · Aerosol Transmission · Serious/Potentially lethal disease	· Max Containment · "Exotic," High-Risk Agents · Life-threatening disease
Sample Organisms	E.Coli	Influenza, HIV, Lyme Disease	Tuberculosis	Ebola Virus
Pathogen Type	Agents that present minimal potential hazard to personnel & the environment.	Agents associated with human disease & pose moderate hazards to personnel & the environment.	Indigenous or exotic agents, agents that present a potential for aerosol trans-mission, & agents causing serious or potentially lethal disease.	Dangerous & exotic agents that pose a high risk of aerosol-transmitted lab-oratory infections & life-threatening disease.
Autoclave Requirements	None	None	Pass-thru autoclave with Bioseal required in laboratory room.	Pass-thru autoclave with Bioseal required in laboratory room.

Strain Identification

BSL-1 (Biosafety Level One) : this level is defined by the American Centers for Disease Control and Prevention (CDC)



We highly recommend only the use of BSL-1 to manufacture Cosmetic ingredients

Strain Identification

Table 1. ***Classification of infective microorganisms by risk group***

Risk Group 1 *(no or low individual and community risk)*
A microorganism that is unlikely to cause human or animal disease.

Risk Group 2 *(moderate individual risk, low community risk)*
A pathogen that can cause human or animal disease but is unlikely to be a serious hazard to laboratory workers, the community, livestock or the environment. Laboratory exposures may cause serious infection, but effective treatment and preventive measures are available and the risk of spread of infection is limited.

Risk Group 3 *(high individual risk, low community risk)*
A pathogen that usually causes serious human or animal disease but does not ordinarily spread from one infected individual to another. Effective treatment and preventive measures are available.

Risk Group 4 *(high individual and community risk)*
A pathogen that usually causes serious human or animal disease and that can be readily transmitted from one individual to another, directly or indirectly. Effective treatment and preventive measures are not usually available.

Table 2. ***Relation of risk groups to biosafety levels, practices and equipment***

RISK GROUP	BIOSAFETY LEVEL	LABORATORY TYPE	LABORATORY PRACTICES	SAFETY EQUIPMENT
1	Basic – Biosafety Level 1	Basic teaching, research	GMT	None; open bench work
2	Basic – Biosafety Level 2	Primary health services; diagnostic services, research	GMT plus protective clothing, biohazard sign	Open bench plus BSC for potential aerosols
3	Containment – Biosafety Level 3	Special diagnostic services, research	As Level 2 plus special clothing, controlled access, directional airflow	BSC and/or other primary devices for all activities
4	Maximum containment – Biosafety Level 4	Dangerous pathogen units	As Level 3 plus airlock entry, shower exit, special waste disposal	Class III BSC, or positive pressure suits in conjunction with Class II BSCs, double-ended autoclave (through the wall), filtered air

BSC, biological safety cabinet; GMT, good microbiological techniques (see Part IV of this manual)

World Health Organization

Laboratory safety manual (Third edition)

Safety measures

Collection strain

Culture

Primary stock

verification of the absence of contaminants
yeast count
regrowth check

Stock validation

Securing primary stock at -80°C

One cryotube of Primary stock

culture

Secondary stock

verification of the absence of contaminants
yeast count
regrowth check

Stock validation

Securing secondary stock at -80°C

The freezers at -80°C should be under reinforced surveillance

Stocks must be placed in different freezers at -80°C

Business Continuity Plan

Taxonomy and INCI names

Sourcing

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Taxonomy and INCI names

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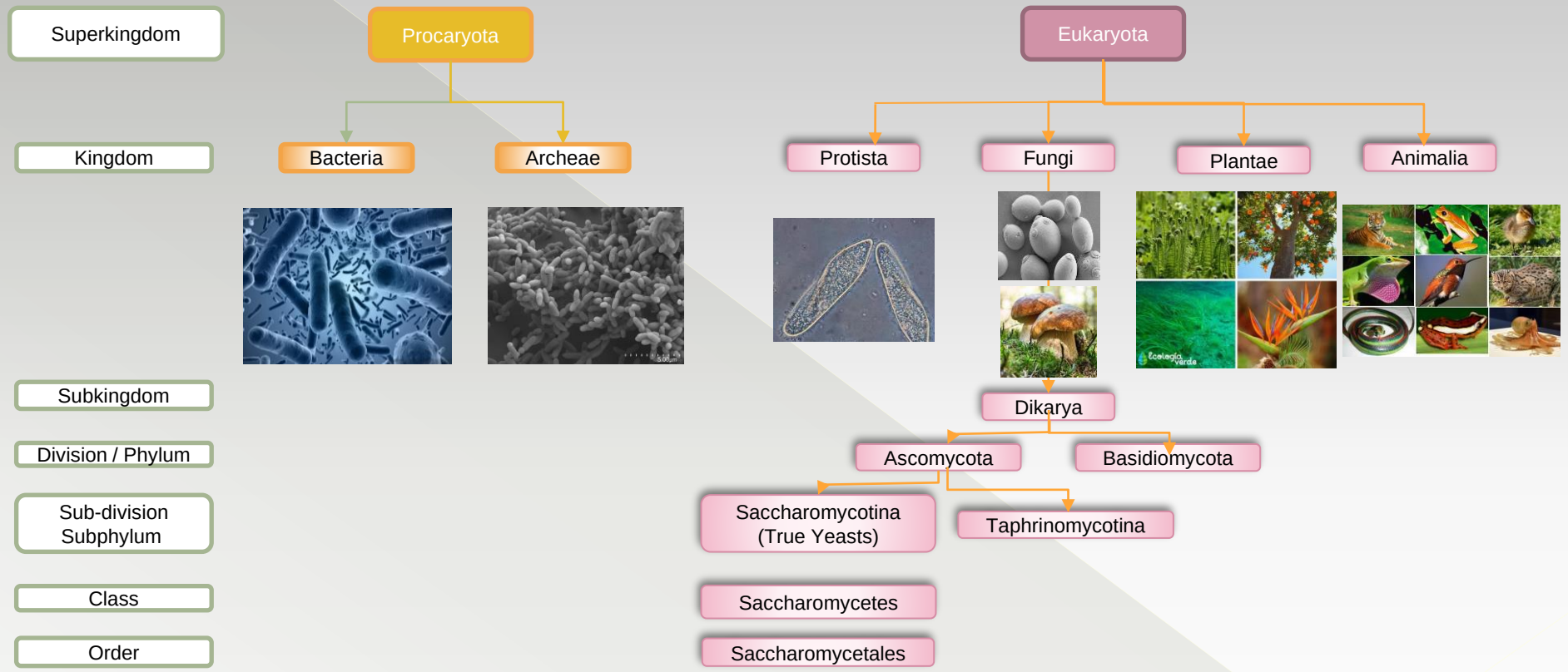
Taxonomy



Taxonomy - Definitions

Basionym : the originally described name, attached to the type material and species description

Homotypic synonym : names generated after the basionym (e.g. by moving it to a different genus) but sharing the same type

Heterotypic synonym : names with a different basionym and type from those mentioned above

Source : NCBI Taxonomy: a comprehensive update on curation, resources and tools

INCI names

- The purpose of this report is to be exhaustive regarding all INCI names used (at least declared) in cosmetic products

- That is why, the choice of INCI names to study is based on :

  - the review of all yeast-related INCI names in the **PCPC dictionary**

  - INCI names referenced in the VCRP (Voluntary Cosmetic Registration Program) (2022)

Identification

- The objective is to check their compliance with the PCPC definition of YEAST:

  Yeast is a class of microorganisms (Saccharomycetes) characterized by their lack of photosynthetic ability, existence as unicellular or simple irregular filaments, and reproduction by budding or direct division

- And to study yeasts that belong to all families of the Saccharomycetes class in order to guarantee the completeness of our study

Identification – INCI names

(1/6) – July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Ascoideaceae	Ascoidea	Ascoidea rubescens	-
		Debaryomycetaceae	Kurtzmaniella	Candida oleophila => Undergoing modification	-
			-	Candida saitoana => Undergoing modification	Hydrolyzed Candida Saitoana Extract
			Debaryomyces	Debaryomyces maramus	-
			Debaryomyces	Debaryomyces nepalensis	-
			Meyerozyma	Meyerozyma caribbica Basionym: Pichia caribbica	Pichia Caribbica Ferment
			Debaryomyces	Priceomyces carsonii Homotypic synonym : Debaryomyces carsonii Basionym: Pichia carsonii	-
			Scheffersomyces	Scheffersomyces stipitis Basionym :Pichia stipitis Homotypic synonym : Yamadazyma stipitis	Pichia Ferment Lysate Filtrate

Source: NCBI : National Center for Biotechnology Information

Identification – INCI names

(2/6) - July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Dipodascaceae	Geotrichum	Geotrichum candidum Basionym: Endomyces geotrichium Heterotypic basionym : Galactomyces candidus	Galactomyces Ferment Filtrate
			Dipoascus	Dipodascus fermentans Basionym: Trichosporon fermentans Homotypic synonym: Galactomyces fermentans	Galactomyces Ferment Filtrate
			Yarrowia	Yarrowia lipolytica Basionym : Endomycopsis lipolytica Heterotypic synonym : Mycotorula lipolytica	Yarrowia Lipolytica Extract Yarrowia Lipolytica Ferment Lysate Yarrowia Lipolytica Oil
		Endomycetaceae	Endomyces	Endomyces decipiens	-

Identification – INCI names

(3/6) - July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Metschnikowiaceae	Metschnikowia	Metschnikowia agaves	Hydrolyzed Metschnikowia Agaves Extract Metschnikowia Agaves Polysaccharides Metschnikowia Agaves Extract
			Metschnikowia	Metschnikowia bicuspidata Basionym: Monospora bicuspidata	-
			Metschnikowia	Metschnikowia gruessii	-
			Metschnikowia	Metschnikowia hawaiiensis	-
			Metschnikowia	Metschnikowia henanensis	Metschnikowia Henanensis Extract
			Metschnikowia	Metschnikowia hibisci	-
			Metschnikowia	Metschnikowia koreensis	-
			Metschnikowia	Metschnikowia lunata	-
			Metschnikowia	Metschnikowia pulcherrima Heterotypic synonym: Candida pulcherrima	-
			Metschnikowia	Metschnikowia reukaufii Heterotypic synonym: Candida reukaufii	Hydrolyzed Metschnikowia Reukaufii Extract Metschnikowia Reukaufii Lysate Extract
			Metschnikowia	Metschnikowia rubicola	-
			Metschnikowia	Metschnikowia shanxiensis	Hydrolyzed Metschnikowia Shanxiensis Extract
			Metschnikowia	Metschnikowia viticola	Metschnikowia Viticola Extract

Identification – INCI names

(4/6) - July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Phaffomycetaceae	Wickerhamomyces	Wickerhamomyces alni Homotypic synonym : Pichia alni	
			Barnettozyma	Barnettozyma populi Basionym : Hansenula populi Homotypic synonym : Pichia populi	Pichia Ferment Lysate Filtrate
			Komagataella	Komagataella pastoris Basionym : Zygosaccharomyces pastoris Homotypic synonym : Pichia pastoris	Pichia Ferment Extract FIltrate Pichia Pastoris Ferment FIltrate Pichia Ferment Lysate Filtrate
			Wickerhamomyces	Wickerhamomyces anomalus Basionym: Saccharomyces anomalus Homotypic synonym : Pichia anomala	Pichia Anomala Extract
		Pichiaceae	Ogataea	Ogataea minuta Basionym : Hansenula minuta Homotypic synonym : Pichia minuta	Pichia Minuta Extract
			Ogataea	Ogataea naganishii Basionym : Pichia naganishii	-
			Ogataea	Ogataea siamensis Basionym: Pichia siamensis	-
			Pichia	Pichia heedii	Pichia Heedii Extract
			Pichia	Pichia membranifaciens Basionym : Saccharomyces menbranifaciens	-
			Pichia	Pichia	Pichia Extract

Identification – INCI names

(5/6) - July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Saccharomycetaceae	Eremothecium	Eremothecium ashbyii	-
			Kluyveromyces	Kluyveromyces lactis Basionym: Torulapora lactis Homotypic synonym: Saccharomyces lactis	Kluyveromyces Extract
			Kluyveromyces	Kluyveromyces marxianus Basionym : Saccharomyces marxianus Heterotypic synonym : Kluyveromyces fragilis Homotypic synonym : Dekkeromyces marxianus	Hydrolyzed Kluyveromyces Extract
			Saccharomyces	Saccharomyces cerevisiae	Saccharomyces Cerevisiae Extract
			Saccharomyces	Saccharomyces sp.	Saccharomyces Saccharomyces Extract Saccharomyces Ferment Filtrate Saccharomyces Ferment Lysate Filtrate Saccharomyces Ferment Saccharomyces Lysate Extract Filtrate Saccharomyces Lysate Extract Saccharomyces Lysate Saccharomyces Polypeptides Saccharomyces
			Torulaspora	Torulaspora delbrueckii Basionym: Saccharomyces delbrueckii	Torulaspora Delbrueckii Extract Torulaspora Delbrueckii Ferment Hydrolyzed Torulaspora Delbruekii Extract

Identification – INCI names

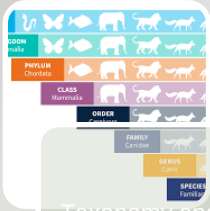
(6/6) - July 2022

Class	Order	Family	Genus	Associated Genus/Species	INCI declared to PCPC
Saccharomycetes	Saccharomycetales	Saccharomycetaceae	Zygosaccharomyces	Zygosaccharomyces rouxii Basionym : Saccharomyces rouxii	-
		Saccharomycetales incertae sedis	Starmerella	Starmerella magnoliae Basionym: Torulaspis magnoliae Homotypic synonym: Candida magnoliae	-
		Saccharomycetales incertae sedis	Starmerella	Starmerella bombicola Heterotypic synonym : Candida bombicola	Hydrolyzed Candida Bombicola Extract
		Saccharomycodaceae	Hanseniaspora	Hanseniaspora opuntiae	-
		Saccharomycopsidaceae	Saccharomycopsis	Saccharomycopsis fibuligera	-
		Trichomonascaceae	Wickerhamiella	Wickerhamiella azyma Current name : Candida azyma ; Basionym : Torulopsis azyma	-

Process

Sourcing

Safety measures and Identification



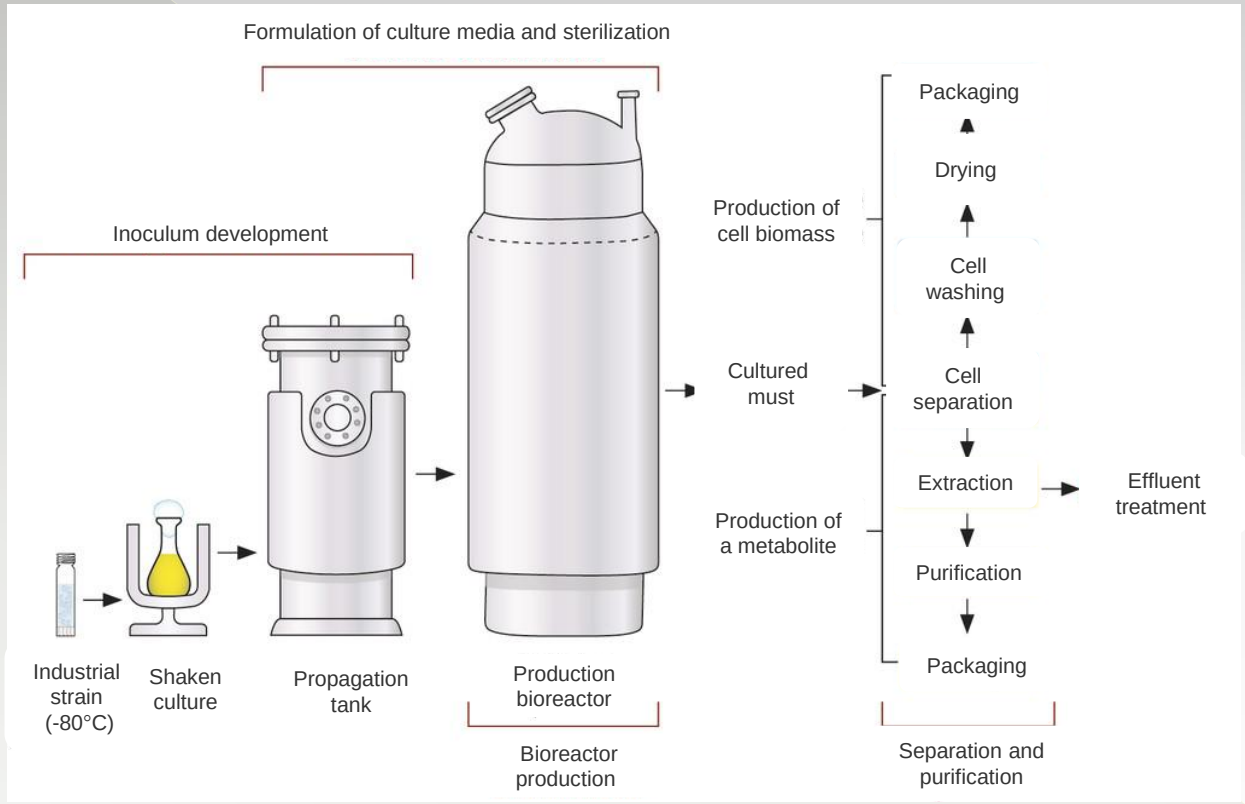
Taxonomy and INCI names

Process

Characterization
Toxicological data

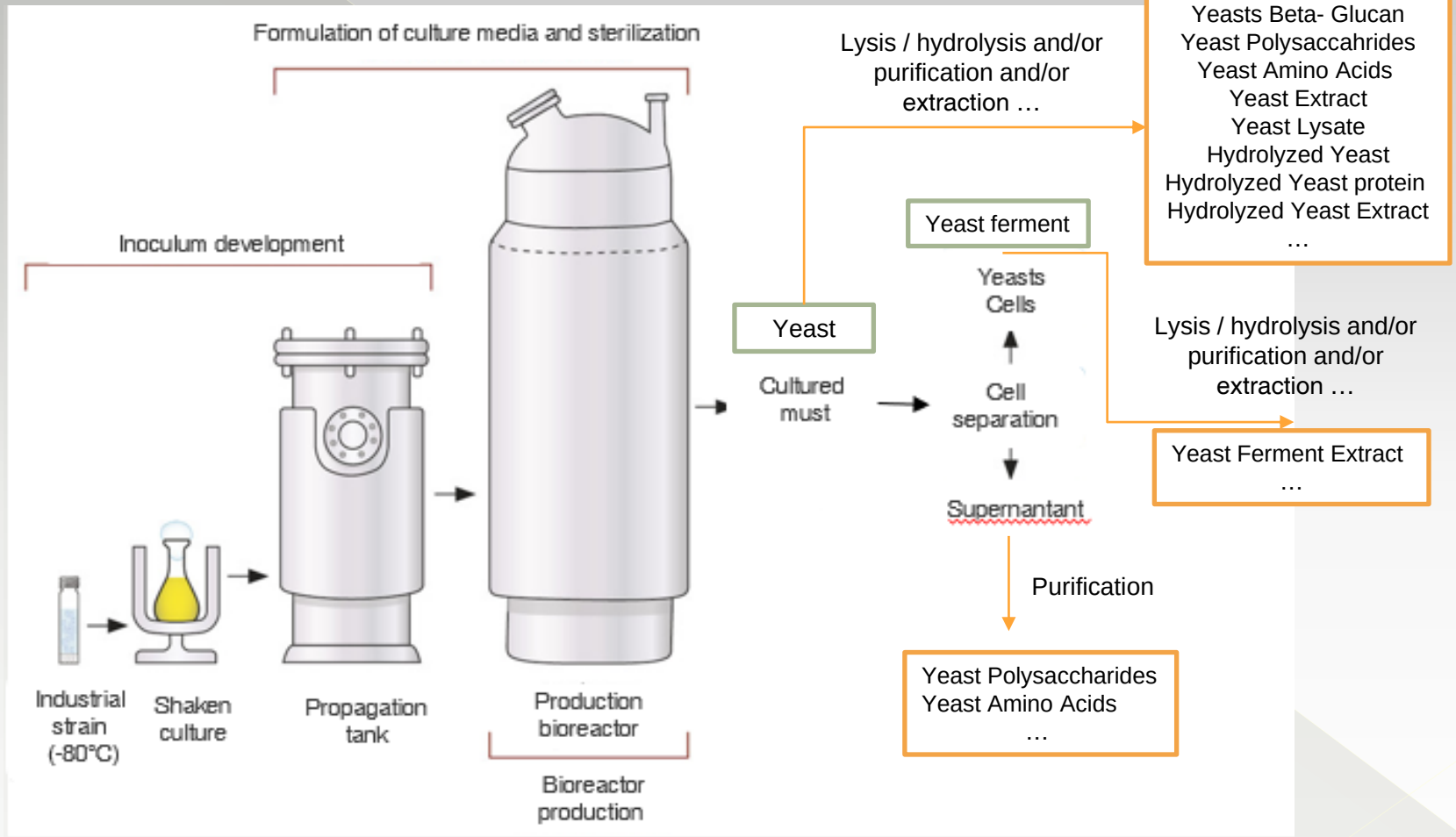
Cosmetic ingredient

Process => culture of Yeast



Technologies des bioprocédés industriels, 2e édition, Louis Tessier

INCI names linked to Manufacturing process



Identification - INCI names

Hydrolyzed Candida Saitoana Extract
Pichia Caribbica Ferment
Pichia Ferment Lysate Filtrate
Galactomyces Ferment Filtrate
Yarrowia Lipolytica Extract
Yarrowia Lipolytica Ferment Lysate
Yarrowia Lipolytica Oil
-Hydrolyzed Metschnikowia Agaves Extract
Metschnikowia Agaves Polysaccharides
Metschnikowia Agaves Extract
Metschnikowia Henanensis Extract
Hydrolyzed Metschnikowia Reukaufii Extract
Metschnikowia Reukaufii Lysate Extract
Hydrolyzed Metschnikowia Shanxiensis Extract
Metschnikowia Viticola Extract
Pichia Anomala Extract
Pichia Ferment Extract FIltrate
Pichia Pastoris Ferment FIltrate
Pichia Ferment Lysate Filtrate
Pichia Heedii Extract
Pichia Extract
Hydrolyzed Kluyveromyces Extract
Kluyveromyces Extract
Saccharomyces Cerevisiae Extract
Saccharomyces Extract
Saccharomyces
Saccharomyces Ferment Filtrate
Saccharomyces Ferment Lysate Filtrate
Saccharomyces Ferment
Saccharomyces Lysate Extract Filtrate
Saccharomyces Lysate Extract
Saccharomyces Lysate
Saccharomyces Polypeptides
Saccharomyces
Saccharomyces Extract
Saccharomyces
Saccharomyces Ferment Filtrate
Saccharomyces Ferment Lysate Filtrate
Saccharomyces Ferment
Saccharomyces Lysate Extract Filtrate
Saccharomyces Lysate Extract
Saccharomyces Lysate
Saccharomyces Polypeptides
SaccharomycesTorulaspora Delbrueckii Extract
Torulaspora Delbrueckii Ferment
Hydrolyzed Torulaspora Delbruekii Extract
Hydrolyzed Candida Bombicola Extract
...

→

Hydrolyzed Yeast
Hydrolyzed Yeast Extract
Hydrolyzed Yeast Protein
Yeast Amino Acids
Yeast Extract
Yeast Ferment Extract
Yeast Beta-Glucan
Yeast Polysaccharides
...

→

Yeast

Genenic
INCI name

Saccharomycetales

Order

Saccharomycetes

Class

Ascoideaceae
Debaryomycetaceae
Dipodascaceae
Endomycetaceae
Metschnikowiaceae
Phaffomycetaceae
Pichiaceae
Saccharomycetaceae
Saccharomycetales incertae sedis
Saccharomycodaceae
Saccharomycopsidaceae
Trichomonascaceae

Families

INCI names – Conclusion

- All families belonging to the « Saccharomycetales » order from «Saccharomycetes » class are reviewed in this report
- From a taxonomy point of view, all yeast-related INCI names can be grouped into one generic INCI name : YEAST
- From a manufacturing process point of view : all yeast-related INCI names can be grouped into one generic INCI name: YEAST
- Great advantage of having only one generic INCI name : Yeast (in accordance with PCPC definition) rather than a multitude of INCI names with the scientific name which may regularly change due to taxonomy evolution

Process => media

- A generical culture media can be used for yeast growth; for example, a synthetic culture medium which allows very good repeatability because it is a standardized medium

Base medium	Quantity (g/L)
Ammonium sulphate	Confidential data
Potassium phosphate	
Sodium phosphate di basic	
Magnesium sulphate	
L-glutamic acid	
Sucrose or glucose or molasses	
Antifoam	
Ammoniac	

Oligo-elements	Quantity (mg/L)
EDTA	Confidential data
ZnSO4. 7H2O	
MnCl2. 4H2O	
CuSO4. 5H2O	
Na2MoO4. 2H2O	
CaCl2. 2H2O	
FeSO4. 7H2O	
KI	

Vitamins	Quantity (mg/L)
Biotin	Confidential data
Pantothenic acid	
Nicotinic acid	
Myo-inositol	
Thiamine-HCl	
Pyridoxine-HCl	
Para-amino-benzoic acid	

Process => Absence of impurities

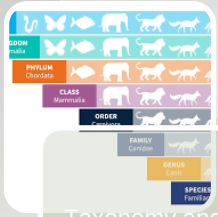
Once the protocol has been established in R&D, this process is always applied in the same way to avoid any contamination / impurities or alteration (reproductible):

Revivification of the strain from the same secondary stock	The same inoculation rate is applied
The same culture medium is always used (preference for a standardized synthetic medium)	The chain of seeding and cultivation is always done over the same period
The sugar used is always the same and in the same quantity (glucose, sucrose or molasses)	The sugar supply is always the same
PH, temperature, oxygen, pressure, aeration are regulated	Many controls during culture : microscope, Optic Density, microbiology to ensure there is no contamination
Cleaning in place is systematically controlled	=> All these controls allow : controlled, repeatable and reproducible culture

Characterization and Toxicological data

Sourcing

Safety measures and Identification



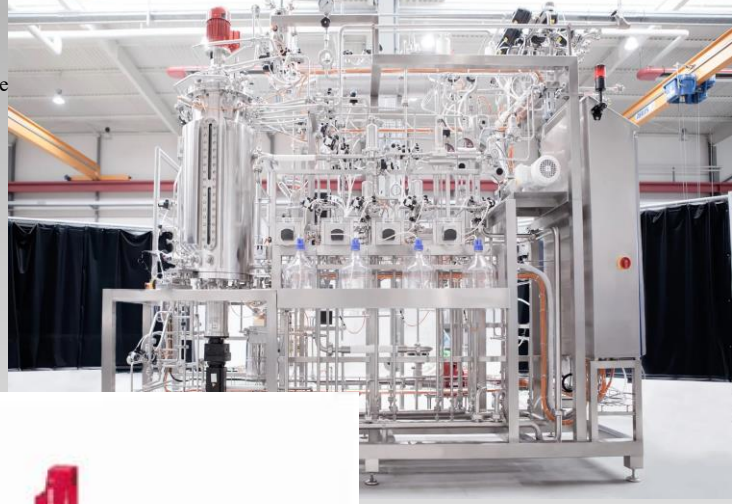
Taxonomy and INCI names

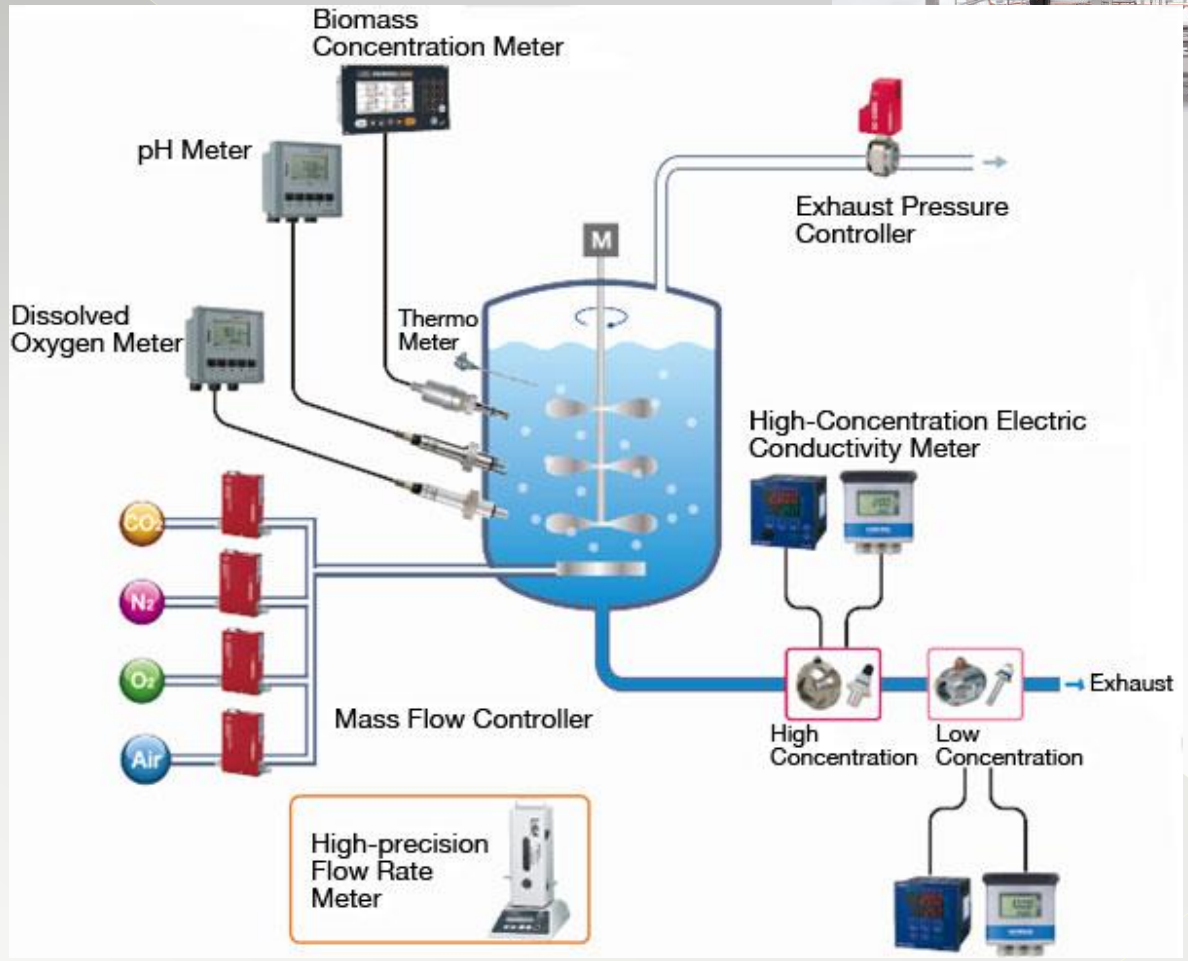
Process

Characterization Toxicological data

Cosmetic ingredient

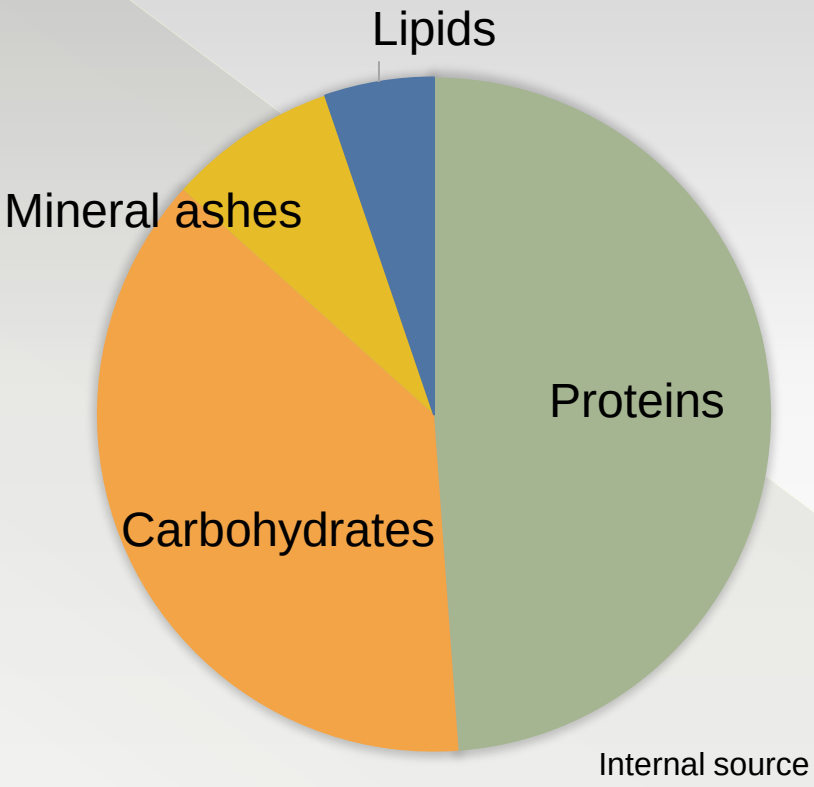
Controlled parameters





Analytical Characterization

Yeasts are always analytically characterized, in general :



Bibliographical characterization

Pathogenic Yeasts are well identified, 5 strains from Saccharomycetes class :

Hazard 2

In Europe :

Candida albicans, Candida dubliensis, Candida glabrata, Candida parapsilosis, Candida tropicalis

In USA :

Candida auris (antibiotic resistance)

According to :

- Directive (EU) 2019/1833 of the commission of the October 24, 2019
- The US Centers for Disease Control (CDC) urgent threats list

Toxicological data – Food uses

- Bibliographical toxicological data has been found on the large majority of yeasts of each family belonging to Saccharomycetes class (complete data available on request)

NB : Data about Biocontrol were not taken into account since fruits and vegetables are supposed to be cleaned before consumption

Family	Food use – Bibliographical data
Ascoideaceae	Listed in the publication : Diganta Narzary, Nitesh Boro et al. (2021), Community structure and metabolic potentials of the traditional rice beer starter 'emao'
Debaryomycetaceae	Most of strains are : - Listed in the publication : François Bourdichon, Serge Casaregola et al. (2011) "**Food fermentations: Microorganisms with technological beneficial use"** - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022** - Listed in publications about fruits fermentation for liquor (Camu-Camu, Agave) - 1 strain notified for **QPS status** : Candida oleophila - Listed in 1 patent : Method for producing beverages by acid removal (EP2866594A1)

Toxicological data – Food uses

Family	Food use – Bibliographical data
Dipodascaceae	Most of strains are : - Listed in the publication : François Bourdichon, Serge Casaregola et al. (2011) "**Food fermentations: Microorganisms with technological beneficial use“** - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022** - 1 strain with **QPS status :** Yarrowia lipolytica
Endomycetaceae	Listed in the Patent US3296090A - Fermentation process for producing 1-tryptophane (one of the essential amino acids necessary for nutrition), 1984

Toxicological data – Food uses

Family	Food use – Bibliographical data
Metschnikowiaceae	Most of strains are : - Listed in publications about fermentations of beers and wines - Listed in publication: Hiroyuki Sasaharaa, Ken Izumori, (2005), **"Production of L-talitol from L-psicose by Metschnikowia koreensis LA1 isolated from soy sauce mash", Journal of Bioscience and Bioengineering** - Listed in the patent: EP 1 065 276 A1, (1999) **Methods for producing D-arabitol, D-xylulose and xylitol using the yeast Metschnikowia** - Listed in the publication : François Bourdichon, Serge Casaregola et al. (2011) "**Food fermentations: Microorganisms with technological beneficial use“** - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022** - 1 strain with **GRAS status:** Metschnikowia pulcherrima

Toxicological data – Food uses

Family	Food use – Bibliographical data
Phaffomycetaceae	Strains are : - Listed in the publication : François Bourdichon, Serge Casaregola et al. (2011) "**Food fermentations: Microorganisms with technological beneficial use“** - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022** - 1 strain with **QPS status :** Wickerhamomyces anomalus - 1 strain notified for **QPS status** : Komagataella pastoris
Pichiaceae	Most of strains are : - Listed in publications about wine and distilled Agave beverages - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022**

Toxicological data – Food uses

Family	Food use – Bibliographical data
Saccharomycetaceae	Strains are : - Listed in the publication : François Bourdichon, Serge Casaregola et al. (2011) "**Food fermentations: Microorganisms with technological beneficial use“** - Listed in the bulletin of the IDF (International Dairy Federation), François Bourdichon, Andrea Budde-Niekiel et al. (2022), **International Dairy Federation bulletin 514/2022** - 3 strains with **QPS status :** Kluyveromyces marxianus, Kluyveromyces lactis, Zygosaccharomyces rouxii - 1 strain notified for **QPS status** : Eremothecium ashbyii - 1 strain with **GRAS status :** Saccharomyces Cerevisiae
Saccharomycetales incertae sedis	- Listed in the publication : Roxane Detry, Noa Simon-Delso, (2020), "**Specialisation of Yeast Genera in Different Phases of Bee Bread Maturation**", Microorganisms

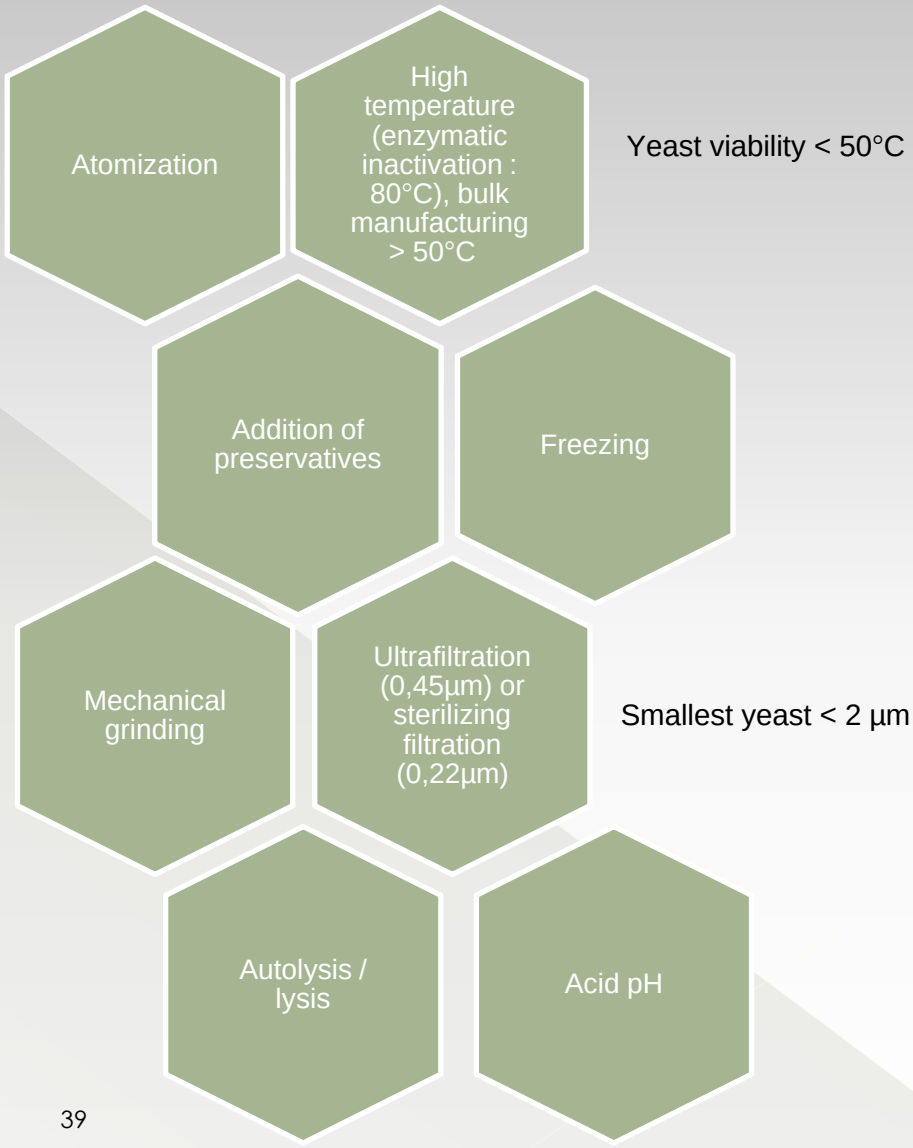
Toxicological data – Food uses

Family	Food use – Bibliographical data
Saccharomycodaceae	Listed in the Publication : Nuno Bourbon-Melo, Margarida Palma, (2021), "**Use of Hanseniaspora guilliermondii and Hanseniaspora opuntiae to enhance the aromatic profile of beer in mixed-culture fermentation with Saccharomyces cerevisiae"**, Food Microbiology
Saccharomycopsidaceae	Listed in the Publication : Zai-Bin Xie, Kai-Zheng Zhang (2021), "**Saccharomycopsis fibuligera in liquor production: A review**", European Food Research and Technology
Trichomonascaceae	Listed in the Publication : Pradnya Chavan, Sarika Mane, Girish Kulkarn et al. (2009), "**Natural yeast flora of different varieties of grapes used for wine making in India**", Food Microbiology

Cosmetic ingredient manufacturing process

Manufacturing processes used to obtain cosmetic ingredients and products are incompatible with the viability of yeast.

Thus, no yeast can be alive in a cosmetic product



Conclusion

- Since the dawn of time, more and more yeasts have been **used in food**, especially in fermentation
- Identification and analytical characterization are key-information to guarantee the **quality, stability and safety** of the yeasts used
- As demonstrated before, from **taxonomy** and **manufacturing process** points of view, all yeast-related INCI names can be grouped into one generic INCI name YEAST
- Thanks to robust and well mastered manufacturing processes of cosmetic ingredients, the quality of yeasts is perfectly **reproductible and stable**

Conclusion

- Due to the existence of food use for the majority of strains from Saccharomycetes class, all **can be grouped together** in the "Yeast" INCI name and can be considered safe for use as a cosmetic ingredient

- Processes used to manufacture cosmetic products guarantee the **absence of live organisms**

- Even if the safety of the yeast is demonstrated, we strongly recommend a pre-market **safety evaluation** of the cosmetic ingredient, consistent with CIR reviews of other ingredients with a history of safe use in the diet, additional data concerning the potential for local effects, e.g., dermal irritation and sensitization, are needed

Thank you for attending
Any questions?

Yeast-Derived Ingredients History

January 2021

- Concentration of use data received on Hydrolyzed Yeast Extract, Hydrolyzed Yeast, Hydrolyzed Yeast Protein, Yeast, Yeast Beta-Glucan, Yeast Extract, Yeast Polysaccharides, and Saccharomyces Cerevisiae Extract

June 2021

- SLR posted
- Summary manufacturing, physical/chemical properties data received from Council on a Saccharomyces Cerevisiae Extract
- Manufacturing, physical properties, and heavy metal specifications data received from Council on Yeast Extract Beta Glucan

July 2021

- Manufacturing, composition, and impurities data received from Council on several Saccharomyces Cerevisiae Extracts
- Comments received from Council on SLR
- FCC monograph received on Yeast, Dried

September 2021

- Expert Panel reviews Draft Report and issues an IDA
- Comments received on Draft Report from Council
- IDA requests:
    - Clarification on which species of yeast used in the manufacturing of cosmetic ingredients
    - Once clarification made, method of manufacturing data, composition, impurities, sensitization, and irritation data requested
        - If GRAS status/food use not noted for species, systemic toxicity data requested (28-d dermal toxicity, genotoxicity, DART)

October 2021

- In vitro dermal and ocular irritation data received on a trade name mixture containing 1.25% Yeast Extract (derived from *Saccharomyces cerevisiae*)
- In vitro dermal and ocular irritation data receive on a trade name mixture containing 4.5% Yeast Extract (derived from *Saccharomyces cerevisiae*)

December 2021

- Manufacturing data received on a Yeast Extract (derived from *Saccharomyces cerevisiae*)
- Physical and Chemical properties data received on a Yeast Extract (derived from *Saccharomyces cerevisiae*)

January 2022

- 2022 VCRP data received and report updated
    - All ingredients have increased number of uses excluding Yeast Beta-Glucan and Saccharomyces Cerevisae Extract

February 2022

- Data received on Yeast Extracts derived from several species – method of manufacture, comp/impurities, derm abs, irr/sens

March 2022

- Strategy memo issued – asked Panel for guidance on if report should focus only on *Saccharomyces cerevisiae*-derived ingredients, or if all yeasts belonging to the class Saccharomycetes should be included

September 2022

- Strategy memo 2 issued – memo contained list of all yeast ingredients in the Dictionary – Panel decided to create Draft Revised Report on all ingredients, regardless of GRAS/food status or VCRP data
- Presentation from SILAB

February 2023

- Concentration of use data received on newly added ingredients

April 2023

- Polysaccharide, protein, beta-glucan, and octenylsuccinate ingredients removed from listing reviewed

June 2023

- Panel reviews Draft Revised Report

Table 1. Data profile on ingredients with reported species (32 total ingredients) - June 2023 – Writer, Priya Cherian

Gemus/Species[a]	Related Ingredients					Toxicokinetics		Acute Tox			Repeated Dose Tox			DART	Genotox		Carci	Dermal Irritation			Phototox	Derm Sens			Ocular Irr	Clinical Studies
		Reported Use	Method of Mfg	Comp/Impurities	Food Use or Presence	log K_{ow}/Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation		In Vitro	In Vivo		In Vitro	Animal	Human		In Vitro	Animal	Human		Case Reports
Candida bombicola																										
	Hydrolyzed Candida Bombicola Extract				X																					
Candida saitoana							X													X				X		
	Hydrolyzed Candida Saitoana Extract	X																								
*Galactomyces candidus*** *Galactomyce fermentans*** *Galctomyces reesii***					X																					
	Galactomyces Ferment Filtrate	X																								
*Kluyveromyces fragilis*** *Kluyveromyces lactis***			X	X	X																					
	Hydrolyzed Kluyveromyces Extract																									
	Kluyveromyces Extract	X										X														
Lipomyces starkeyi																										
	Lipomyces Oil																									
	Lipomyces Oil Extract																									
Metschnikowia agaves					X																					
	Hydrolyzed Metschnikowia Agaves Extract																									
	Metschnikowia Agaves Extract						X													X				X		
Metschnikowia henanensis																										
	Metschnikowia Henanesis Extract																									
Metschnikowia reukaufii							X											X		X				X		
	Hydrolyzed Metschnikowia Reukaufii Extract																									
	Metschnikowia Reukaufii Lysate Extract																									

Table 1. Data profile on ingredients with reported species (32 total ingredients) - June 2023 – Writer, Priya Cherian

Gemus/Species[a]	Related Ingredients					Toxicokinetics		Acute Tox			Repeated Dose Tox			DART	Genotox		Carci	Dermal Irritation			Phototox	Derm Sens			Ocular Irr	Clinical Studies
		Reported Use	Method of Mfg	Comp/Impurities	Food Use or Presence	log K_{ow}/Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation		In Vitro	In Vivo		In Vitro	Animal	Human		In Vitro	Animal	Human		Case Reports
Metschnikowia shanxiensis																										
	Hydrolyzed Mestchnikowia Shanxiensis																									
Mestchnikowia viticola																										
	Metschnikowia Viticola Extract																									
Phaffia rhodozyma				X																						
	Phaffia Rhodozyma Extract											X			X	X										
	Phaffia Rhodozyma Ferment Extract																									
Pichia anomala					X																					
	Pichia Anomala Extract	X					X													X				X		
Pichia caribicca																										
	Pichia Caribbica Ferment																									
Pichia heedii																										
	Pichia Heedii Extract						X													X				X		
Pichia minuta																										
	Pichia Minuta Extract						X													X				X		
Pichia pastoris							X																			
	Pichia Ferment Extract Filtrate																									
	Pichia Pastoris Ferment Filtrate																									
*Pichia populi*** *Pichia stipitis***																										
	Pichia Ferment Lysate Filtrate	X																								
Torulaspora delbrueckii					X																					
	Hydrolyzed Torulaspora Delbrueckii Extract																									
	Torulaspora Delbrueckii Extract																									

Table 1. Data profile on ingredients with reported species (32 total ingredients) - June 2023 – Writer, Priya Cherian

Gemus/Species[a]	Related Ingredients					Toxicokinetics		Acute Tox			Repeated Dose Tox			DART	Genotox		Carci	Dermal Irritation			Phototox	Derm Sens			Ocular Irr	Clinical Studies
		Reported Use	Method of Mfg	Comp/Impurities	Food Use or Presence	log K_{ow}/Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation		In Vitro	In Vivo		In Vitro	Animal	Human		In Vitro	Animal	Human		Case Reports
	Torulaspora Delbrueckii Ferment																									
Saccharomyces cerevisiae			X	X	X				X	X		X			X	X			X			X				X
	Saccharomyces Cerevisiae Extract	X	X	X				X										X		X		X			X	
Schizosaccharomyces pombe					X																					
	Schizosaccharoymces Pombe Extract			X																						
Yarrowia lipolytica			X		X																					
	Yarrowia Lipolytica Extract																									
	Yarrowia Lipolytica Ferment Lysate																									
	Yarrowia Lipolytica Oil																									

[a]when data is marked as present in a row that states the species only (e.g., *Candida saitoana*), data was found for the general species (or synonymous species) used in the production of the ingredients, or an ingredient similar to an ingredient in this report, using the relevant species (e.g., data was not found on Hydrolyzed Candida Saitoana Extract, but data was found on a Candida Saitoana Extract; since these are not the same ingredient, but are similar ingredients, the notation of present data would be placed in the species (*Candida saitoana*) row

*in some cases, multiple species are listed in a singular cell – this is because the related ingredient may be derived from either of these species (e.g., Pichia Ferment Lysate Filtrate may be derived from either *Pichia populi* or *Pichia stipitis*)

Table 2. Data profile on generic yeast ingredients*

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Hydrolyzed Saccharomyces Cell Wall							X	X	X						X	X				X			X					
Hyrdrolyzed Saccharomyces Extract																													
Hydrolyzed Saccharomyces Lysate Extract																													
Hydrolyzed Yeast	X							X			X																		
Hydrolyzed Yeast Extract																													
Lactic Yeasts																													
Lipomyces Lipid Bodies																													
Pichia Extract																													
Saccharomyces																													
Saccharomyces Extract																													
Saccharomyces Ferment	X						X				X				X														
Saccharomyces Ferment Extract																													
Saccharomyces Ferment Extract Lysate Filtrate																													
Saccharomyces Ferment Filtrate	X																												
Saccharomyces Ferment Lysate Extract																													
Saccharomyces Ferment Lysate Filtrate	X																												
Saccharomyces Lysate	X																												
Saccharomyces Lysate Extract	X																												
Saccharomyces Lysate Extract Filtrate																													
Saccharomyces Lysate Filtrate																													
Schizosaccharomyces Ferment Extract Filtrate																													
Schizosaccharomyces Ferment Filtrate	X																												
Yeast	X		X																										
Yeast Extract	X	X	X			X													X		X			X		X			
Yeast Ferment Extract	X																												

As these are generic ingredients, several species of yeast may be used in the preparation of these ingredients; a notation (X) was placed in the table above if toxicity data were present on these ingredients, when derived from a particular yeast species (e.g., Yeast Extract derived from Pichia anomala); it is unknown whether this data is representative of the generic ingredient as a whole, as it is unkown which/how many species are used in the production of these ingredients

It should be noted that searches for most generic yeast ingredients (both ingredients with no reported genus or species, and ingredients with only genus reported (according to the wINCI Dictionary), as presented in Table 2, could not be adequately performed as it is unknown which species are being referred to in the production of these ingredients.

Yeast-Derived Ingredients – June 2023– Writer, Priya Cherian

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Galactomyces Ferment Filtrate		✓							✓								
Hydrolyzed Candida Bombicola Extract		✓							✓								
Hydrolyzed Candida Saitoana Extract		✓							✓								
Hydrolyzed Kluyveromyces Extract		✓							✓								
Hydrolyzed Mestchnikowia Reufaukii Agaves Extract	1309127-75-0	✓							✓								
Hydrolyzed Metschnikowia Reufaukii Extract									✓								
Hydrolyzed Mestchnikowia Shanxiensis		✓							✓								
Hydrolyzed Torulaspora Delbruekii Extract									✓								
Hydrolyzed Yeast Extract									✓								
Hydrolyzed Yeast		✓							✓								✓
Kluyveromyces Extract		✓	✓						✓								
Lactic Yeasts	68876-77-7								✓								
Lipomyces Lipid Bodies									✓								
Lipomyces Oil									✓								
Lipomyces Oil Extract									✓								
Metschnikowia Agaves Extract									✓								
Metschnikowia Henanensis Extract									✓								
Metschnikowia Reukaufii Lysate Extract									✓								

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Metschnikowia Viticola Extract									✓								
Pichia Caribbica Ferment									✓								
Pichia Ferment									✓								
Pichia Ferment Extract Filtrate		✓							✓								
Pichia Ferment Lysate Filtrate		✓							✓								
Pichia Pastoris Ferment Filtrate		✓							✓								
Phaffia Rhodozyma Filtrate									✓								
Phaffia Rhodozyma Ferment Extract									✓								
Pichia Anomala Extract	1033319-29-7	✓							✓								
Pichia Heedii Extract	1801269-82-8								✓								
Pichia Minuta Extract									✓								
Saccharomyces									✓								
Saccharomyces Cerevisiae Extract	84604-16-0	✓	✓						✓	✓							✓
Saccharomyces Extract		✓							✓								
Saccharomyces Ferment									✓								
Saccharomyces Ferment Filtrate									✓								
Saccharomyces Ferment Lysate Filtrate									✓								
Saccharomyces Lysate	8013-01-2								✓								
Saccharomyces Lysate Extract	8013-01-2								✓								
Saccharomyces Lysate Extract Filtrate	8013-01-2								✓								
Schizosaccharomyces Ferment Extract Filtrate									✓								

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Schizosaccharomyces Ferment Filtrate									✓								
Schizosaccharomyces Ferment Filtrate									✓								
Schizosaccharomyces Pombe Extract		✓							✓								
Torulaspora Delbrueckii Extract	1291071-26-5	✓							✓								
Torulaspora Delbrueckii Ferment	1291071-26-5	✓							✓								
Yarrowia Lipolytica Extract		✓	✓						✓								
Yarrowia Lipolytica Ferment Lysate		✓	✓						✓								
Yarrowia Lipolytica Oil		✓	✓						✓								
Yeast	68876-77-7	✓	✓						✓								✓
Yeast Extract	68876-77-7; 8013-01-2								✓								
Yeast Ferment Extract									✓								

Search Strategy

- All search terms were used in PubMed
- Search terms were searched in the “Pertinent Websites” listed below

Typical Search Terms

- INCI names
- Species names (e.g., Pichia anomala)
- CAS numbers

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

SEPTEMBER 2021 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 13, 2021

DR. BELSITO: Okey-doke. Okay, so we now will soon be rising after we do yeast. This is the first time that we're reviewing eight ingredients. It went out in June of 2021, unpublished data from the Council put into the report summarizing manufacturing visible chem property data on Saccharomyces Cerevisiae: manufacturing physical properties, heavy metal specifications on yeast extract made of glucan, and manufacturing, composition, impurities on several other Saccharomyces Cerevisiae Extracts in concentration of use data.

The issue was the term "yeast" which pertains to a wide variety of species, and it's not known what is being used in the cosmetic ingredient. So, you will see how this has been posed to us. We should choose to cite this lack of clarification as a data insufficiency or choose to limit our report conclusion to the uses of the yeast where the ingredient exclusively comprises Saccharomyces Cerevisiae, which would be the only yeast species that would be covered by this report. And I sort of felt like, let's just go with Saccharomyces Cerevisiae but I want to open that up for discussion.

DR. LIEBLER: Well, I think the available information strongly implies that it's Saccharomyces Cerevisiae but it doesn't explicitly state it, so that's our challenge. So that second option is to treat this as if it's a Saccharomyces Cerevisiae report and maybe even change the title.

DR. BELSITO: Yeah.

DR. LIEBLER: And then indicate in the introduction that we are proceeding on the understanding that yeast used in cosmetic ingredients will be Saccharomyces which is widely used in food and is widely regarded as safe in food additives, as food substances, and so forth. So I'm okay with taking that approach.

DR. BELSITO: Paul? You must be muted.

DR. SNYDER: No, I was just -- so what is the basis for that reasoning? The yeast not otherwise specified is somehow being different than Saccharomyces Cerevisiae?

DR. BELSITO: We don't know.

DR. SNYDER: I'm not a yeast person, so I can't imagine there's that much difference across yeast.

DR. LIEBLER: Well, in their genetics and functions but there's some yeast pathogens obviously but the ones that are (Inaudible) yeah.

DR. SNYDER: I'm fine with that then.

DR. LIEBLER: Yep.

DR. BELSITO: Okay, so we're going to change the title of this to Safety Assessment of Saccharomyces Cerevisiae Derived Ingredients. Is that correct?

DR. SNYDER: well, the only tox data we have then is a dermal acute study because all the rest of it is all the other ingredients.

DR. BELSITO: But it's GRAS.

DR. SNYDER: Oh, true, yeah. Okay.

DR. LIEBLER: It's GRAS and it's food.

DR. SNYDER: Yep, yep, yep.

DR. BELSITO: So then some of these, I mean basically all of the -- well, I guess we can deal with beta-glucan right?

DR. LIEBLER: Yeah.

DR. BELSITO: And polysaccharides?

DR. LIEBLER: Yep.

DR. BELSITO: But the hydrolyzed yeast, yeast extract, yeast protein, yeast, yeast extract will get removed, and we'll be left with yeast beta-glucan, yeast polysaccharides, and Saccharomyces Cerevisiae Extract. Then, a note into the introduction why we're deleting, why we're not including these yeast ingredients that are in the *Dictionary*. Is that what I'm hearing us agreeing to?

DR. HELDRETH: Could I propose one different strategy?

DR. BELSITO: Sure.

DR. HELDRETH: So, in a past report we had a single ingredient that was an oligopeptide. However, we found in the process of reviewing it that there were three different sequences that were all folded in under this single oligopeptide ingredient name, but we only had data on the one sequence. And so we went forward with the report concluding safety on that ingredient but only when it was the sequence that we knew something about.

So what we were proposing here in our question to the Panel of choosing a conclusion to use yeast that exclusively comprises of Saccharomyces Cerevisiae was to suggest that you could conclude on all these ingredients if you chose to and have that conclusion only reflect when yeast means Saccharomyces Cerevisiae. Part of the reason we're suggesting that is the highest frequency of yeast ingredient in this report is yeast extract, and so if we delete it we'll have to pick it right back up again in another report.

DR. BELSITO: Right, so how would you word- -- you'd wordsmith that in the introduction, Bart?

DR. HELDRETH: I think you would have to put it in the conclusion like we did with the oligopeptide. You would say something like, let's say we come with a safe conclusion, these ingredients are safe as used when yeast is defined as Saccharomyces Cerevisiae, something to that effect.

DR. BELSITO: That's fine with me. I mean, that solves the issue that Priya had brought up with the problem of the definitions of yeast.

DR. LIEBLER: I'm okay with that.

DR. BELSITO: Paul?

DR. SNYDER: I'm fine. That works.

DR. BELSITO: Okay, good. Good compromise there, Bart.

DR. HELDRETH: Thanks.

MS. FIUME: I think Priya did address some of it in the introduction, the third paragraph after the listed ingredients, also addresses what species we're looking at. So that was a start.

DR. BELSITO: Okay, so she says the Panel could choose to site this lack of clarification as a data insufficiency. I think we should strike that and say the Panel has proceeded with this review on the assumption that these yeast products are derived from Saccharomyces Cerevisiae.

MS. CHERIAN: Yes, I was referring to the introduction on page 10. The third paragraph on page 10 after the list of ingredients. Is that wording okay there as well.

DR. BELSITO: Okay. According to -- majority agreement.

MS. CHERIAN: Because the term yeast pertains to a wide variety of species.

DR. LIEBLER: The third paragraph.

DR. BELSITO: Yes, okay. So, yeah, I actually put a comment on that. Do we limit yeast ingredients to this? If not, how handle? So we're going to limit the yeast ingredients to this.

DR. SNYDER: Now could you just change the wording to just say that yeast, not otherwise specified can refer to a wide variety of species including Saccharomyces Cerevisiae based on the definition in the cosmetic ingredients dictionary, this report is evaluating only Saccharomyces Cerevisiae. Something like that.

DR. BELSITO: Yeah. So, I mean, I think maybe just an intermediary sentence between the first sentence and the second again saying that the Panel is operating on the assumption that all of the yeast-derived products in this report are from Saccharomyces Cerevisiae and then we'll have that in the conclusion as well.

DR. SNYDER: Okay, whatever language we use in our conclusion should just be replicated up here in the intro.

DR. BELSITO: Okay. Okey-doke. So method of manufacture, we only have for the Saccharomyces Cerevisiae extract. Do we need for the other ingredients, Dan, Paul?

DR. LIEBLER: We have it for the beta-glucan.

DR. BELSITO: That's true, okay. But what about the others?

DR. LIEBLER: I think this is sufficient, really.

DR. BELSITO: Okay. Composition and impurities, do we need for the hydrolyzed yeast extract?

DR. LIEBLER: We've got it for hydrolyzed yeast protein.

DR. BELSITO: So you're okay?

DR. LIEBLER: Yeah, again, I don't think their additional content is needed for these, but if the other team pushes for it, I won't put up a fight. Okay?

DR. BELSITO: Okay, but we're going to say that we don't need it based upon the hydrolyzed yeast protein data.

DR. LIEBLER: Right.

DR. SNYDER: So, Don, if we go back to that introduction on page 10.

DR. BELSITO: Yeah.

DR. SNYDER: That first sentence, "This assessment reviews the safety of the following eight ingredients," as derived from Saccharomyces Cerevisiae, you just state it right up there, right up front.

DR. BELSITO: We could do that. What do you think, Dan?

DR. LIEBLER: Say that again, Paul? I'm sorry.

DR. SNYDER: Under the introduction, the first sentence just put it right up front. This assessment reviews the safety of the following eight ingredients as derived from Saccharomyces Cerevisiae.

DR. BELSITO: And as used.

DR. SNYDER: And as used in cosmetic formulation.

DR. LIEBLER: Yeah, that's fine. I don't think we need that paper -- I mean, that other paragraph can actually go away.

DR. BELSITO: Well, I mean, I think it's important that we do point out that we're knowledgeable that yeast could refer to a huge number of species and just to reiterate it again, but I'm fine with deleting the paragraph too. Dan, what do you think?

DR. LIEBLER: The very first paragraph of the introduction after the list?

DR. BELSITO: No, third paragraph, where we go into yeast of various species. We're limiting it to Saccharomyces. So would you --

DR. LIEBLER: Yeah, I think Paul's sentence is a little more succinct than this paragraph. It's sufficient.

DR. BELSITO: Okay, so we'll just get rid of that whole paragraph. Okay. Good job, Paul. That makes it easy. So we'll need the respiratory boilerplate I believe. So the repro DART, we don't need because of GRAS status. Same with Genotox.

So under other relevant studies, the immunomodulatory effects, I just have a comment. It's not the correct grading for IgE prick test studies, but I presume this is just how it's reported so it's probably just me being a little too anal. Okay, so I'll get rid of that. Okay, so --

DR. SNYDER: Don, can we go back to that one? On page 16 at the top there. Oh, okay, never mind. It does. When I first read the list, I didn't see the Saccharomyces in there, but it is in there. Never mind.

DR. BELSITO: Okay, so the irritation and sensitization, we have just for the extract, which is the one that's most used. I didn't really think we needed it on the other components. Are you okay with that?

DR. SNYDER: I am.

DR. LIEBLER: I am too.

DR. BELSITO: (Audio gap) what David says tomorrow. Okay, so PDF page 18, the sentence just above the summary. It says that, "Saccharomyces Cerevisiae is responsible for up to 3.6 percent of all episodes of fungemia" in immunosuppressed patients. Do we need to discuss this in relation to the inhalation issue?

DR. LIEBLER: I can't address that.

DR. BELSITO: Paul, you're muted. Any comments?

DR. LIEBLER: You're muted.

DR. SNYDER: Oh, damnit. What I was going to say, was the data we're missing here is how many non-diarrhea patients also were cultivated for Saccharomyces Cerevisiae in the hospital? They were taking a probiotic.

DR. BELSITO: Okay.

DR. SNYDER: I mean, I don't understand what they're attribu- -- I mean, are they interpreting this to mean that it was the cause of their diarrhea?

DR. BELSITO: Well, if they had fungemia, presumably they cultured it from the product.

DR. SNYDER: That's true, yeah.

DR. BELSITO: But, again, this was nasogastric feeding of a probiotic capsule.

DR. SNYDER: Yeah. I wouldn't put too much weight into that. I wouldn't, I mean --

DR. BELSITO: Do we even discuss it or is that putting too much weight on it?

DR. SNYDER: I think it puts too much weight on it. To me, you just bring too much attention to it.

DR. BELSITO: Dan, are you okay with just ignoring it in the discussion?

DR. LIEBLER: It sounds like that's okay.

DR. BELSITO: Okay. Okay, so discussion. We have the respiratory boilerplate. We're not going to deal with a fungemia. We have this issue of melanogenesis. For some reason, I skipped over that. Where was that?

DR. LIEBLER: PDF 17, top.

DR. BELSITO: Oh yeah, I missed that. So how do we deal with that? Basically, say that cosmetic formulated, you should take caution to avoid this. It would not be a cosmetic. It shouldn't have that activity. I mean, we have some type of boilerplate.

DR. SNYDER: Yeah, we have a language where it's not in the purview. We should be aware of the pigmentary issues or something. We had another report. Didn't we have it in another report we looked at today? That language?

MS. FIUME: We did. We do have some standard language for that.

DR. BELSITO: Okay, so we just need to bring that language into the discussion.

DR. LIEBLER: Once again, when we see these, it's almost always something like this. It's some cells treated with a relatively high concentration of the ingredient we're studying, it affects melanin synthesis in vitro. Without some more convincing evidence that this could be even an in vivo effect in an animal model, I don't think we really have -- at most we can handle it in the discussion by saying that the concentrations used to produce this effect in in vitro models far in excess of expected exposure in cosmetic products. Is that similar to what our boilerplate says?

DR. SNYDER: That's very consistent to the language you used in one other report that we did this time.

DR. LIEBLER: Yeah.

DR. BELSITO: Right. Okay. Anything else that needs to go into the discussion? Okay, so then based upon our limitations with Saccharomyces Cerevisiae, we basically have a safe as used conclusion. Is that what I'm hearing?

DR. LIEBLER: Yes.

DR. SNYDER: Yes.

DR. BELSITO: All right. Anything else that needs to be discussed on this? Okay, hearing no one piping up, although, Paul, you're muted if you're trying to say something. We're not hearing you. We'll see you all tomorrow morning at 8:30.

DR. SNYDER: All right, good job.

DR. LIEBLER: Yes, sir. Thanks. Bye-bye.

DR. BELSITO: Have a good afternoon.

DR. LIEBLER: Bye-bye.

MS. FIUME: Everybody, have a good night.

Cohen Team – September 13, 2021

DR. COHEN: This is a --

DR. BERGFELD: Microorganism.

DR. COHEN: Yes. It's a -- yes, this is a draft report. It's the first time we're reviewing this. The safety assessment has eight derived ingredients, although there's considerable ambiguity in making an assessment or a read across. We are presented specific data on Saccharomyces Cerevisiae. It's used as a skin conditioning agent, hair conditioning agent, film former, protectant, and viscosity increasing agent. We have max use for yeast polysaccharides in leave-on products up to 0.36 percent in face powders, and we have frequency of use reported.

We have to make some decision on what we want to do with this list of eight derived ingredients, and we do have information that the Saccharomyces is GRAS used as a flavor. We have method of manufacturing for Saccharomyces extract and yeast beta-glucan, and we have composition and impurities for Saccharomyces Extract. I think there's a hypopigmentation signal.

I think we need sensitization data on max use concentration. I can open it up. There's a lot to discuss on yeast. Lisa, what do you think about the read across table?

DR. PETERSON: Well, I guess for me the big question was, does the Saccharomyces Cerevisiae represent what's in cosmetics? That is what counsel supplied, but I guess I was just curious if they could make a comment on, is that the predominant strain of yeast that's used or something else?

Then, I thought, what was missing was the method of manufacturing on the hydrolyzed yeast products. I guess I didn't really understand what hydrolyzed yeast would be. How is the hydrolysis done? So that would be for the hydrolyzed yeast, yeast extract, and protein, again, all hydrolyzed. Then, I thought, there's missing yeast -- generally, yeast polysaccharides, but it turns out the beta-glucan is a polysaccharide, so that can probably stand in for the -- I thought the yeast beta-glucan method could probably stand in for the yeast polysaccharides because beta-glucan is a polysaccharide.

My biggest question had to do with the method of manufacturing for the hydrolyzed ingredients. Again, the composition for the hydrolyzed in the report was basically using the non-hydrolyzed yeast protein, which is, I guess, okay, but again, I was curious what hydrolyzed meant. I mean, what are they hydrolyzing with? Are they treating it with a base? Are they giving it an enzyme treatment? What is the hydrolysis supposed to be accomplishing? That was my big question.

DR. COHEN: Lisa, in the uses, the Saccharomyces are used in 74 formulations, but the rest of the 267 are others, right? I'm very confused as to what the term "yeast" means --

DR. SLAGA: Right.

DR. COHEN: -- in this whole thing.

DR. PETERSON: Yeah, I agree.

DR. COHEN: I know Saccharomyces' a yeast, but I'm not an expert in this, but there's a lot of yeasts out there, right?

DR. PETERSON: Right, and you would think that they could provide some additional information. Like, when they say yeast generically, are they really talking about this one that's known?

DR. COHEN: Ron, what do you think?

DR. SHANK: My take was to limit the scope of this report to Saccharomyces Cerevisiae and drop all of the others.

DR. BERGFELD: Right. I agree.

DR. SHANK: Then you have a very neat report.

DR. SLAGA: Right.

DR. SHANK: You can actually conclude it's safe as used.

DR. SLAGA: I agree because there were statements in here stating about some of the other products that could be a mixture. They didn't know what it really was. I would go with Ron, that we pick out something that we know, and call it safe, and take the rest away.

DR. COHEN: So --

DR. BERGFELD: I totally agree with that, and I think that you would clarify that in your title.

DR. SLAGA: Right.

DR. HELDRETH: So, by removing all others, do you mean actually remove ingredients like yeast extract or limit the scope of conclusion of yeast extract to when Saccharomyces Cerevisiae is the species used?

DR. BERGFELD: Right.

DR. SLAGA: I don't understand what you mean.

DR. BERGFELD: You assume that everything's -- that if you limit it to the Saccharomyces, then everything you talk about is that.

DR. HELDRETH: Right, so I was just trying to get clarification. When you said keep Saccharomyces Cerevisiae Extract and get rid of the rest, did you mean that just have that one solitary ingredient, Saccharomyces Cerevisiae Extract, and delete all the others? Or did you mean to look at all of the yeast ingredients that are in here and limit the conclusion so that, per se, like when we're looking at yeast extract safety, it only pertains to those incidences where they used Saccharomyces Cerevisiae as the yeast species?

We did something similar to my second alternative there. Previously, we were looking at a specific oligopeptide. And, under that one name of the oligopeptide, it turns out that the definition allowed for you to have three different sequences, all with the

same ingredient name. But we only had data for one of those sequences, and so the Panel's conclusion was on the safety of that ingredient, but only when the sequence that we knew about was used.

I mean, I'm just suggesting that's one possibility here that you could include it on other ingredients, like yeast, yeast extract, yeast polysaccharides only when Saccharomyces Cerevisiae is used. Or you could delete the other ingredients and have it just be on the one ingredient, Saccharomyces Cerevisiae Extract. The only problem with that is that ingredient's not the one with the highest frequency of use.

DR. BERGFELD: Right.

DR. HELDRETH: The whole reason that this came up on our priority list was because of yeast extract with 267 uses. So then you're still left with the need to review the safety of that ingredient if you cut it out of this report.

DR. BERGFELD: Can I ask a question, a clarification on that? When you say yeast extract, what are you including in that yeast? Everything? Anything?

DR. HELDRETH: No, that's what I'm suggesting. You could either say we're insufficient for yeast extract, or you could say here's our conclusion on yeast extract when Saccharomyces Cerevisiae is used. Those are options.

DR. COHEN: Carol had a comment.

DR. BERGFELD: I assumed that.

DR. EISENMANN: A couple things. Historically, ingredient names came from some food definitions, and yeast, in the Food Chemical Codex, dried yeast has three species in addition to the one that you're talking about. I agree with the general approach that this report you should, in the conclusion, limit it to the one species.

Food is also Saccharomyces fragilis and torula utilis, so I suspect that was the original, but I've also discussed with Joanne what would happen if another species of yeast came in currently. They would give it the new genus-species name. They would not put it under yeast extract. If that makes you -- so any new material, but unfortunately, occasionally you get people that self-name, so I think if you limit it to defining yeast extract for the purposes of your report as only Saccharomyces Cerevisiae that would probably be the best approach.

DR. COHEN: From a technical standpoint, this is a draft report, right? We're issuing an IDA, and, so far, we're asking for methods of manufacturing for the hydrolyzed ingredients. We need -- let's see, we have an irritancy study, but we don't have sensitization data on max use for Saccharomyces. We still need that.

What else are we asking for because we're either going to take out all those other terms, or we're in the draft report stage and we're going to ask for more information to clarify it. We're not late stage here, so do we try to keep it in and ask for greater detail on the definitions of these and what they're including?

DR. SLAGA: That would be helpful.

DR. EISENMANN: Well, you're not going to get more clarification at this point, but I have asked every supplier we have listed, and I've given you the data that has come back. The suppliers did not come back with other species.

DR. COHEN: So we're back to keeping everything in, but our conclusion is just on yeast. Our comments are related to Saccharomyces.

DR. EISENMANN: Correct.

DR. SLAGA: Right.

DR. COHEN: So, in our IDA, right, where we've asked for hydrolyzed ingredients, sensitization data, are we asking for irritancy and sensitization on all of the other components? Right? I mean, we can't -- it's not dead yet, right? This is still a draft early report, so when we issue the IDA, we have to provide some guidance on what we're looking to get back. Is it just going to be those two things, or are we going to ask for everything: method of manufacturing, impurities on the things we don't already have, irritation and sensitization? Are we going to ask for those things for the next iteration?

DR. SHANK: We have irritation and sensitization for Saccharomyces Cerevisiae Extract.

DR. COHEN: Do we have human data on Saccharomyces?

DR. SHANK: No.

DR. BERGFELD: Lymph node assay.

DR. SHANK: The sensitization is a local lymph node assay.

DR. COHEN: So I was going to ask for sensitization in humans at max use. No?

DR. SLAGA: It's early in the game. Go ahead and ask for it.

DR. COHEN: Well, wouldn't we normally ask -- I mean, wouldn't we normally ask for that data?

DR. BERGFELD: Well, sometimes we've used the lymph node assay, but that would be the end. I mean, that would be the final.

DR. COHEN: Okay.

DR. BERGFELD: I'm not sure I understand why all this discussion on the -- which species you're going to use, I guess you'd call it that, because most of the information here is on the Saccharomyces Cerevisiae and why not go with that one since you have most of your information there? Including some of the cell walls and, let me see, what else is in there? The hydrolyzation, the beta-glucan, it's all on the Saccharomyces.

DR. COHEN: Yeah. Yeah, the comment before was we have a pretty good draft report for Saccharomyces.

DR. BERGFELD: Right.

DR. COHEN: So it'll all rest in the conclusion.

DR. BERGFELD: Yeah, so why are you even thinking about adding another one? Or other two species?

DR. COHEN: Not adding the species, just to define the terms, which seem vague.

DR. BERGFELD: Oh. Well, in this case, it's specific because you have a yeast, Saccharomyces Cerevisiae. It's specific.

DR. COHEN: But does that -- is the totality of hydrolyzed yeast extract that seems to include things other than Saccharomyces and in the --

DR. BERGFELD: Then ask for composition and impurities of the hydrolyzes.

DR. COHEN: Yeah. Yeah. Okay.

DR. BERGFELD: There are two mentions there under composition impurities. One does not suggest a species; the other does.

DR. COHEN: Okay. So we're going to have an IDA on this. Ron, is that right?

DR. SHANK: Okay, I'll go along with it, but what are you going to call this report? Yeast?

DR. BERGFELD: No.

DR. SHANK: Or you're going to call it Saccharomyces Cerevisiae?

DR. BERGFELD: Call it that.

DR. COHEN: I thought we were going to call it yeast and then, in the conclusion, hone in on the fact that our conclusions are based on Saccharomyces.

DR. BERGFELD: But, if the new dictionary is coming in with the yeast species, specifically for yeast, then why don't we start there? Start it now.

DR. COHEN: So, Wilma, you're saying we should excise the other seven lines in the read across. My concern is the use, right, where there's heavy use and, of the --

DR. BERGFELD: And it's a food.

DR. COHEN: Yep. There's 267 formulations, of which Saccharomyces only accounts for 74. So, if we excise the rest of them, we're leaving a large portion of products not covered by this report. So I wanted to resist just making this a Saccharomyces report and try to get as much information as we can because we're early in the game.

DR. SLAGA: That's fine. I mean, we may go eventually with the one ingredient, but let's see what we can get.

DR. SHANK: Okay.

DR. COHEN: I think Don's presenting this one tomorrow, so we could see what -- how they adjudicate it. That did come into my mind when I was reviewing this. It's like, how am I going to articulate all this? But our team will remain on standby for this as a seconders.

DR. BERGFELD: So you're sort of leaning towards going to a specific Saccharomyces Cerevisiae, and, if Don offers another option, you go with that? Or you're going to hold out for the, what, 30 or 40 percent that are uncovered?

DR. COHEN: I was, my gut was to hold out to get as much information and to include as much as I could at the next round before we just make this a Saccharomyces report. Bart, any comments?

DR. HELDRETH: I agree. I think it always makes sense to, when we're in the early stages like this, ask for any data that might help the Panel feel more comfortable making a decision. I don't think there's any reason to rush forward and declare safety or lack of safety or some qualifications at this stage.

If there's any missing information or ambiguity to the information we have that the Panel would feel more comfortable with if they had a better explanation or more data, by all means, ask, and we can think about the what the safety conclusion or the scope of that conclusion at a later stage.

DR. BERGFELD: Can Carol give us the list of those that she thinks are included in that group of absent information? She had (audio gap). It's nowhere in the --

DR. EISENMANN: All I was saying, the Food Chemical Codex definition for dried yeast includes two other species.

DR. BERGFELD: Yeah.

DR. EISENMANN: So, in other words, if you saw yeast on a food package, it could mean also Saccharomyces fragilis and torula utilis. I wasn't suggesting that you put a lot of information on it, other than the statement that what the Food Chemical Codex definition includes.

DR. COHEN: That's pretty helpful information, though, don't you think?

DR. BERGFELD: Yeah.

DR. COHEN: I mean, it adds a little color to the GRAS issue, no?

DR. PETERSON: Right, so do we get a -- is there a statement saying that, how yeast is defined as a food in the document under other uses or non-cosmetic? I think a statement like that should be added to the non-cosmetic use, that would be helpful.

DR. COHEN: Yeah, if you look at the screen, it lists those other ingredients: the fragilis and the torula.

DR. BERGFELD: Did you find that, David?

DR. COHEN: No, no, no. Is this -- Priya, did you put this up?

DR. HELDRETH: No, I put it up.

DR. COHEN: Oh.

DR. HELDRETH: It's Bart.

DR. COHEN: I like Lisa's comment. We could put this in the other uses. All right. We'll have Don describe their findings. We can make our comments about trying to keep as much in as possible, ask for further information, and see what we get. So we could put yeast aside, and let it rise later. Couldn't help myself.

DR. BERGFELD: What specific -- you're going to have to have a list of specifics that you want.

DR. COHEN: Yeah. I was going to ask for sensitization data on Saccharomyces at mass use in people, method of manufacturing for the hydrolyzed ingredients, composition impurities for the ones that are not listed already.

DR. PETERSON: Are you going to add composition of the hydrolyzed use protein because there is a list of non-hydrolyzed use protein, but it's not the hydrolyzed? I don't know how, again, if it defines what the hydrolysis method is maybe then you can do the read across, but I wasn't a hundred percent convinced of that.

DR. COHEN: Okay. Are we okay to move on to that one? From that one.

DR. SHANK: Yeah.

DR. SLAGA: Okay.

Full Panel – September 14, 2021

DR. BELSITO: Yeah, so, we initially struggled with this, but Priya sort of helped us out as did Bart. So, Yeast is a broad range of ingredients, and there is no idea what if you just say "yeast extract" you're referring to. And so the first thing we wanted to do here is change the title of this assessment to the "Safety Assessment of Saccharomyces Cerevisiae-Derived Ingredients as Used in Cosmetics. And then, once we do that and we restricted it to these yeast products that are derived from Saccharomyces cerevisiae we found that we could go with a safe as used conclusion. And in the discussion include the respiratory boilerplate and the language that we typically use when there are reports of melanogenesis.

DR. BERGFELD: And that's a motion?

DR. BELSITO: That's a motion.

DR. BERGFELD: Dr. Cohen.

DR. COHEN: So, I'm not sure whether we should second that. We grappled with this as well, and, the reason we decided not to limit the report was because of the frequency of use, right. There were 74 formulations for Saccharomyces but the totality had over 250 -- 267. So, we didn't want to close the report, or narrow it too quickly, if we were able to cover those other uses.

We were asking for a high-fidelity definition of the yeast in this assessment other than the Saccharomyces, and it's GRAS, so we may be able to get some more information about the species that fall within the yeast moniker. We wanted method of manufacturing and composition and impurities for the hydrolyzed yeast products. And, we have irritancy data, Don, do we have sensitization data on Saccharomyces? Yeah, we do. So --

DR. BELSITO: I'll past this over to Bart, because I think he was the one who sort of discussed this with us about holding -- that your understanding, if I recall our discussion yesterday, was that most of these yeast-derived products are in fact from Saccharomyces. Is that correct, Bart?

DR. HELDRETH: Yeah, I mean, that is our suspicion, although we don't know. But the proposal that I was making was that your conclusion could say whatever your safety conclusion is, whether it's safe or safe the qualification, but would have a caveat when yeast means this particular species.

So your conclusion would only apply when someone's using yeast extract, they actually meant Saccharomyces cerevisiae Extract. Or when someone's using yeast polysaccharides, what they really meant is Saccharomyces cerevisiae Polysaccharides. So, it's limiting it to Saccharomyces cerevisiae, but it's not limiting it just to the one that has the genus and species in the name. All of the other ones would still be covered in this assessment, but only when the formulator is using that genus and species. That was the proposal, but it's up to the panel to decide if they'd like to use it.

DR. COHEN: In our discussion yesterday about the foods, two other yeasts were discussed. And, we thought we would keep the door open for more information to come in to see if we can expand that. I mean, is your plan not limiting and excluding yeast products that don't have Saccharomyces in them? It seems like it would, and I don't know if all those uses are all Saccharomyces that aren't listed as Saccharomyces. I don't know if that made any sense, but.

DR. BERGFELD: Well, you were actually asking to explore the other two yeasts that are in the dictionary. And that's the leaving the door open to see if there's anything on those two other species. And we also heard yesterday that the dictionary is not going to be using the name "yeast" anymore, but specific to the species.

MS. EISENMANN: No, it is going to be using the name, yeast. If somebody new applied for a name with a different specific species -- I discussed this with Joanne (phonetic) -- they would name it with the genus species name, but the yeast name will stay in the dictionary. Because there's a European name, I think it's Faex (phonetic), which she can't get rid of and it's a general yeast term that they use. So, no, they won't be getting rid of the yeast name.

DR. BERGFELD: Is it true that there are only two other yeast genus and species under the category of yeast in the dictionary?

MS. EISENMANN: No, that's in the food chemical codex, how it's defined. Dried yeast, if you see the name yeast on a food package, there are three species that are used as dried yeast in the definition in the food chemical codex. I was just suggesting that that be put in the other use information. That's all.

DR. BERGFELD: So, any discussion regarding the more restricted presentation?

DR. COHEN: Well, is there a reason to restrict it at this stage in the development of the report? Is there value to that, or, do we see this again?

DR. SNYDER: So, my question is when we did a search for safety data, did we search those other yeast or did we just search Saccharomyces cerevisiae?

DR. HELDRETH: It was all searched; it's a very broad topic to go out and search for all yeast.

DR. SNYDER: No, but, specifically the two that the Cohen team is thinking about including in this assessment, did we search for those two genus and species of yeast, because basically 99 percent of the data is on the Saccharomyces cerevisiae?

MS. CHERIAN: No, we purposely didn't include any information on any other genus or species because it was just such a broad title. And, I mean, in the dictionary there are other yeasts outside of that food chemical codex that I did see that are yeast ingredients. But it was just so broad, so we decided to use this method instead.

And, I think, yesterday, Carol, did you say that even if we did ask for clarification -- we already did -- would we actually receive clarification on what genus and species are being used right now?

MS. EISENMANN: I did ask all the suppliers we have listed under the yeast ingredients, and of course I never get response from everybody. The ones that did respond are using Saccharomyces cerevisiae. They didn't indicate other species to me. For the ones that (audio skip) names registered.

DR. SNYDER: My concern here is that we have an unintended bias for Saccharomyces cerevisiae-derived yeast extracts or whatever, because we only looked for that. And, if we bring those others forward and say they're insufficient, well, then we didn't really look for those. Is that not correct?

DR. HELDRETH: I mean, the panel can go whichever direction you want, but my suggestion was not to say insufficient for the other species, but to simply conclude on Saccharomyces cerevisiae as the only species in this report. And then if someone comes forward in the future and says, hey, hey, I'm using one of these other species that is listed in the food chemical codex, like the Saccharomyces fragilis, or the Torula utilis, then those can be brought back into the report assuming that data comes with it. I mean, we're only at the draft report stage.

DR. COHEN: Well, for a couple of questions. If we knew this was the dataset, why weren't we presented just Saccharomyces? And, in that table why did all those other ones show up there for us to look at? And then, to your other point, Bart, we have two other yeasts that are in the food codex that I don't know how they relate to the other uses that are not listed as Saccharomyces, why limit it now in the draft report? Why not talk about this later?

DR. HELDRETH: Yeah, I mean, it's certainly the panel's choice to limit it or not limit it. The reason that we brought in yeast extract specifically is because that is the one that has the highest frequency of use. So, that was actually the driving ingredient that brought this ingredient group to the priority list.

So, ultimately, if we wanted to start cutting this report apart and taking ingredients out, if we take the generic yeast name out of the report, then we're going to have to have a separate report on it somewhere else. So, it's really the cerevisiae that was added into this report as we thought it belonged with it. And, ultimately the data that we found relating to yeast ingredients was almost exclusively on the Saccharomyces cerevisiae. So, that is why we suggested possibly limit the scope of this report to that genus and species, but, again, it's your choice.

DR. BERGFELD: So, it's easy to limit it but it's harder to expand it. So, David, you're up for a second to this motion to limiting it to this species, or do we open it up. We have to have a consensus here.

DR. COHEN: I'll look to our team. I don't know if it's that convincing to limit the report at this stage. Lisa, Ron, Tom?

DR. SHANK: This is the first time we've seen the report, and the search was done just for Saccharomyces cerevisiae. So, I think we should keep it open and see if we can get any information submitted to the panel on the other strains of yeast. If we don't, then we limit it to just Saccharomyces cerevisiae. But I think it's premature to do it now.

DR. SLAGA: I agree.

DR. PETERSON: I agree with Ron.

DR. BERGFELD: Okay, so, the Cohen team agrees. What's with the Belsito team?

DR. BELSITO: I'm fine. This is the first time we're looking at it.

DR. LIEBLER: Yeah.

DR. BELSITO: If we wanted to -- I just got the impression from Priya and Bart yesterday that if we ask them to proceed looking at anything other than Saccharomyces cerevisiae that we'd be spinning a lot of wheels and wasting a lot of time.

DR. COHEN: Let's just limit it to the other two food yeast for now.

DR. BERGFELD: Is that agreeable?

DR. BELSITO: So what are we specifically asking for, that Carol go out and ask manufacturers whether they produce yeast extract from those two species as well? How do we get -- what is our IDA?

DR. SNYDER: Well, Priya said there were other genus and species in the dictionary. So, why would we restrict it to food ones if there're other ones in the dictionary, unless they're also the food ones? So, that's what I'd like to know, if we going to expand it.

DR. COHEN: Well, I guess you'd have -- as GRAS it'd just be an easier way to go through the report for tox.

DR. BERGFELD: Dan?

DR. LIEBLER: So I agree with my distinguish colleagues on the Cohen team to keep it wider open at this point. And, I think we just trust Priya and Bart to make best judgements as to -- or make our best efforts to data gathering for us. And then when we discuss this next time we can decide if we need to close this down a little bit.

I mean, we're going to have to -- aside from the selection of the ingredients, the supporting data are always going to have this level of ambiguity because much of the data is with yeast. It's not really labeled as the species. So we're simply going to have to, I think in the final report we're probably going to have to outline our assumptions that led to our evaluation of the totality of the data for the report so.

DR. BERGFELD: Well, I'm going to ask Bart. Bart, if it's a consensus that we're opening it and we need some information, this will be done by Carol. Do we need an IDA yet, or do we go for the IDA with the insufficient?

DR. HELDRETH: Yeah, I think if you have insufficiencies, especially at a draft report stage like this, I would issue an IDA with whatever specific needs you have. And then, the CIR staff will do what we can to gather information that we can. And, of course, industry will also do their part to try to find what's out there, if there's anything out there, in addition to what we found.

DR. BERGFELD: So, let's see, Dr. Belsito, you did your motion that wasn't seconded. So, are you rescinding your motion at this point and time?

DR. BELSITO: Yes, so the data will be insufficient for determination of what other yeast species could be used in the formulation of these yeast-derived ingredients.

DR. BERGFELD: Is there a second to that?

DR. COHEN: Second.

DR. BERGFELD: Okay. And, the needs that would be then listed in our discussion under IDA?

DR. BELSITO: Well, the first need would be what are the ingredients that we're adding, are they GRAS, if not, then we may need to look at other toxicity data. We may want sensitization and irritation. So, I mean, I think that it's hard to give a list when we don't know what we're dealing with. So I would say that the IDA is for what other genus and species of yeast might be used in these yeast-derived products, if they're not GRAS, a 28-day dermal or other toxicity endpoints to be satisfied, sensitization and irritation, composition, manufacturing, impurities. I mean, the list goes on and on.

DR. BERGFELD: The whole list, okay. David, you want to add something to that?

DR. COHEN: No, Don actually summarized it. But I think I recall Lisa wanted specifically method of manufacturing, composition and impurities of the hydrolyzed yeast products.

DR. BERGFELD: Okay.

DR. COHEN: Yeah, how were they hydrolyzed, what are the impurities and composition?

DR. BERGFELD: And, I'm sorry, I don't have the scientific writer for this one at my fingertips.

DR. LIEBLER: It's Priya.

DR. BERGFELD: Priya, have you got what you need?

MS. CHERIAN: I've got what I need, thank you.

DR. BERGFELD: Okay. So, the motion has been made and seconded. Discussion regarding the needs for the IDA have been stated and understood. So, I'm going to call for the question unless there's another comment to be made. Seeing none, all those that oppose? Abstain? A unanimous agreement to proceed with an IDA. Okay, so our next biggie, Barley, Dr. Cohen.

MARCH 2022 MEETING – STRATEGY MEMO 1

Belsito Team – March 14, 2022

Dr. Donald Belsito
OK, we're back. Well, maybe we can at least start this discussion cause we got some tough ones coming up. So, the major discussion is how to handle these yeasts? Should we just consider Saccharomyces cerevisiae? And that's what we feel represents yeast. Or should we add other yeast ingredients like PGonArmada extract in the assessment, which I guess has what, 4 uses or something? Or 4 reported uses? I can't even keep it straight. I mean, I just felt we should go with Saccharomyces cerevisiae. I just I don't know how we can wrap our heads around all of the yeast, but maybe chemist like Dan can help me out.

Dr. Dan Liebler
Oh, I don't. I don't think this is really a chemistry issue. I think that I came down on the side of including the other yeasts. Because of the very broad, INCI definition and the fact that there are at least some uses, and I thought that we could essentially apply the same logic we use for allergy. Which is if we've got food uses to cover, you know, the broad safety endpoints and we had sensitization data then we're going to be able to clear these. There will be lots of data for SarahBCA. So I'm trying to read Priya's face here. I don't know if that was smirk or and itch, but anyway that that's what I thought we could do. I think we could

take an allergy type approach to this. I don't know if you guys think that that this fits the same framework is Algae in terms of the available information Pryia to the extent you've looked. Do you think that makes any sense?

Priya Cherian (CIR)
The problem is that there are other species of yeast being used right now and the dictionary and then in that supplement that we got there were different unison species that weren't in the dictionary, so it would just depend on what exactly are we going by which genus and species of any sort or being used right now and what are we including?

Dr. Dan Liebler
I'm my suggestion ass ed that we only would include what's in the dictionary.

Priya Cherian (CIR)
OK.

Dr. Dan Liebler
Yeah. So, if it's not included in the dictionary, it's off limits for us and you know, but I mean still what's in the dictionary is still broad enough that it's more than Sarahvca.

Dr. Donald Belsito
What? Exactly is in the dictionary. Can someone read that?

Priya Cherian (CIR)
I made a documents a while back about the yeast that I found in the dictionary. And I can probably find that and send that out.

Dr. Dan Liebler
I mean if the if the panel all kind of came in on let's just do Saccharomycesservice, then I'm going to argue for the others. But I think that we could handle the ones that are in the dictionary based on that sort of the algae framework which is if there are food uses and if we have sensitization data, we can clear them or we can at least that that's the approach we could take to clearing them.

Dr. Paul Snyder
I had the same approaches, Dan, I said. If they're in the dictionary and their use, let's just add them and get them off the table.

Dr. Curtis Klaassen
Further question is do you want to divide the yeast up into three or four different groupings?

Dr. Dan Liebler
Different reports.

Dr. Curtis Klaassen
Yeah.

Dr. Dan Liebler
I personally don't think that's necessary, but you know because we are again the Algae approach was to avoid having to do that, that's.

Monice Fiume (CIR)
We just lost, Don.

Dr. Dan Liebler
OK.

Monice Fiume (CIR)
Create do you have a number? While we're waiting, maybe for Don to come back, on. How many ingredients there are in the dictionary under that yeast? Family.

Priya Cherian (CIR)
I'm trying to. Am I allowed to share my screen here?

Monice Fiume (CIR)
Yes, you should be able to share.

Priya Cherian (CIR)
OK.

Dr. Donald Belsito
I got. I got kicked out. Can you hear me now?

Priya Cherian (CIR)
So when I.

Dr. Curtis Klaassen
Yeah.

Priya Cherian (CIR)
Yes.

Dr. Curtis Klaassen
Yes.

Dr. Donald Belsito
OK, sorry. Go ahead Priya.

Priya Cherian (CIR)
So when I was looking through the dictionary, all of these ingredients, all these yeast ingredients or they ingredients that I've found this was last year. I can look again and see if there are any is if there's anything new and this is also according to 2021 VCRP the ones that are also recorded to be used are these ingredients. And that's according to 2021. I'll have to double check with 2022.

Dr. Donald Belsito
And what's the red mean?

Priya Cherian (CIR)
These are the ones that are included right now in our report.

Dr. Donald Belsito
OK. So Dan, you're saying include all of them?

Dr. Dan Liebler
The ones that are maybe I can get it. Could you leave your screen up, Priya? Sorry.

Priya Cherian (CIR)
Oh yeah, sorry.

Dr. Dan Liebler
So if you scroll up so we can see that first group. OK, so you've got potential ingredients. The everything listed here is in the INCI Dictionary.

Priya Cherian (CIR)
Yes, as of 2021.

Dr. Dan Liebler
OK. So, and then the ones that are red are currently part of the ingredient group. I see. OK, so we've got maybe less than a dozen. In the ingredient group, the red ones, and then all of these others, setting aside what's in use, just staying out in the upper grouping, we've got all of these others. This is similar to the scope of the of the red algae. I think in terms of numbers of substances to be considered.

Dr. Dan Liebler
Most of these are like hydrolyzed. You know other stuff like the Candida, Banda cola, etc. Anyway, it it's approachable by these sort of the LG type framework. I notice that you've got some Saccharomyces cerevisiae that are not included, like the cirlarsa extract lysate extract filtrate etc., it could be brought in because they'd be under sarahvca. Yeah, and I would expect once we learn a little bit more. Or about the sarahvca and some of the extracts and manufacturing and such. We probably be able to include many of these uses again using the same framework we did with algea, where we knew that these were sub components of a larger group that have food uses or you know or acceptable uses that allow us to clear, you know, most of the safety endpoints and then we can have our discussions about, you know, sensitization. That's kind of what it would boil down to keeping, you know, to clearing these.

Dr. Donald Belsito
And then it sounds like a plan. Or we can try it. Paul, Curt.

Dr. Paul Snyder
Yeah, that was my that was my initial take is just to include them all. If they're, if they're in the dictionary and there used.

Dr. Curtis Klaassen
Yeah, give it a try. See how it works.

Priya Cherian (CIR)
So are we including all of these in the dictionary because these ones are just in the dictionary, the ones at the bottom are in the dictionary and reported having use.

Dr. Donald Belsito
No, I think what I heard is all that are in the dictionary.

Priya Cherian (CIR)
OK.

Dr. Dan Liebler
Correct. I think if we don't have uses, we can deal with that. You know later on. But to start with, I think this upper group is starting list.

Priya Cherian (CIR)
OK. And so? In that documents that we send out and it was sent to us from the Council with the yeast extract and all of those genus and species. What do I do with those genus and species? Because some of those don't correspond to an ingredient that's in the dictionary right now.

Dr. Dan Liebler
I think we only do it in the dictionary. Right. Its not the dictionary. It's not our problem.

Priya Cherian (CIR)
Well, the problem is that we haven't ingredient that's called yeast extract in the dictionary.

Dr. Dan Liebler
Oh, I see. Well, if Council is, you know, sending things our way that that they think there are producers and users of uses of and they're not on your list, but they're on that other list, which I don't remember looking at but, then we should include them because of the broader dictionary definition. But if they're just sending us every name that they can come up with. You know it I mean, if it's arguably within the dictionary, then it belongs on the list that you had and then we still apply their framework, food use and sensitization. We can, you know, we can get them through. And if there's no food use and no sensitization, then will simply be insufficient.

Dr. Donald Belsito
OK, so approach it like we approach the algea.

Dr. Dan Liebler
Yeah.

Dr. Donald Belsito
OK. Is that clear Priya.

Priya Cherian (CIR)
Yep.

Dr. Donald Belsito
OK, good. So, let's move on to the priorities for 2023. So, the list needs to be publicly made June 1. Comments on the list.

Cohen Team – March 14, 2022

[Insert Marks Team Minutes]

Dr. David Cohen
And Yeast. And this is a bit complicated, so this was for additional information and clarification. In that, you know Priya went through a lot of this data and the definition of yeast is extremely broad and it's not very informative. And a lot of this data is on Saccharomyces. And with two additional species you mentioned toriola and candidate Utilis? I know Toriola is candidate you tillison Saccharomyces fragilis. But you indicated that there's no evidence that they're being used in cosmetics. So the question is, are we lumpers or splitters on this? Is it just Saccharomyces? Or is it going to be yeast extract?

Dr. Ron Shank
I would limit it too only. To only this species used in cosmetics.

Dr. Thomas Slaga
I totally agree. I think we ought to go with the 1st. One and only go with.

Dr. Wilma Bergfeld
Sacrifices.

Dr. Thomas Slaga
Yeah, it it's used in cosmetics and leave the other two out.

Dr. David Cohen
So. That, that that wasn't my initial impression, but I could be persuaded, which is when you look at the constituents of these things, is there anything in there from my perspective that was going to be an irritant or contact sensitizer I couldn't come up with anything just on the top of my head. And if we do it in such a narrow way, or we going to have to have reports in the future if another.. Yeah, Bart.

Dr. Bart Heldreth
So maybe I misread it, but I I've read the situation very differently. So at the last meeting it was brought to our attention that we should look to the Food Chemical Codex to see what species are considered for a yeast that type that we consume and food. And so we looked at the Food Chemicals Codex that that's where we found that truly utilities and the Saccharomyces fragilis. And so that's why we brought those in. Not really a problem, at least from our, you know, amateur staff side. What did strike us as something we didn't know what to do with is, we made the assumption at the last meeting that we would just assume whenever we looked at least extract or yeast anything that didn't have a genus and species that we were going to only you look at Saccharomyces Servasa. If somebody was using something else other than Saccharomyces Servasa, we weren't concluding on it. However, we got this document back from industry and if you look the page 4 of that strategy memo you see listed under the generic yeast extract cosmetic name we have Candida Sitona anDeborah, *(inaudible) and the list goes on and it goes back to the notion we had before the yeast meant a whole slew of not only species, but geniuses. And so our question is you want to continue and just head down or only going to review Saccharomyces surveysay? When we're talking about yeast and yeast extract or do we want to include these other genus and species in our review? That's the impression I got.

Dr. David Cohen
Now I think we had similar impressions. I we I saw those lists and I'm saying all right, there's a lot here. Are we going to have individual reports for each one of these when most of it is protein, sugars and this it.

Dr. Wilma Bergfeld
General ash.

Dr. David Cohen
Yeah. So. Why not take the opportunity to lump them together if we, if we can, I suppose?

Dr. Bart Heldreth
OK.

Dr. Wilma Bergfeld
Well, we always have the opportunity later to split.

Carol Eisenmann (PCPC)
Where do you?

Dr. David Cohen
Yeah. Hi, Carol.

Carol Eisenmann (PCPC)
I just wonder where you stop because that list probably is not I didn't try to look and see, but I suspect there's a lot more. I mean this this is partly a naming issue.

Dr. Bart Heldreth
Mostly.

Carol Eisenmann (PCPC)
Currently. If you if you wanted a new name for a for your material made of yeast, you'd have to tell him the genus species, and they would name it using the genus species name. So there's going to be a lot more. There's always going to be more. This is like allergy. There's always going to be a new yeast coming in. So that that's me is a difficulty how do you stop but the main ones still, of the ones that? That they reported, they hardly have any uses reported to the VCRP. I still think that Saccharomyces surveysay is the one with the most uses. And you could limit it just because you're going to focus on the one with the most uses. And you already have a report pretty much prepared, which you could finish up and be done with.

Dr. Thomas Slaga
Right.

Dr. David Cohen
OK. I mean it makes sense and it's expedient certainly.

Dr. Wilma Bergfeld
Yep. It's still doable.

Dr. Bart Heldreth
Yeah. And that and.

Dr. Wilma Bergfeld
Alge wasn't doable.

Dr. Bart Heldreth
Thats great. That's easy for us. But then that leads to another question. What do we do with this data on CandidaSitona and DeborahMyhineas that if we just say thanks and put it in a folder? Or is it relatable to Saccharomyces surveyssay?

Dr. Ron Shank
Are they used in cosmetics?

Dr. Bart Heldreth
Yes, and under the name, yeast extract.

Carol Eisenmann (PCPC)
But I can also say that supplier has names, has trade name, materials under the genus, species names also. So. But I think you could say yes, thank you. But we're going to wait and review them.

Dr. Thomas Slaga
Later.

Carol Eisenmann (PCPC)
Right. When the when I when the genus species name comes.

Dr. Bart Heldreth
So then we would have a conclusion whether it's safe or safe with qualifications or unsafe or whatever for yeast extract when the species is Saccharomyces surveysay. Is that?

Carol Eisenmann (PCPC)
And you might change the name to Saccharomyces surveysay, and then do it the opposite way.

Dr. Thomas Slaga
Right.

Dr. David Cohen
You mean the title of the report?

Carol Eisenmann (PCPC)
Right to try to learn.

Dr. David Cohen
With these Saccharomyces.

Carol Eisenmann (PCPC)
Right. Whether or not it's called if it's called, yeast extract or the Saccharomyces surveysay extract.

Dr. David Cohen
I think if we kept it as yeast extract, it's going to be pretty confusing if the whole report is on Saccharomyces.

Dr. Thomas Slaga
Yeah.

Dr. David Cohen
I think we have to call it Saccharomyces, if that's what we're if we're deciding to split. That's what we need to do. But then that leaves all these other yeasts. Dangling.

Dr. Wilma Bergfeld
We've done that before. We can also open up in 15 years and add a few. I mean, they're all kinds of ways of handling the additions.

Dr. Ron Shank
Can the other yeast species be handled in the discussion? Or an appendix. To the report. Or do they have a lot of uses? The other species.

Dr. Bart Heldreth
At least from my perspective. It's absolutely impossible to know, so a little history on this, I think it was nine years ago I started pushing to put yeast extract on the priority list. At that time yeast extracts was one of the very few yeast ingredients in the dictionary, and it had about 1000 uses. And I kept getting pushed back. Oh, we're going to change the name. We're going to make be more specific. And nothing really happened there. And so I kept bringing it forward because it had very high frequency of use. So. My best understanding is right now, there's flooding of products on the market that's a yeast extract on the label. At some of them, say Saccharomyces surveysays the species they use, some of them are DeborahCS,. I don't think there's, at least I haven't seen any data to show us how many products have this one and how many products have that species. It's unknown.

Dr. Wilma Bergfeld
Pandora's box.

Dr. Bart Heldreth
That's right.

Priya Cherian (CIR)
So. Just to be thorough, before this report started, I did go through the Winky Dictionary and I looked and try to find every single yeast species that's currently reported to be in the Winky Dictionary. And then I have a document with those I can share my screen. I can show you. Great. So yeast at the top, are the ones that I found to be in the Winky dictionary in 2021. I haven't done another search this year. And then these at the bottom are ones that are in the Winky dictionary and have at least one reported using the VCRP according to 2021. But not all of the genus and species that were reported to be under the yeast extract, and that data supplement that you got, correspond to a Winky ingredient as of now.

Dr. David Cohen
Right. We don't know what yeast extract really means in that VCRP list.

Dr. Bart Heldreth
Right.

Priya Cherian (CIR)
Right.

Dr. Bart Heldreth
So I you know if you're looking for a direction to go, I think you're right to narrow it down to two a species you can handle instead of looking at all of them at once. When we don't even know you know what the uses are for all these other ones. So it does make sense, I think, to stay with just the Saccharomyces surveysay and will save this data for a future date and the maybe things will be cleared out further at that point.

Dr. Wilma Bergfeld
So the intent is to change the name of this yeast Saccharomyces?

Dr. David Cohen
Change the name of the report, right?

Dr. Wilma Bergfeld
Yeah, right. And so if when it goes out for comment if someone comes back and says, how about this yeast, we could reconsider it that time.

Dr. Bart Heldreth
I mean, that's the panel prerogative to consider it at any time I would suggest you know put this Saccharomyces surveysay extract and yeast extract generic name when it's Saccharomyces surveysay and keep it to that.

Dr. Wilma Bergfeld
I think that's a good strategy, yeah.

Dr. Thomas Slaga
Yeah.

Dr. Wilma Bergfeld
Took us a long time to do some of these products at so many extensions and round, round, Red Alge. There were some other rice come to mind.

Dr. Bart Heldreth
Yeah, yeah.

Dr. David Cohen
Which was the last one? Wilma. I remember Alge very well.

Dr. Wilma Bergfeld
Well, I rice was much earlier, but that we own that was that was like a headache and a half.

Dr. David Cohen
Which? Oh, rice.

Dr. Bart Heldreth
Yeah, not sure was.

Dr. David Cohen
Yeah, alright it. It's not terribly satisfying to have such a narrow focus, but at least we'll get to report out.

Dr. Bart Heldreth
Right.

Dr. Wilma Bergfeld
Well it will bring up other conversations and other responses though, so we will maybe find out what other ones are in use and have a higher priority. So we could tackle those in the future.

Dr. Thomas Slaga
Yeah.

Dr. David Cohen
K.

Dr. Bart Heldreth
Right.

Dr. David Cohen
OK, I think that. Brings us to the conclusion any. Comments. Advice. Suggestions. For tomorrow.

Dr. Thomas Slaga
You did a great job. Just continue to Marvel.

SEPTEMBER 2022 MEETING – STRATEGY MEMO 2

Belsito Team – September 26, 2022

Minutes not available.

Cohen Team – September 26, 2022

Dr. David Cohen - OK. I think, we got through our summaries. OK. Yeast.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - Well, that gosh.

Dr. Tom Slaga - I wish them stated that can we put it at the end?

Dr. David Cohen - I thought I knew where we were going to go. Look, so I think the CIR staff was great in just focusing us a bit, right. I guess the question is ultimately, are we going to include all of those yeasts in a future in a future review or are we going to keep it narrow to the species Saccharomyces cerevisiae?

Any top blind comments from the group after the lecture today?

Dr. Tom Slaga - Well, if we were sure, did we could. That only a species would use, but my understanding, several different species could be used at any time and you know how? How can we separate that out unless we do all of them? It's just a comment.

Dr. David Cohen - It seemed to me.

Dr. Tom Slaga - It's a very difficult when you don't, you know.

Dr. David Cohen - Look, I.

Dr. Tom Slaga - If we were only dealing one species, it would be fine, but we're really not. Right Monice?

Monice Fiume (CIR) - It sound to me that they've grouped every species under the name yeast.

Dr. Tom Slaga - Yeah.

Dr. Wilma Bergfeld - The class of Saccharomyces.

Dr. David Cohen - Well.

Dr. Tom Slaga - Yeah.

Dr. David Cohen - So class is really high up right? It has all the genus and all the species.

Dr. Tom Slaga - Yeah.

Dr. Wilma Bergfeld - Alright.

Dr. David Cohen - It did. I read it wrong, or did it seem to me? Well, I don't think it should have been any surprise, one species versus another is going to have some similarities. I mean, if you ground me and Don up and did an analysis, we would not be the same. Right? Would be a little bit different. And we're in the same species ostensively, right?

Dr. Tom Slaga - Right. A good bit of difference.

Dr. David Cohen - Thomas, you had your hand up. Maybe you can help.

Thomas Gremillion (CFA) - I don't. I don't know. I don't feel this is going to be but it. I just wanted to ask the question, are the pathogenic yeast in the same class as they're not OK?

Dr. Wilma Bergfeld - No.

Alex Kowcz (PCPC) - No, they're not.

Dr. David Cohen - It seemed to me that we could put them all in a single report, right? Understanding that the systemic talks would probably have a lot of data on. And then the question would be how much dermal tox would we really need to clear the whole group, right? Because it seemed it sounded like there when they're declaring something safe, they're doing some sensitization data and they're looking to make sure that everything falls into this class the way it's supposed to be and everything is, is inactive. There's no live material. And the class that broadly is used in food so, I guess would we go with, Yes, let's put them all together. And then when we get the report, we'll have to see what sensitization and irritation data and we would want. I remember we what did we have to do this with some was it wasn't Carl was it.

Monice Fiume (CIR) - Algae.

Dr. David Cohen - With some algae. Yeah. Thank you.

Dr. Wilma Bergfeld – (*inaudible).

Dr. David Cohen - We had to do it with algae, so when we handle this the same way.

Susan Tilton - David, can you or can I get a clarification just on the question that we're trying to answer. So one option is to only review data for the species cerevisiae. And the other option is to include other species in the evaluation. Would it be evaluated under yeast as a together, not differentiating amongst what data is included? Or would we be discriminating? Like would be. Would they be listed like they were different ingredients in terms of how they're evaluated?

Dr. Wilma Bergfeld - I think it's going to be due to the chemistry of the protein.

Dr. Susan Tilton - Or how we would evaluate?

Dr. David Cohen - But the report's going to be yeast, right? Not I. I don't think we're shoot. I'm moving away from saying we're just going to have a report on Saccharomyces cerevisiae when moving to a report that says yeast. Right?

Dr. David Ross - Well.

Dr. Wilma Bergfeld - Yeah.

Dr. David Ross - Because you're in products that you used is a yeast. It's yeast and it contains everything. My understanding in the presentation was that. Yeah, these different things, these different yeasts are going to be different. They've got, you know, ask the question on cast members. They're going to have different chemical and protein properties and they go to induce different effects. But the product you're using is them all mixed up altogether, right. So that's what we're going to be considering with respect to dermal and ocular irritation.

Dr. Tom Slaga – Right.

Dr. David Ross - And doing sensitization.

Dr. Tom Slaga – Well, we could try it with all and see what happens.

Dr. David Cohen - Monice, so we answering the question that you guys want us to answer, I hope we're. Monice, so we answering the question that you guys want us to answer, I hope we're getting close.

Monice Fiume (CIR) - It's good. So I think yes and no. I think the panel is in a very tough situation when we did algae, those ingredients were separate ingredients, so each Algae ingredient had its own INCI name, so you could go through and see, does this genus species have systemic tox have sensitization data or topical what the other the dermal aspect and make a decision? For this, they're telling us that the name yeast is the INCI name, but it could be any of these genus species under this class, so it makes it a little more difficult, I think, in determining safety. I know in the past when we've had a situation where. What's in the ingredient may not have been clear. The discussion address the fact that this is what we found safe the information if it, if it's this genus and species, and we had information on it, we can rule on the safety because that's the information we have in the report. If it is different than the specifications listed in the report, then either the data or insufficient or whatever conclusion you would draw. So we would the panel would craft the discussion to say. Say it. It's not I'm Saccharomyces cerevisiae. Say it's something else and you had information on it and it was enough for you to say yes, that's genus and species would be fine. It

would be covered, but if it is not included in the report, you can't comment on it. So a lot of times we would have a table in the report that would show say exactly which genus and species were referred to in the document that you had information on. That would be OK and that if industry was using something different, they would either have to independently have safety data for that ingredient because the CIR report does not cover that genus and species, even though it's under the umbrella of yeast or yeast extract. Does that make sense? What I'm trying to say?

Dr. Wilma Bergfeld - That's the only way you can go.

Dr. David Cohen - It actually. It does make sense. The during the lecture though in the conclusion slide they said we can group the class of Saccharomyces together right, which would include enumerable, genus and species, right?

Monice Fiume (CIR) - But they also did say for systemic, but for the dermal like irritation and sensitization. Those data would be needed.

Dr. Tom Slaga - Right.

Monice Fiume (CIR) - So I think that might be where it would come into play as you've done in the past where you know which you do have a full complement of safety data that you would need for a report in which you want it. And so it wouldn't be that you would have to say. These are not, if it you're yeast extract includes this genus, and this species is insufficient, I think you could probably flip it and say if you're yeast extract includes this genus and species, then it is sufficient we have sufficient safety data and we know a yeast ingredient that is manufactured using this genus and species. From a CIR standpoint, has a conclusion.

Dr. David Cohen - Yeah. And so that's a discussion item we could, we might consider going out with after adjudication safe as used, right? But in the discussion say, hey, we based it on these, the data on this genus and species, if you have another genus and species, you're going to have to do some additional safety work on it. That that's what you're saying, right?

Monice Fiume (CIR) - Yes, that's what we've done in the past and that's why the conclusion goes to say, as described in this report, to point people to yes, you really need to look and see what we're saying here.

Dr. David Cohen - I think we would have to really Illite the unique nature of this because that kind of sort of loose language could come up. You know, when we have, you know, 18 derived chemicals and you know, we may not have data on some of them or there's a 19th one that's kind of close. So yeah, alright it is it is tricky.

Monice Fiume (CIR) - And I will say the panel has become very creative as you've encountered these issues because brown algae, the first meeting or so was very vague and very confusing. And then the panel did develop a strategy, so that was the strategy that was done for that. Maybe, maybe not for this. You know, I don't know if anyone has, you know, you may come up with a better strategy to Illite it, but that's one thing that we've definitely done in the past.

Dr. David Ross - And it's just one question, but I don't really understand the extracts is as a whole here, but you know, are we likely the things we're going to get are going to be mixtures of yeasts, is that correct? Or they're going to be, they're going to be Peaky or they're going to be Saccharomyces. They're going to be mixed?

Dr. Wilma Bergfeld - You don't know that actually.

Dr. David Cohen - I know I that I don't know. We heard that either way.

Dr. Wilma Bergfeld - Don't know that.

Carol Eisenmann (PCPC) - That's my understanding. They use a specific Organism for each for a specific ingredient they don't for at least for the ones that you're reviewing now, they're one that part of the problem is INCI names have evolved, so they used to name everything just by yeast. So a number of specific species got named under yeast. Now they are naming them using at least the genus name.

I'm sometimes the genus species name. So I think you're just looking at I a single species at a time I don't think you they're. I mean, yes, there are other ingredients that are specifically named where they, They're doing these ferments with multiple yeast and bacteria and they may have different fruits and vegetables. We're not looking at those. I think we're just looking at yeast, a single yeast in standard media and then, they're extracting or they're looking at the filtrates of the ferments, something general for this report. There are more complex permutations going on. But that's not going to be what's in this report.

Monice Fiume (CIR) - And David, the only other thing I was going to say is, if the panel is not comfortable on ruling on safety, there is the insufficient data conclusion is always a valid conclusion. If you really don't understand the compass, because I know Dan Liebler is.

Dr. David Cohen - Of course.

Monice Fiume (CIR) - You know, made this point if we don't understand the composition, how do we rule on safety? So that is also another valid conclusion.

Dr. David Ross - Or another approach that I thought of when I read the information was that we would restrict it to the to use the were A used in cosmetics and B how to define CAS number. And that's why I asked the question on CAS number, and I don't even know if that's a valid approach or not. Everything is used as a mixture of and it's not, but if they're separate, then you know it potential is.

Dr. David Cohen - Yeah, we split decisions we've, we've put out insufficient data. We do that all the time. Right? I mean we could in the come out and just say this genus and species is what we feel comfortable with and we don't feel comfortable with the rest of them based on what we look at.

Dr. Wilma Bergfeld - Unless they can show us the composition.

Monice Fiume (CIR) - I wish Priya was here because she's more familiar. So I'm to remember if one of the options on PDF page four of the Yeast Strategy memo lists all the INCI ingredients in the dictionary that are yeast, and right now the highest frequency of use does fall to those that are named a yeast ingredient or Saccharomyces cerevisiae so you can see there are other genus and species that are named as individual ingredients.

Dr. David Cohen - Yes, I saw that. I think they fall under the family of Saccharomyces, right?

Dr. Wilma Bergfeld - Right the class.

Dr. David Cohen - Under the family.

Monice Fiume (CIR) - I think so, yes.

Dr. Wilma Bergfeld - The family, rather than the class.

Dr. David Cohen - Yeah, I think the, I don't know if they fault.

Dr. Wilma Bergfeld - The class is the is the broadest. I mean, I just looked that up.

Dr. David Cohen - Yeah. No, no, you're right. But I think I think when we review them, we should have that level of detail like what, where is it in the order? Well, what I shouldn't use that term, where is it in the table of organization? In there so we could figure out how close they may be.

Monice Fiume (CIR) - Yes. So Saccharomyces is the family, but the other?

Dr. David Cohen - They used class I think in their conclusion.

Dr. Wilma Bergfeld - I ask. And there outline use a class.

Monice Fiume (CIR) - Yes, so it is, it is the class.

Dr. David Cohen – The class. Yeah. The conclusion was in their class we could group them together. So I remember it was a we didn't have a long time to look at that slide. These other associated genus and species were under that class.

Monice Fiume (CIR) - Yes.

Dr. Wilma Bergfeld - Yes, all of it. I have it here. So I'm looking at it.

Dr. David Ross - Yeah.

Dr. David Cohen - So. We're going to go out as a team right now as groupers, as opposed to splitters for now, right? Is that? Is that fair?

Dr. Susan Tilton - I agree.

Dr. David Cohen - OK. Tom, David, any other further comments about yeast?

Monice Fiume (CIR) - And so David, they will still be yeast and not include any of the other name genus, species ingredients, even though they fall under that class?

Dr. David Cohen - No, no, I thought we were going to. We were going to include them.

Dr. Wilma Bergfeld - Yeah.

Monice Fiume (CIR) - Oh. Oh, OK. That's why I just wanted to be clear. Thank you.

Dr. David Cohen - Yeah.

Dr. Wilma Bergfeld - We're going to include the cosmetic grade.

Monice Fiume (CIR) - So that would be all of the ingredients listed on PDF pages four and five?

Dr. Wilma Bergfeld - Like it?

Dr. David Cohen - That that was my thought. It was. Did anyone have a different thought on that? There was certainly in the class.

Dr. Susan Tilton - No, I agree. And So what that? What that would mean is that, data that's available for any yeast within the class would be included as available within a report for evaluation. Is that right? It we wouldn't be limiting ourselves to just data cerevisiae for instance. And then we can make a decision based on what's under evaluation as to whether we feel that it's in the scope of this data set for the class?

Dr. David Cohen - Yeah, I think Monice's point, the hydrolyzed yeast protein and yeast extract, they're they're a major part of the in use products. And if we if we just go too tight, we we're not going to cover really important uses.

Dr. Susan Tilton - Yeah.

Dr. David Cohen - Or yeast extract.

Monice Fiume (CIR) - Yes, because those.

Dr. Susan Tilton - Alright, that that is the largest category.

Monice Fiume (CIR) - And those were the ingredients that were originally in the report, I think. And I have to look back for sure. The ones that are in the yellow were part of the original grouping of the yeast report. All of the others would be added into the document now. For the next iteration.

Dr. David Cohen - Yes, we'll need a lot of time with that one.

Monice Fiume (CIR) - OK, great. I'll make a note of that.

Dr. Wilma Bergfeld – Oh dear.

Dr. David Cohen - That was a hint Monice that was just like a yeah, that was like a that's just a subtle remark.

Monice Fiume (CIR) - I have it in big letters in my notes, David. It is noted.

Dr. David Cohen - OK. So let's move on to glycol lactones. In March we reviewed this and we concluded that Gluconolactone was safe as used and we had insufficient data for the remaining other derived ingredients and we asked for impurities. A method of man and method of manufacturing specifically for, glucarolactone, glucarolactone and we received no additional information. I think if when we look back on our judication of the glycol lactones, I think we were a little bit less restrictive on it. We've we thought we might be able to read across but when we got to group together Don and his team had maintained their IDA for the insufficiencies. And we agreed with them. Now that we have no additional information, our heels as dug in. Because now this is this is a draft final, right?

Monice Fiume (CIR) - Yes.

Dr. David Ross - Yeah.

Dr. David Cohen - Yeah.

Dr. Dr. Tom Slaga - I agree final.

Dr. David Cohen - Yeah. So, Tom, what are what are your thoughts? Are we splitting this decision or are we going to utilize what we have on, gluconolactone?

Dr. Tom Slaga - Use what we have.

Dr. Wilma Bergfeld - Well, that means splitting is. Is that what you mean Tom?

Dr. Tom Slaga - No.

Dr. Wilma Bergfeld - There's 1 (*inaudible) for so you're going back to the original. So that makes a difference because this is gone out already for review.

Dr. Tom Slaga - Yeah.

Dr. Wilma Bergfeld - You're changing the conclusion.

Dr. Tom Slaga - We can't change conclusion.

Dr. David Cohen - Well.

Dr. Wilma Bergfeld - You can change it, but just understand it would have to go out for review again.

Dr. Tom Slaga - Yeah. No, no, I understand that, but.

Dr. David Ross - I thought, you know, David said we didn't get any new data, right? And so, you know, in my notes I just said in conclusion safe as used for gluconolactone insufficient for the others? I don't. I'm not. Not sure why you do read across now when you didn't do read across before because you have no new data.

Dr. David Cohen - Well, I listen. I'm still, I think this is a continuing learning process. But we do ask for things I'm hoping will get additional information. Sometimes it's a bit aspirational on what we ask for and then when we get to a certain point, we settle in with what we have and make conclusions on that. Am I overstating it, Wilma?

Dr. Wilma Bergfeld - No, we you can do anything just to know that you're going to delay it another 60 days. That's all. That's all I'm stating. You can do anything you want. You can say I'm not comfortable with this conclusion.

Dr. David Cohen - Susan, any thoughts on your read? Because this is more of a first read for you.

Dr. Susan Tilton C - It is a first read I was comfortable with the split conclusion moving forward based on the data available for. Gluconolactone but insufficient data for the others. With lack of a read across to apply that one data set to the others.

Dr. David Ross - So first read for me too, and so just to recap, read lack of read across because was because of the lack of impurities. Was that correct?

Dr. David Cohen - Yeah, the from, from my recollection of the transcripts and the meetings, right, we didn't have impurities and some method of manufacturing. And I think Priya am I right that that kind of hold up the Belsito team from clearing the group.

Dr. Tom Slaga - Yeah, that was it.

Priya Cherian (CIR)- I'm so sorry. I just jumped into this meeting. They just talked to me about yeast.

Dr. David Cohen - No, no, no, that's OK.

Monice Fiume (CIR) - I'll answer for.

Dr. David Cohen - No, no, no. We're past yeast. We definitely don't want to hit replay on yeast, but we're on glucono lactones.

Priya Cherian (CIR)- OK.

Monice Fiume (CIR) - So yes, David, on PDF page 32, the discussion, the second paragraph saves that requires impurities, data and cosmetic specific method of manufacture.

Dr. David Cohen - And. Yeah. Yeah, that's, that's what the held it up. So it sounds like from the team, we're going to carry the last motion to final.

Dr. Tom Slaga - That that's what I say.

Dr. Wilma Bergfeld - They can. They can always come back. That industry can always come back and say ohh here it is. Then we'd have to amend.

Dr. David Cohen - Yeah. I just.

Dr. David Ross - What's that?

Dr. David Cohen - I look, that was my gut. But I want to make sure that we don't do I just a pro forma.

But you know, carry the motion when we're going into final. Because sometimes there are things that we'd like to have, but we may be able to imply from others, so we will carry the motion. From last time because we don't have anything new.

Dr. David Ross - Are you (*inaudible) ending that one David?

Dr. David Cohen - No.

Monice Fiume (CIR) - And David, if it's OK if I jump , since there are new members just to let everyone know, when we have an insufficient conclusion. That puts a two year clock on those ingredients. And then after two years, if ingredients have 0 uses and were insufficient data and we've received nothing new, they go to a category called 0 use and the four that are listed here. Unless something changes will eventually change to that category. If any of the ingredients that were insufficient as a final conclusion. If we don't receive data and they do have use, it switches category to called use not supported, which implies that these are ingredients are in use and there are no data to support use in cosmetics, so it's not called insufficient data at that point, but use not supported.

Dr. David Cohen - And that happens automatically. That's not a we don't adjudicate that at all, right?

Monice Fiume (CIR) - Bart will provide the updates at some point during each year as to which ingredients are changing category. But it does give industry two years to submit data before the conclusion switches.

Full Panel – September 27, 2022

Dr. Don Belsito - Yeah. So in addition to the almost one hour presentation on yeast or panel spent probably more than one hour discussing these and going around in circles and you know noting that the vast majority of them were largely undefined as yeast or Saccharomyces. And how would we deal with these and that manufacturing seem to be the same, but composition might be different. So in the end we decided to look at only those knowing despite everything I've said before at this point where either industry or VCRP has told us that they are actually being used and that we would look at, we were trying in a sense to have Priya do the same type of thing she did with red algae and to look at where there are food uses. That might give us confidence and lack of systemic toxicity data and whether where there's a dermal sensitization and irritation, but we are not going to look at all the yeasts that are listed in the chemical dictionary, only those where there are reported uses either VCRP or industry. Take a dive into that and maybe based upon what we see, want to split them off like we did with algae. I think we started with algae and then we went to red algae blue algae and different colored brown algae. So that's where we ended up with the Yeast.

Dr. David Cohen - That's Don. We use the algae.

Dr. Don Belsito - We didn't quite rise to the occasion.

Dr. David Cohen - We use the exact same analogy of the algae in our in our group. It's interesting the that's a good idea. With the VCRP data. And we thought based on the presentation, we could review up to the class of saccharomyces because that last slide or that summary slide when it's high as class, right and some of the yeasts that were mentioned, some of the genus and species were not saccharomyces, they had other names, but they belong to the class of saccharomyces. So we could include that in in one review. If I don't have an issue with you using the VCRP as a guide.

Dr. Wilma Bergfeld - But they will also ask industry.

Dr. Don Belsito - What's your question, Wilma?

Dr. Wilma Bergfeld - I just adding to the VCRP that you were asking industry as well for the use of yeast and information on these. So there were two prongs.

Dr. Don Belsito - Yeah, we would. What we suggested is, is any materials reported to be used by industry or VCRP. The problem we had, David would going up to saccharomyces's was that in the end our understanding was that cell wall lysates from these different saccharomyces's could be chemically very different and you can't we could not read across from them. So.

Dr. David Cohen - When we had that problem before, so the point is, I don't know if we would read across, remember what we did with the algae. We said if they're eaten and we have dermal tox or sensitization, we cleared them. And if they didn't, we didn't clear them. We I think Dan mentioned it before we could keep them in the same report, it just didn't mean we had to drag all the data across for all of them.

Dr. Don Belsito - I mean the this is a beginning. You know, so poor Priya, she did the algaes too. She's doing this. I mean, we can start that way and take a look and then decide to split it up. I mean I don't have a problem. We're just trying to make it easier for Priya. This was Bart's suggestion that we finally agreed with. So Bart, maybe you want to chime in here.

Dr. Bart Heldreth Yeah. I mean hearing, I only got to hear of course the Belsito teams discussion on this yesterday. But one thing that I thought was interesting was you know, within that saccharomyces class, we do have some pathogenic yeast like the Candida albicans. And so one suggestion was that we have a table that says, hey, here's these pathogenic saccharomyces, (*inaudible). But then from the tox we had yesterday, I think a question that I had was maybe we should consider in addition to looking for grass status for these, these ingredients, since they are all Organism based, should we consider a in our safety assessment whether each Organism is BSL, one level, another word a very safe Organism? Could that considered?

Dr. Wilma Bergfeld - I think that's important, yeah.

Dr. Bart Heldreth - In instances where we don't know about GRAS status.

Dr. Don Belsito - Or weren't we told by the manufacturers that that's their, that's their first step with the cosmetic ingredients. So by definition, anything in cosmetics would be BSL1?

Dr. Wilma Bergfeld - Yes. That's correct.

Dr. Don Belsito – Paul, you were in our group, had the most to say about this. You want to chime in here?

Dr. Paul Snyder - Sure. I think you've already captured it. I mean the only issue to me was that there's classification we know about pathogenic yeast and it's based upon their exoenzymes or phospholipases proteinases and things like that as an issue. And so I really want to see profiles of the constituents in there, the mathematic fracturing and composition of those only as it pertains because there are pathogenic yeast and those are typically pathogenic as opportunistic infections. And were normal barriers are breached. I mean, we're in the normal immune response is compromised or something. And so if people are, if there's ingredients containing these constituents that are the sort of the pathogenic factors, I mean, even if they're not in the pathogen, we just don't know. I don't know them that well. I'm not a yeast person. So and then of course the cross linking of IGE and bypassing again like on inhalation and stuff like that. So that was that was the only issues that, that I talked about, I thought we should start like, like Bart said with the use that are in the VCRP in 2022 and kind of see how it goes and instead of trying to make too much of a cumbersome process.

Dr. Wilma Bergfeld - Paul, does that negate asking industry for information on the yeast?

Dr. Paul Snyder – No, I think we need to have a clarification. I wasn't clear in the discussion, (*inaudible). I did have some trouble understanding her. I even spent some time last night trying to see if the pathangenic yeast rose to a BSL2 level. And I actually couldn't find that information. But I was trying to do it hurriedly so, those are some of the questions we need to ask. If they are in fact BSL1's, then I think we're fine other than the composition and knowing where they contain peptides sufficient enough to cross link IGE molecules on the surface of mast cells.

Dr. Don Belsito - But then we have the, you know, hydrolysis. And we also have already resolved that issue with hydrolyzed wheat. So all of that information from hydrolyzed wheat in terms of, you know, the likely their weight and the peptide size that it takes to link the FCFsalon receptors on mast cells, we know about from that data. So that would be brought in for these.

Dr. Paul Snyder - Yeah, we kind of laid the road map of how to do it and what to look for.

Dr. Don Belsito - Right.

Dr. Wilma Bergfeld - David, do you have anything to offer here or add?

Dr. David Cohen - No, I think. We've already suggested that we start up high and we'll use those filtering criteria. I would have expected. Pathogenic yeast to be more than BSL one. But we'll be able to review that as we see them come in and if we could keep them in one report it you know, the algae were very difficult to get through, but I think it would be even more difficult if we if we initially started breaking them up. Don, you've made a number of suggestions over the years to break out groups like the clays and they worked out very well. But I think starting with them all together is better.

Dr. Wilma Bergfeld - Anyone else have any comments to make Bart? Do you do hear the marching orders for this?

Dr. Bart Heldreth - Heard.

Dr. Wilma Bergfeld - I think that won't.

Dr. Don Belsito – Priya I can see you crying now.

Dr. Wilma Bergfeld - The poor thing she may need help.

Dr. Bart Heldreth - We will help her.

Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics

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Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume. This safety assessment was prepared by Priya Cherian, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

2-AA	2-aminoanthracene
ADME	absorption, distribution, metabolism, and excretion
AF-2	2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide
ALT	alanine aminotransferase
BAL	bronchoalveolar lavage
BSL	biosafety level
B16F10	melanocytes
Caco-2	adenocarcinoma of the colon
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CFU	colony-forming units
CIR	Cosmetic Ingredient Review
CL	chemiluminescence
Council	Personal Care Products Council
DART	Developmental and Reproductive Toxicity
DLD1	adenocarcinoma of the colon
DNA	deoxyribonucleic acid
DPM	disintegrations per minute
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EPA	eicosapentaenoic acid
EP-2	natural yeast extract isolated by ethanol precipitation
FDA	Food and Drug Administration
GRAS	generally recognized as safe
GST	glutathione S-transferase
HaCaT	human keratinocytes
HCC70	non-metastatic breast cancer cell line
HCT116	adenocarcinoma of the colon
HeLa	human cervical cancer cells
HRIPT	human repeated-insult patch tests
HSCAS	hydrated sodium calcium aluminosilicate
ICU	intensive care unit
IFN	interferon
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IL	interleukin
kDa	kilodaltons
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LDH	lactate dehydrogenase
LLNA	local lymph node assay
MCF-7	human metastatic breast cancer cell line
α-MSH	α-melanocyte-stimulating hormone
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NCBI	National Center for Biotechnology Information
NOAEL	no-observable-adverse-effect-level
NR	not reported
Nrf2	nuclear factor erythroid 2-related factor 2
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PMN	polymorphonuclear leukocytes
RAST	radioallergosorbent test
SI	stimulation index
S180	murine sarcoma cancer cell line
SCC-4	squamous cell carcinoma of the tongue
SPF	specific pathogen free
TG	test guidelines
TGF	transforming growth factor
T_{max}	time to maximum blood perfusion
US	United States
VCRP	Voluntary Cosmetic Registration Program
wINCI; *Dictionary*	web-based *International Cosmetic Ingredient Dictionary and Handbook*
ZR-75-1	human metastatic breast cancer cell line

INTRODUCTION

This assessment reviews the safety of the following 56 yeast-derived ingredients as used in cosmetic formulations:

Galactomyces Ferment Filtrate
Hydrolyzed Candida Bombicola Extract
Hydrolyzed Candida Saitoana Extract
Hydrolyzed Kluyveromyces Extract
Hydrolyzed Metschnikowia Agaves Extract
Hydrolyzed Metschnikowia Reukaufii Extract
Hydrolyzed Metschnikowia Shanxiensis Extract
Hydrolyzed Saccharomyces Cell Wall
Hydrolyzed Saccharomyces Extract
Hydrolyzed Saccharomyces Lysate Extract
Hydrolyzed Torulaspora Delbruekii Extract
Hydrolyzed Yeast
Hydrolyzed Yeast Extract
Kluyveromyces Extract
Lactic Yeasts
Lipomyces Lipid Bodies
Lipomyces Oil
Lipomyces Oil Extract
Metschnikowia Agaves Extract
Metschnikowia Henanensis Extract
Metschnikowia Reukaufii Lysate Extract
Metschnikowia viticola Extract
Pichia Anomala Extract
Pichia Caribbica Ferment
Pichia Extract
Pichia Ferment Extract Filtrate
Pichia Ferment Lysate Filtrate
Pichia Heedii Extract
Pichia Minuta Extract
Pichia Pastoris Ferment Filtrate
Phaffia Rhodozyma Extract
Phaffia Rhodozyma Ferment Extract
Saccharomyces
Saccharomyces Cerevisiae Extract
Saccharomyces Extract
Saccharomyces Ferment
Saccharomyces Ferment Extract
Saccharomyces Ferment Extract Lysate Filtrate
Saccharomyces Ferment Filtrate
Saccharomyces Ferment Lysate Extract
Saccharomyces Ferment Lysate Filtrate
Saccharomyces Lysate
Saccharomyces Lysate Extract
Saccharomyces Lysate Extract Filtrate
Saccharomyces Lysate Filtrate
Schizosaccharomyces Ferment Extract Filtrate
Schizosaccharomyces Ferment Filtrate
Schizosaccharomyces Pombe Extract
Torulaspora Delbrueckii Extract
Torulaspora Delbrueckii Ferment
Yarrowia Lipolytica Extract
Yarrowia Lipolytica Ferment Lysate
Yarrowia Lipolytica Oil
Yeast
Yeast Extract
Yeast Ferment Extract

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), the majority of these ingredients are reported to function in cosmetics as skin protectants or skin-conditioning agents (Table 1).[1] Other reported functions for this ingredient group include hair-conditioning agent, surfactant, humectant, antioxidant, colorant, anti-acne agent, anti-microbial agent, film former, and viscosity-increasing agent.

Some of the species of yeast reviewed in this report are naturally present or are used in foods (e.g., *Saccharomyces cerevisiae* is generally recognized as safe (GRAS) as a flavoring agent and adjuvant at a level not to exceed 5% in food [21CFR184.1983]). For the ingredients that are affirmed GRAS or are used/present in foods, systemic toxicity via the oral route will not be the focus of this safety assessment. Although oral exposure data are included in this report, the primary focus for the safety of such ingredients is topical exposure and local effects.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; a search was last conducted March 2023. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited**.**

The cosmetic ingredient names, according to the *Dictionary*, are written as listed above, without italics and by capitalizing the first letter of each word in the name. In many of the published studies, it is not known how the substance being tested compares to the ingredient as used in cosmetics. Therefore, if it is not known whether the ingredient being discussed is a cosmetic ingredient, for the generic yeast ingredients, the name of the test substance will be written using all lower-case letters (e.g., yeast extract); however, if it is known that the substance is a cosmetic ingredient, the first letter of each word in the name will be capitalized (e.g., Yeast Extract). For the genus/species ingredients, if it is not known whether the ingredient being discussed is a cosmetic ingredient, the , the standard scientific practice of using italics will be followed

(e.g., *Saccharomyces cerevisiae* extract); if it is known that the substance is a cosmetic ingredient, the *Dictionary* terminology (e.g., Saccharomyces Cerevisiae Extract) will be used.

In many instances, data were found on the species of yeast (e.g., *Yarrowia lipolytica*), and not on specific ingredients that are reviewed in this report (e.g., Yarrowia Lipolytica Ferment Lysate). Because of this, information is primarily organized by species names, rather than ingredient names, throughout the report. However, when it is known that the test substance used is a cosmetic ingredient, the INCI name will be used. It should be noted that some ingredients reviewed in this report (e.g., Galactomyces Ferment Filtrate) may be derived from more than one species of yeast (i.e., Galactomyces Ferment Filtrate may be derived from *Galactomyces candidus*, *Galactomyces fermentans*, or *Galactomyces reessii*).

In addition, many of the species of yeast reviewed in this report have synonymous names, according to the National Center for Biotechnology Information (NCBI) taxonomy database. When studies state the use of a yeast species (e.g., *Starmerella bombicola*) that is synonymous to a species reviewed in this report (e.g., *Candida bombicola*), the species name stated in the study is used as the header (e.g., *Starmerella bombicola*), with a notation stating the synonymous species that is relevant to this report (e.g., *Starmerella bombicola* (synonymous to *Candida bombicola*)).

It should also be noted that the generic yeast ingredients (e.g., Yeast Extract) named in this report may refer to several different species of yeast under the class Saccharomycetes. When the species used in an assay is known, it will be stated in text (e.g., Yeast Extract derived from *Candida saitoana*), and the data will be associated with the specific ingredients derived from the genus and species. In addition, because the *Dictionary* does not define the species of yeast used in the production of these generic ingredients, when data are provided on these ingredients, the generic ingredient name will be used as the header, instead of a species name.

CHEMISTRY

Definition

According to the *Dictionary*, Yeast (CAS No. 68876-77-7) is a class of microorganisms (Saccharomycetes) characterized by a lack of photosynthetic ability, existence as unicellular or simple irregular filaments, and reproduction by budding or direct division. *Saccharomyces cerevisiae,* a yeast strain widely used in the preparation of foods and cosmetics, is a highly adaptable, unicellular fungus, capable of growth both aerobic and anaerobically.[3-5] All ingredients reviewed in this report are derived from various yeast species.[1] The definitions of the ingredients included in this report are provided in Table 1.

Yeasts are ubiquitous microorganisms that may be present in a diverse range of habitats, including the air, animals, water, and plants.[6,7] Yeasts are typically nomadic, resilient, and are able to survive in a wide range of conditions. In addition, phenotypic characteristics of yeasts may vary dependent upon environment.[8] Although yeasts can be found in natural habitats, they are typically laboratory-grown for industrial purposes.

Chemical Properties

Dried yeast (*Saccharomyces cerevisiae*) occurs in the form of powder, granules, or flakes, and is typically light brown to buff in color.[9] According to a supplier, a Saccharomyces Cerevisiae Extract was reported to be a clear, yellow-colored liquid, with a pH value of 4.0 - 5.0, and a density of 1.035 - 1.055 (at 20° C).[10] The water solubility of a *Saccharomyces cerevisiae* extract is reported to be > 200 g/l, with the majority of particle sizes ranging from 50 to 220 µm (only 3% of particles < 10 µm in size).[2] Other properties of yeast-derived ingredients can be found in Table 2.

Taxonomy

The majority of the ingredients in this report, including the generic yeast ingredients (e.g., Yeast Extract), correspond to yeasts that are part of the Saccharomycetes class.[1] However, ingredients derived from the species *Phaffia rhodozyma* and the genus *Schizosaccharomyces* belong to the class Tremellomycetes and Schizosaccharomycetes, respectively.[11] The taxonomic profile, as well as relevant synonymous genus/species names of these ingredients, are provided in Table 3.

Yeast Strain Identification and Biosafety

In order to ensure the proper strain of yeast is used in manufacturing, taxonomic identification is performed, typically via r-28S deoxyribonucleic acid (DNA) sequencing and Internal Transcribed Space.[12] According to the US Centers for Disease Control and Prevention, biosafety level (BSL) classifications are given to biological agents, including yeasts, based on the level of protection provided to workers, the environment, and the public. These levels range from 1 (no or low individual and community risk; e.g., baker's yeast) to 4 (high individual and community risk; e.g., Ebola virus). According to a manufacturer, only BSL-1 yeast species should be used in the manufacture of cosmetic ingredients. In Europe and the US, pathogenic yeasts under the Saccharomycetes class with a BSL-2 categorization include *Candida auris*, *Candida albicans*, *Candida dubliensis*, *Candida glabrata*, *Candida parapsilosis*, and *Candida tropicalis*, none of which are used in the manufacturing of cosmetic ingredients.

Method of Manufacture

Unpublished data were submitted describing methods of manufacture for some It is unknown if the general methodologies described herein apply to the manufacture of cosmetic ingredients.

According to a manufacturer, yeast ingredients are manufactured via atomization, high temperature enzymatic inactivation (80°C), addition of preservatives, freezing, mechanical grinding, ultrafiltration (0.45 µm or sterilizing filtration (0.22 µm), autolysis/lysis, and acid pH adjustment.[12] Because yeasts are only viable at temperatures < 50°C, no live yeasts would be present in the finished cosmetic product.

Kluyveromyces marxianus (synonymous to *Kluyveromyces fragilis*) and *Saccharomyces cerevisiae*

Extract powders (derived from *Kluyveromyces marxianus* and *Saccharomyces cerevisiae*) are created by first producing yeast biomass via molasses (medium of cultivation).[13] Molasses solutions (molasses and distilled water) are subjected to heavy metal removal, boiled, autoclaved, cooled, filtered, and fermented. Yeast cultures are inoculated into the bioreactor and subjected to a fermentation process under aerobic conditions. After fermentation, the fermentation medium is centrifuged, and the supernatant is decanted and the pellet is washed with saline and centrifuged again. Yeast cells are autolyzed, cooled, and centrifuged to remove cell wall components. The supernatant is then dried in a freeze-dryer, yielding the extract powder.

Saccharomyces cerevisiae

In order to obtain a baker's yeast extract (derived from *Saccharomyces cerevisiae*), dry baker's yeast (50 g) is ground using a mortar, and stirred overnight with water (100 ml).[14] The mixture is then centrifuged for 30 min, filtered, dialyzed, and freeze-dried, ultimately obtaining approximately 1 g baker's yeast extract.

Saccharomyces Cerevisiae Extract

According to data submitted by industry, Saccharomyces Cerevisiae Extract is prepared via an extraction using 1,2-propylene glycol.[10] The extract is sterile filtered and combined with 0.35% potassium sorbate and 0.35% sodium benzoate for preservation. According to a different industry submission, Saccharomyces Cerevisiae Extract is prepared by first concentrating or spray-drying a solution obtained via yeast autodigestion.[15] The resulting solution is extracted with purified water, filtered, and evaporated. The remaining substance is then combined with either ethanol or 1,3-butylene glycol, followed by sedimentation, filtration, and combination with 50% ethanol or a 50% butylene glycol solution.

Yarrowia lipolytica

A biomass of *Yarrowia lipolytica* is prepared by first grafting the yeast from an agar slant.[16] Proliferation of the yeast is continued in tanks of increasing capacity with consistent culture conditions. Yeast is harvested (centrifuged, rinsed with water, and again centrifuged) after the appropriate concentration of yeast dry matter is reached, followed by drying until a moisture content of < 5% is reached (yeast are killed during this step).

Yeast Extract

According to a manufacturer, Yeast Extract is prepared via extraction with a specified eluent (e.g., water, butylene glycol, glycerin, propylene glycol, carthamus tinctorius (safflower) seed oil), to yield a concentrate.[17] The concentrate is then blended with a diluent and preservation system to produce the final result. According to a different manufacturer, Yeast Extract is prepared via solubilization of yeast (e.g., *Candida saitoana*) in water, separation of soluble and insoluble phases, filtration, followed by sterile filtration.[18]

Composition and Impurities

Candida kefyr (synonymous to *Kluyveromyces fragilis*)

The total saturated, monounsaturated, and polyunsaturated fatty acid composition of *Candida kefyr* was determined to be 23.79, 52.79, and 23.42% (of total fatty acids), respectively (measured via gas chromatography mass spectrometry).[19] The specific fatty acids observed can be found in Table 4.

Kluyveromyces fragilis

The composition of a biomass of *Kluyveromyces fragilis* grown on deproteinized whey supplemented with 0.8% diammonium hydrogen phosphate and 10 ppm indole-3 acetic acid was evaluated.[20] The biomass was reported to consist of 37 g/100 g crude protein, 16 g/100 g ash, 4.9 g/100 g crude fiber, 7.8 g/100 g fat, and 34.3 g/100 g carbohydrates. Also reported was a total nitrogen content of 5.92% and total nucleic acid content of 4.82% in *Kluyveromyces fragilis* cells. The essential amino acid profile of the biomass is as follows: arginine (4.30 g/100 g protein), histidine (1.98 g/100 g protein), isoleucine (3.82 g/100 g protein), leucine (5.47 g/100 g protein), lysine (6.91 g/100 g protein), methionine (0.38 g/100 g protein), phenylalanine (3.98 g/100 g protein), threonine (4.45 g/100 g protein), tryptophan (1.07 g/100 g protein), and valine (5.02 g/100 g protein).

Kluyveromyces lactis

A quantitative analysis of sterols in *Kluyveromyces lactis* cells was performed using high-performance liquid chromatography.[21] Ergosterol represented more than 80% of the total amount of yeast sterols.

Kluyveromyces marxianus

Prominent volatile compounds found in a *Kluyveromyces marxianus* extract include hexadecane, pentanoic acid, phenol, γ-decalactone, 3-octanone, and 2-methylpentanal.[13] Other volatile compounds found in this extract in lesser amounts

include acetic acid, 2-phenylethyl ester, benzaldehyde, 2,3-butanediol, 2-ethyl,3,5-dimethylpyrazine, nonanal, benzyl alcohol, 2-phenylethanol, (-)-citronellol, geranyl acetate, 2,3,5-trimethylpyrazine, pentadecane, 2-phenyl-2-butenal, tetradecane, 2-nonanone, ethyl phenylacetate, β-myrcene, 2-ethyl-2,5-dimethylpyrazine, and 2-ethyl-6-methylpyrazine. This extract was reported to contain amino acids in an amount of 42.31 g/100 g protein). Alpha-mannans are reported to be present in *Kluyveromyces marxianus* cell walls.[22]

Phaffia rhodozyma

The carotenoid, sterol, and ubiquinone content of a *Phaffia rhodozyma* yeast biomass sample consisted of the following: ergosterol 1.121 ± 0.013 mg/g, ubiquinon 1.548 ± 0.009 mg/g, torularhodin 0.856 ± 0.009 mg/g, torulen 0.058 ± 0.002 mg/g, and beta-carotene 0.024 ± 0.001 mg/g.[23] This biomass sample contained 20% saturated fatty acids, 42% monounsaturated fatty acids, and 38% saturated fatty acids.

Saccharomyces cerevisiae

In order for baker's yeast extract (mechanically ruptured cells of *Saccharomyces cerevisiae*) to meet GRAS specifications for food use, the ingredient must contain, on a dry weight basis, < 0.4 ppm arsenic, < 0.13 ppm cadmium, < 0.2 ppm lead, < 0.05 ppm mercury, < 0.09 ppm selenium, and < 10 ppm zinc [21CFR184.1983]. In addition, dried yeast (*Saccharomyces cerevisiae*) may be safely used in food provided the total folic acid content of the yeast does not exceed 0.04 mg/g yeast [21CFR172.896]. The composition of a cleaned natural yeast (*Saccharomyces cerevisiae*; g/100 g dry yeast) was reported to be 42.83 ± 0.11 protein, 1.45 ± 0.40 total lipids, 1.74 ± 0.17 ashes, and 53.91 carbohydrates.[24] This sample of yeast contained moisture in an amount of approximately 0.07 g/100 g dry yeast.

The essential amino acid profile, amount of mineral elements, and fatty acid composition of whole yeast cells (*Saccharomyces cerevisiae*) was evaluated.[25] The mineral elements observed in the largest quantities were phosphorous (1516.0 mg/100 g) and potassium (2035 mg/100 g). All other mineral elements were present in amounts of 147.7 mg/100 g or less. The essential amino acids observed were threonine (4.7 g/100 g protein), methionine + half-cystine (2.4 g/100 g protein), valine (4.8 g/100 g protein), isoleucine (4.2 g/100 g protein), leucine (6.0 g/100 g protein), tyrosine + phenylalanine (6.5 g/100 g protein), lysine (8.0 g/100 g protein), histidine (4.2 g/100 g protein), and tryptophan (1.2 g/100 g protein). The total saturated and monounsaturated fatty acid composition in *Saccharomyces cerevisiae* was determined to be 29.32 and 70.69% (of total fatty acids), respectively (measured via gas chromatography mass spectrometry). The specific fatty acids observed can be found in Table 4. In addition, the nutrient, amino acid, and mineral composition of a *Saccharomyces cerevisiae* sample can be found in Table 5.

The main classes of lipids observed in *Saccharomyces cerevisiae* extracts were determined to be glycerophospholipids, sphingolipids, sterols, and glycerolipids.[26] Forty percent of the identified lipids were polar lipids, while the remaining 60% were neutral lipids. In addition, the cell wall of *Saccharomyces cerevisiae* contains layers predominantly consisting of beta-glucans.[27] The inner layer of the cell wall contains (1→3) β- and (1→6) β-linked glucose residues, and chitin. The outer layer of the cell wall is mainly composed of α-mannan and glycoproteins.

Prominent volatile compounds found in a *Saccharomyces cerevisiae* extract include acetic acid, 2-phenylethyl ester, benzaldehyde, 2,3-butanediol, 2-ethyl-3,5-dimethylpyrazine, nonanal, benzyl alcohol, 2-phenylethanol, (-)-citronellol, hexadecane, and pentanoic acid.[13] Other volatile compounds found in lesser amounts include phenol, γ-decalactone, 3-octanone, 2-methylpentanal, geranyl acetate, 2,3,5-trimethylpyrazine, pentadecane, 2-phenyl-2-butenal, tetradecane, 2-nonanone, ethyl phenylacetate, β-myrcene, 3-ethyl-2,5-dimethylpyrazine, and 2-ethyl-6-methylpyrazine. This extract was reported to be rich in amino acids (47.41 g/100 g protein).

The chemical composition of yeast hydrolysate obtained from *Saccharomyces cerevisiae* was reported to be 4.7% moisture, 68.3% crude protein, 0.3% crude lipid, 3.1% crude ash, and 23.6% carbohydrate.[28]

According to the Food Chemicals Codex, dried yeast (*Saccharomyces cerevisiae*) may not contain more than 1 mg/kg lead.[9] In addition, dried yeast may not contain more than 8% ash.

Saccharomyces Cerevisiae Extract

According to a supplier, Saccharomyces Cerevisiae Extract may not contain more than 20 ppm heavy metals or 2 ppm arsenic.[15]

Schizosaccharomyces pombe

The fatty acid profile of a *Schizosaccharomyces pombe* extract was evaluated via gas chromatography.[29] These fatty acids include palmitic acid (C16:0), palmitoleic acid (C16:1), stearic acid (C18:0), and oleic acid (C18:1). The *Schizosaccharomyces pombe* cell wall contains two electron-dense layers formed by galactomannan and a central electron-transparent layer consisting of β- and α-glucans (e.g., β-(1,3)-, β-(1,6)-, and α-(1,3)-glucan).[30]

Yarrowia lipolytica

Yeast biomass derived from *Yarrowia lipolytica* (a novel food according to the European Food Safety Authority (EFSA)) is reported to consist primarily of proteins (45 - 55 g/100 g), dietary fiber (25 g/100 g), and fat (7 - 10 g/100 g (the majority being mono-and polyunsaturated fatty acids).[16] When pesticide evaluations were performed on yeast biomass

samples, the analyzed pesticides (e.g., organochlorinated and organophosphate pesticides, pyrethroids) were below limits of quantification. Specifications for yeast biomass derived from *Yarrowia lipolytica* as a novel food include the following: ≤ 3.0 mg/kg lead, ≤ 1.0 mg/kg cadmium, ≤ 0.1 mg/kg, ≤ 5000 colony-forming units (CFU)/g total aerobic microbial count, ≤ 100 CFU/g total yeast and mold count, < 10 CFU/g viable *Yarrowia lipolytica* cells, and ≤ 10 CFU/g coliforms.

The total saturated, monounsaturated, and polyunsaturated fatty acid composition of *Candida lipolytica* (synonymous to *Yarrowia lipolytica*) was determined to be 13.63, 63.36, and 23.01% (of total fatty acids), respectively (measured via gas chromatography mass spectrometry).[19] The specific fatty acids observed can be found in Table 4. In addition, the nutrient, amino acid, and mineral composition of a *Yarrowia lipolytica* sample can be found in Table 5.

Yarrowia lipolytica can accumulate lipids to levels > 50% of cell dry weight.[31] These lipids consist mostly of triglycerides and steryl esters. This accumulation, however, depends on multiple factors including environmental conditions, tempaure, pH, production of secondary metabolites, nutrient limitation, and microorganism physiology.

Yeast Extract

According to a supplier, a Yeast Extract derived from several different yeast species (*Candida magnolia, Candida oleophilia, Candida saitoana, Debaryomyces nepalensis, Metschnikowia reukaufii, Metschnikowia pulcherrima, Pichia naganishii*) contained 10-53% sugars, 38-39% mineral ashes, and 7-60% proteins.[18] The sum of heavy metals in these extracts were reported to be < 20 ppm.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP survey data, Yeast Extract is reported to be used in 398 formulations (343 leave-on formulations and 55 rinse-off formulations; Table 6).[32] All other in-use ingredients are reported to be used 81 formulations or less. The results of the concentration of use survey conducted by the Council indicate Galactomyces Ferment Filtrate has the highest concentration of use in a leave-on formulation; it is used at up to 90.7% in moisturizing products (not spray).[33] The 39 ingredients not in use according to the VCRP and industry survey are listed in Table 7.

Incidental ingestion of several of these ingredients may occur as they are reported to be used in lipstick formulations (e.g., Saccharomyces Ferment is used in lipstick formulations at 0.00013%). These ingredients are also reported to be used in products that may result in mucus membrane (e.g., Saccharomyces Ferment Filtrate is used at up to 0.038% in feminine deodorants) and eye exposure (e.g., Galactomyces Ferment Filtrate is used in eye lotions at up to 37.5%). Saccharomyces Lysate Extract is used at up to 0.067% in baby lotions/oils/powders/creams.

Some of these ingredients are used in cosmetic sprays and powders, and could possibly be inhaled; for example, Saccharomyces Ferment Filtrate and Yeast Extract are used in colognes and toilet waters at 0.065% and Galactomyces Ferment Filtrate is reported to be used at 1.1% in face powders. In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The yeast-derived ingredients reviewed in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[34]

Non-Cosmetic

Yeasts are commonly used worldwide in the food and beverage industry, mainly in baking and alcohol production as a fermentative agent.[35] The use/presence of several of the species reviewed in this report in foods, their GRAS status, and information regarding other non-cosmetic uses of these species are provided in Table 8. Specifications required for the GRAS ingredients derived from *Saccharomyces cerevisiae* are described in the Composition and Impurities section of this report.

TOXICOKINETIC STUDIES

Dermal Absorption

Details of the in vitro dermal absorption studies summarized below can be found in Table 9.

Several in vitro dermal absorption assays were performed according to Organisation for Economic Cooperation and Development test guideline (OECD TG) 428 on 30% emulsions of Metschnikowia Agaves Extract, Pichia Anomala Extract, Pichia Heedii Extract, Pichia Minuta Extract, a Yeast Extract derived from *Candida saitoana*, and a Yeast Extract derived from *Metschnikowia reukaufii*.[18] Dermal absorption in these studies ranged from 0.2 to 4.6% of the applied dose 24 h after application.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Pichia pastoris

The dissemination of live *Pichia pastoris* cells (1 x 10^6 colony forming units (CFU); in sterile saline) was evaluated in female BALB/c mice (5/group).[36] Intravenous administrations were performed via the lateral tail vein. Animals were euthanized at 4 h, 24 h, 48 h, and 6 d post-administration, and samples of sera and tissues (kidney, liver, brain, spleen, heart, and lung) were collected. Dissemination of *Pichia pastoris* cells to the heart, kidney, and spleen was apparent, but was quickly eliminated during the first 48 h post-administration. Clearance of *Pichia pastoris* cells in the liver was achieved by day 6 post-administration. No colonization in the brain was detected.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Details on the acute toxicity studies summarized below can be found in Table 10.

An LD_{50} of > 2000 mg/kg was determined in rats in acute dermal toxicity assays using 49.5% *Saccharomyces cerevisiae* cell wall (in hydrated sodium calcium aluminosilicate) and a *Saccharomyces cerevisiae* extract (in water).[2,4] Similarly, no toxicity was observed in an acute oral toxicity assay performed in rats using yeast hydrolysate obtained from *Saccharomyces cerevisiae* (5000 mg/kg bw).[28] No toxicity was observed in acute oral toxicity assay performed in rats using 49.5% *Saccharomyces cerevisiae* cell wall (in hydrated sodium calcium aluminosilicate and water).[4] No signs of toxicity were observed in an acute oral toxicity assay in which rats were given 2000 mg/kg fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water).[37] Acute inhalation toxicity was evaluated in rats using 49.5% *Saccharomyces cerevisiae* cell wall (in hydrated sodium calcium aluminosilicate and water; at gravimetric chamber concentrations of 2.09 mg/l).[4] The LC_{50} was determined to be > 2.09 mg/l. No adverse effects were observed in acute toxicity assay performed in mice inoculated with live *Pichia pastoris* cells (in saline; 1 × 10^6 CFU).[36]

Repeated-Dose Toxicity Studies

Details on the repeated-dose oral toxicity studies summarized below can be found in Table 11.

No significant adverse effects were noted in a 14-d assay in which rats (5/sex/group) were orally administered 1000 mg/kg bw/d yeast hydrolysate derived from *Saccharomyces cerevisiae* (method of oral administration and vehicle not stated).[28] In a different 14-d study, *Kluyveromyces marxianus* extracts (strains A4 and A5; 1.0 x 10^6 CFU/ml or 1.0 x 10^8 CFU/ml; in sterilized saline) were orally administered to female mice (6/group; method of oral administration not stated).[38] Statistically significant lower spleen to body ratios and liver to body ratios were noted in mice treated with the high concentration of the A5 strain, and the low concentration of the A4 strain, respectively. No other adverse effects were observed. *Phaffia rhodozyma* extract (up to 1000 mg/kg) in corn oil was given to rats (6/sex/group), via gavage, for 28 d.[39] The no-observed-adverse-effect-level (NOAEL) was determined to be > 1000 mg/kg. Fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water) was given to rats (20/sex/group) in a 90-d study (rats given up to 1500 mg/kg bw/d), and a 1-yr study (rats given up to 800 mg/kg bw/d).[37] All administrations were performed via gavage. The NOAELs for the 90-d and 1-yr study were determined to be 1500 mg/kg bw/d and 800 mg/kg bw/d (the highest dose administered in each study), respectively.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No relevant developmental and reproductive toxicity studies on the yeast-derived ingredients evaluated in this report were found in the published literature, and unpublished data were not submitted.

GENOTOXICITY STUDIES

Details on the genotoxicity studies summarized below can be found in Table 12.

Negative results were obtained for Ames assays performed on *Phaffia rhodozyma* extract (in acetone; up to 5000 µg/plate), fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water; up to 5000 µg/plate), and 90% yeast (*Saccharomyces cerevisiae*) cell wall (in hydrated sodium calcium aluminosilicate; up to 3500 µg/plate).[4,37,39] Negative results were also obtained in mammalian cell gene mutation assay performed using a fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water; up to 5000 µg/plate). Mammalian bone marrow chromosomal assays were performed using a *Phaffia rhodozyma* extract (in corn oil; up to 2000 mg/kg bw/d; performed in male mice (3/group) and 90% yeast (*Saccharomyces cerevisiae*) cell wall (in hydrated sodium calcium aluminosilicate; up to 2000 mg/kg bw/d; performed in mice (28/sex/group). Both test substances were considered to be non-clastogenic.

CARCINOGENICITY STUDIES

No relevant carcinogenicity studies on the yeast-derived ingredients evaluated in this report were found in the published literature, and unpublished data were not submitted.

ANTI-CARCINOGENICITY STUDIES

In Vitro

Saccharomyces cerevisiae

Treatment with *Saccharomyces cerevisiae* resulted in the growth inhibition or apoptosis of several cancer cell types in multiple anti-carcinogenicity assays.[40-43] Cell lines that were inhibited by *Saccharomyces cerevisiae* include human metastatic breast cancer cells (MCF-7 and ZR-75-1), non-metastatic breast cancer cells (HCC70), squamous cell carcinoma of the tongue (SCC-4), adenocarcinomas of the colon (Caco-2, DLD1, and HCT116; concentrations not reported), and cervical cancer cells (HeLa; up to 1000 µg/ml yeast cells).

OTHER RELEVANT STUDIES

Anti-Inflammatory Effects

The following study is included as it may help in providing information regarding dermal irritation/allergy alleviation following exposure to Saccharomyces Ferment, when derived from *Saccharomyces cerevisiae*.

Saccharomyces cerevisiae

The anti-inflammatory properties from a dried fermentate derived from *Saccharomyces cerevisiae* was evaluated using a single-blind, placebo-controlled assay (n = 12 subjects). To induce inflammation, 0.01 ml of a dilute solution of histamine was applied to the forearm of each subject, and a scratch was performed using a sterilized lancet. One min after the scratch, the histamine solution was removed, and 0.01 ml dried fermentate (0.1 g/ml) was applied to the site. After 1 min, the dried fermentate was removed, and laser Doppler probes evaluated skin sites (evaluation for 10 min). Doppler probe measured parameters included the time to maximum blood perfusion (T_{max}), and the slope of the curve generated during the resolution phase over time, as a measure of the speed of resolution. This same procedure was performed on the other forearm using saline (negative control) instead of dried fermentate. After probes were removed, each subject was asked to score the level of itching on each skin site using a 100 mm Visual Analogue Scale. Among the 12 test subjects, the observed average time to T_{max} on sites treated with dried fermentate were significantly shorter than sites treated with saline ($p < 0.05$). In addition, the slope of the curve after T_{max} was significantly lower compared to saline treated site s ($p < 0.05$), indicating that treatment with dried fermentate resulted in a faster process of inflammation resolution.

Immunomodulatory Effects

The following studies are included as they may be helpful in providing information regarding potential allergenicity/ hypersensitivity of the yeast-derived ingredients evaluated in this report.

Candida pseudotropicalis (synonymous to *Kluyveromyces fragilis*), *Geotrichum candidum* (synonymous to *Galactomyces candidus*), and *Saccharomyces cerevisiae*

Immunological cross-reactivity of several yeast species (*Candida albicans*, *Candida pseudotropicalis*, *Candida krusei*, *Candida parapsilosis*, *Candida tropicalis*, *Candida guilliermondi*, *Candida humicola*, *Canidida norwegica*, *Candida utilis*, *Cryptococcus albidus*, *Geotrichum candidum, Pityrosporon pachydermatis, Pityrosporon ovale, Rhodotorula minuta, Rhodotorula rubra, Saccharomyces cerevisiae, Torulopsis glabrata*, and *Trichosporon cutaneum*) was evaluated.[44] Cross-reactive components of yeast extracts were measured via an enzyme immunoassay using rabbit anti-*Candida albicans* antiserum. Results were expressed relative to the absorbance observed with *Candida albicans* extract. Significant cross-reactivity was only observed between Candida species. Skin prick tests were performed in 67 atopic patients using whole cell and disrupted cell extracts several yeast species including *Saccharomyces cerevisiae*. Whole cell and disrupted cell extracts of Saccharomyces cerevisiae resulted in positive results in 41 and 31% of patients, respectively.

Pichia pastoris

A delayed-type hypersensitivity test was performed in female BALB/c mice to evaluate cell-mediated immunity to live *Pichia pastoris* cells.[36] Four groups of 5 adult mice were anesthetized and abdominal skin was shaved. Approximately 50% of the stratum corneum was removed, and *Pichia pastoris* cells (2×10^8 CFU in 50 µl sterile saline) were applied epicutaneously. Vehicle group mice received applications of 50 µl sterile saline on stratum corneum-removed skin. Another

group of control mice consisted of shaved animals without disruption of the stratum corneum, and were used to evaluate baseline measures. Seven days after administration, ear thickness was measured with a micrometer. To achieve the efferent phase of the delayed-type hypersensitivity response, mice were challenged with inoculation into the ears with heat-killed *Pichia pastoris* cells (1 x 10^7 CFU). Swelling was calculated by subtracting the ear thickness 24 h after the challenge to the baseline thickness. Results between control, vehicle-control, and *Pichia pastoris*-treated groups were similar, indicating that *Pichia pastoris* did not induce a cell-mediated immune response.

Saccharomyces cerevisiae

Forty-seven patients with inhalant allergy to fungi were tested for allergic sensitivity to baker's yeast (*Saccharomyces cerevisiae*).[14] Baker's yeast extract and purified enolase obtained from baker's yeast were each formulated at concentrations of 1 and 10 mg/ml in a diluent of 50% glycerin in sterile saline. Skin prick testing was performed using both the baker's yeast extract and purified enolase on each of the 47 patients. Non-fungi allergic control subjects (10 non-allergic subjects and 10 grass-pollen and/or mite-allergic patients) were subjected to skin prick tests with baker's yeast extract. Wheal sizes were recorded 15 min following skin prick. Clear wheal and flare skin reactions to baker's yeast extract were observed at both test concentrations (wheal sizes of at least 3 mm) in fungi-allergic patients. No skin reactions were seen at either test concentration in control subjects that were not reported to have fungi allergy. Twenty-three of the fungi-allergic patients showed an allergic response to baker's yeast enolase. Sera from all 47 fungi-allergic patients were subjected to radioallergo-sorbent testing (RAST) using both baker's yeast extract and enolase. Sera from 10 of these patients were RAST-negative to baker's yeast extract and enolase, and 5 other sera were considered doubtful positives. Thirty-two patients were RAST-positive, 22 of which showing RAST uptakes with enolase that were equal to, or higher than, the uptakes recorded with baker's yeast extract. Skin prick tests for these 32-RAST positive patients revealed that in 25 subjects, wheal sizes to enolase were equal to, or greater than, wheal sizes recorded for baker's yeast extract.

In a different study, the potential sensitizing effects of a *Saccharomyces cerevisiae* extract was evaluated in 449 patients (229 with atopic dermatitis, 50 with allergic rhinitis and/or asthma, and 173 non-atopic controls) via a skin prick test.[45] Skin prick tests were performed in duplicate, and the results were evaluated after 15 min. Serum samples were taken for total serum immunoglobin E (IgE) determinations. Twenty percent of patients (92) had positive skin prick tests to the extract. Of these subjects, 85 were atopic dermatitis patients, 4 had allergic rhinitis and/or asthma, and 3 were nonatopic controls. There was a significant correlation between the severity of eczema and frequency of positive skin test results to *Saccharomyces cerevisiae*. Patients with moderate to severe dermatitis displayed positive skin prick test reactions significantly more frequently than allergic rhinitis/asthma patients or nonatopic controls ($p < 0.001$). In addition, a parallel skin reactivity assay was performed with other yeasts and common allergens. Parallel skin reactivity was observed with yeasts (*Pitryosporum ovale* and *Candida albicans*), molds, and animal dander, but not with pollen or dust mites. In addition, a significant correlation between total serum IgE and positive skin prick test results with *Saccharomyces cerevisiae* was seen ($r = 0.53$, $p < 0.001$).

Allergens of *Saccharomyces cerevisiae* were evaluated via an IgE-immunoblotting assay performed on 83 subjects.[46] Sixty-three of these patients were previously diagnosed with atopic dermatitis with positive skin prick tests or RAST for *Saccharomyces cerevisiae*, and 7 subjects were diagnosed with atopic dermatitis, but did not have positive skin prick tests or RAST for *Saccharomyces cerevisiae*. The remaining 13 subjects were non-atopic controls. A disrupted whole-body extract of *Saccharomyces cerevisiae* was used for evaluation. Forty-one atopic subjects were positive in the IgE immunoblotting assay, revealing 22 IgE stained bands (10 bands represented immediate allergens, and 12 bands represented minor allergens). In 39% of positive subjects, staining of the 48 kD band was observed. Non-atopic (control-subject serum) and sera from atopic patients with negative skin prick tests to *Saccharomyces cerevisiae* were IgE negative in this experiment.

IgE, IgA, and IgG responses to common yeasts, including *Candida albicans*, *Candida utilis*, *Cryptococcus albidus*, *Rhodotorula rubra*, and *Saccharomyces cerevisiae*, were evaluated via an immunoblotting assay.[47] In addition, the cross-reactivity of their IgE-binding components were also evaluated. Twenty atopic subjects with asthma, allergic rhinitis, or atopic dermatitis, were included in the study (16 patients skin prick test-positive to yeast, 4 were not and served as controls). IgE immunoblotting revealed IgE-binding bands in all species (*Candida albicans* (11 bands), *Candida utilis* (8 bands), *Saccharomyces cerevisiae* (5 bands), *Rhodotorula rubra* (5 bands), and *Cryptococcus albidus* (4 bands)). The 46-kDa band was shared by all 5 yeasts, and the 13-kDa band was shared by 4 yeasts. Prominent IgE binding was seen to a 46-kDa band of *Candida albicans* (7 subjects), *Candida utilis* (5 patients), and *Saccharomyces cerevisiae* (1 patient). Strong IgG responses were observed against *Saccharomyces cerevisiae* (19 patients had a response; 14 patients had a response to *Saccharomyces cerevisiae* mannans) and *Candida albicans* (18 patients had a response; 17 patients had a response to *Candida albicans* mannans). The corresponding patient numbers in IgA immunoblotting were 17 (*Candida albicans*), 17 (*Candida albicans* mannans), 15 (*Saccharomyces cerevisiae*), 7 (*Saccharomyces cerevisiae* mannans), 5 (*Rhodotorula rubra*), 11 (*Cryptococcus albidus*), and 2 (*Cryptococcus albidus* mannans). An IgA response to the 20-kDa band of *Saccharomyces cerevisiae* was observed in 12 patients.

Pulmonary Toxicity

The following studies are included in this report as they may be helpful in evaluating the inhalation toxicity potential of yeast-derived ingredients.

Geotrichum candidum (synonymous to *Galactomyces candidus*)

The cause of allergic alveolitis was evaluated in 12 Australian patients.[48] The houses of all patients were evaluated and inspected. Extensive wood decay was found in 10/12 houses, while 4/12 also had obvious fungal growth on damp walls. Twelve fungal species were observed in homes, including *Geotrichum candidum* (synonymous to *Galactomyces candidus*). Precipitin tests were performed on the 12 patients, along with 14 controls, using freeze-dried fungal extracts (30 mg/ml) of the 12 observed fungal species, in addition to several other species and allergens. If results were negative, tests were repeated using serum that had been concentrated to 20% of the original volume by desiccation. Six of the 12 patients exhibited positive precipitins to one or more of the fungi when unconcentrated serum was used. Nine of 12 patients displayed positive precipitins with concentrated serum (2 positive reactions to *Geotrichum candidum* extract). No precipitins were found to any of the fungal groups in control subjects. Skin prick tests were performed in all patients (number of control subjects not specified) using freeze-dried fungal extracts (10 mg/ml) and other allergens. One patient displayed a positive reaction to *Geotrichum candidum* extract. Inhalation tests were performed with 3 control subjects and 6 patients with alveolitis using solutions of nebulized yeast (*Serpula lacrymans*, *Geotrichum candidum*, and *Aspergillus fumigatus*; 1 mg/ml). Measurements (spirometry and single breath diffusion capacity) were taken every 15 min for the first hour, and every 30 min for at least 8 h. No immediate positive responses were observed; however, positive late responses were obtained to *Serpula lacrymans* (3 positive reactions), *Geotrichum candidum* (2 positive reactions), and *Aspergillus fumigatus* (2 positive responses). Relocation of patients resulted in improvement of symptoms in all cases.

Effect on Pigmentation

The following study is included in this report as it may be helpful in evaluating the potential anti-pigmentation effects of yeast-derived ingredients.

Galactomyces Ferment Filtrate

The effect of Galactomyces Ferment Filtrate on melanization was evaluated in vitro. Cultured normal human melanocytes were exposed to Galactomyces Ferment Filtrate in concentrations of 15, 20, and 30%.[49] Galactomyces Ferment Filtrate at a concentration of 15% did not affect melanocyte viability; however, concentrations of 20 and 30% reduced melanocyte viability by 20 and 50%, respectively. Human melanoma cells and normal human melanocytes (derived from both light and dark skin) were treated with either 5 or 10% Galactomyces Ferment Filtrate, every other day, and evaluated for melanin content. In melanoma cells, a 60% reduction in melanin was noted after treatment with both 5 and 10% Galactomyces Ferment Filtrate, within 12 d. In normal human melanocytes, melanin was reduced by 30 and 55%, after treatment with 5 and 10% Galactomyces Ferment Filtrate, respectively, within 25 d. Galactomyces Ferment Filtrate appeared slightly more effective on normal human melanocytes from dark skin as opposed to light skin. According to this study, Galactomyces Ferment Filtrate did not influence the expression of tyrosinase related protein 1 or premalanosome protein 17, and had a minimal effect on reducing the expression of tyrosinase. In order to determine the mechanism of action of Galactomyces Ferment Filtrate, the effect of Galactomyces Ferment Filtrate on the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and glutathione S-transferase (GST) was evaluated in human melanoma cells. Galactomyces Ferment Filtrate (10%) increased the expression of Nrf2, over 70%, within 16 d. In addition, an 8-d treatment of 10% Galactomyes Ferment Filtrate on human melanoma cells increased the expression of GST.

The effect of three Galactomyces Ferment Filtrate-containing skin care products (concentration of Galactomyces Ferment Filtrate in product not stated) on hyperpigmented spots (as induced by skin aging) was evaluated in 86 volunteers over a 1 yr treatment period.[50] An original evaluation was performed in 1999. In 2010 (11 yr later), subjects were instructed to apply all three products (2 essence preparations and 1 cream preparation) twice daily for 1 yr. Skin was evaluated at 2, 8, and 12 mo during this period. Hyperpigmented spots were significantly aggravated when evaluated in 2010 prior to the 12 mo treatment with Galactomyces Ferment Filtrate-containing products ($p < 0.01$). Hyperpigmentation gradually decreased during the 12-mo treatment period, and eventually recovered to a level close to that in 1999.

Saccharomyces cerevisiae

The effect of a natural yeast extract isolated by ethanol precipitation from *Saccharomyces cerevisiae* on melanogenesis was evaluated in an in vitro assay.[51] To evaluate the melanin synthesis inhibition, B16F10 cells (melanocytes) were exposed to the extract (50, 100, and 200 µg/ml) for 72 h. The test substance inhibited melanin synthesis from α-melanocyte-stimulating-hormone (α-MSH)-stimulated B16F10 cells in a dose-dependent manner. Melanin synthesis was also evaluated in melanocytes co-cultured with human keratinocytes (HaCaT), and treatment with the same test substance at concentrations of 50, 100, and 500 µg/ml. Melanin synthesis in these co-cultured melanocytes was also decreased in a dose-dependent manner. The inhibitory effect of the same *Saccharomyces cerevisiae* extract on tyrosinase was examined by a cell-free tyrosinase assay with mushroom tyrosinase, and by an intracellular tyrosinase assay in B16F10 cells. Cells were treated with the test substance (50, 100, and 500 µg/ml), or the positive control, arbutin. The test substance decreased the activity of intracellular tyrosinase in a dose-dependent manner, but had no direct inhibitory effect on tyrosinase itself. The positive control showed significant inhibitory effect on tyrosinase activity in the cell-free assay, in a dose-dependent manner.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Details of irritation and sensitization studies summarized below are provided in Table 13.

All in vitro dermal irritation assays yielded negative results (performed using a powdered *Saccharomyces cerevisiae* extract (tested neat), a Yeast Extract derived from *Metschnikowia reukaufii* (tested neat), a trade name mixture containing 1.25% Saccharomyces Cerevisiae Extract (tested neat), and a trade name mixture containing 4% Saccharomyces Cerevisiae Extract (concentration tested not stated).[2,18,52,53] Slight irritation was observed in an irritation assay performed in rabbits using a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% hydrated sodium calcium aluminosilicate (HSCAS; tested at 55% in water under semi-occlusive conditions).[4] All test substances were considered to be non-irritating in patch tests performed in humans using Metschnikowia Agaves Extract (15% in water), Pichia Anomala Extract (15% in water), Pichia Heedii Extract (15% in water), Pichia Minuta Extract (15% in water), a cosmetic formulation containing 1% *Saccharomyces cerevisiae* extract (tested neat), a Yeast Extract derived from *Candida mangoliae* (15% in water), a Yeast Extract derived from *Candida saitoana* (15% in water), a Yeast Extract derived from *Metschnikowia pulcherrima* (15% in water), and a Yeast Extract derived from *Metschnikowia reukaufii* (15% in water).[18,54]

Several local lymph node assays (LLNAs) were performed in mice using *Saccharomyces cerevisiae* extract, at concentrations of up to 50%.[2] In one assay, the test substance was considered to be sensitizing at concentrations > 10%; however, in four other assays performed according to the same procedures, the test substance was considered to be non-sensitizing. No sensitization was observed in an assay performed in guinea pigs using a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% hydrated sodium calcium aluminosilicate (tested at 49.5% in water and carboxymethylcellulose).[4] Human repeated-insult patch tests (HRIPTs) were negative in assays performed using Metschnikowia Agaves Extract (15% in water), Pichia Anomala Extract (15% in water), Pichia Heedii Extract (15% in water), Pichia Minuta Extract (15% in water), a Yeast Extract derived from *Candida saitoana* (15% in water), and a Yeast Extract derived from *Metschnikowia reukaufii* (15% in water).[18]

OCULAR IRRITATION STUDIES

In Vitro

Saccharomyces cerevisiae

The ocular irritation potential of a powdered *Saccharomyces cerevisiae* extract (750 µl; 20% in physiological saline) was evaluated via a bovine corneal opacity and permeability test (performed according to OECD TG 437; this method is used to identify ocular corrosives and severe irritants).[2] The test substance was topically applied to bovine corneas for 240 ± 10 min. An opacity meter and microplate reader were used to evaluate irritation. A negative control (physiological saline) and positive control (20% imidazole) were also used. The mean irritancy score for the negative control was below the upper limits of the laboratory historical range, and the mean irritancy score for the positive control was 119. The test substance resulted in a mean irritancy score of 3.3 and was not considered to be a severe irritant or corrosive.

Saccharomyces Cerevisiae Extract

An EpiOcular™ assay was performed in order to evaluate the ocular irritation potential of a trade name mixture containing 1.25% Saccharomyces Cerevisiae Extract.[53] Two tissues were dosed with the test substance (50 µl; tested neat), and incubated for 90 min. Phosphate-buffered saline (PBS) and methyl acetate were used as the negative and positive control, respectively. The test substance was considered to be non-irritating. Negative and positive controls performed as anticipated.

An Irritection® assay was performed using a trade name mixture containing 4.5% Saccharomyces Cerevisiae Extract.[52] (A general description of an Irritection® assay can be found in the Table 13 footnotes section.) Irritation scores resulting from doses of 25, 50, 75, 100, and 125 µl were 5.2, 5.5., 6.1, 6.4, and 7.2, respectively. According to the ocular irritancy scale, the test substance was considered to be minimally irritating at all tested concentrations.

Animal

Saccharomyces cerevisiae

A powdered *Saccharomyces cerevisiae* extract (59 mg) was placed, undiluted, in one eye of 3 male New Zealand White rabbits.[2] Eyes were examined 1, 24, 48, and 72 h after instillation of the test substance. Twenty-four hours after instillation, a solution of 2% fluorescein in water was instilled into the eyes of each animal to determine epithelial damage. Irritation of the conjunctivae, presenting as redness, chemosis, and discharge, was noted in treated eyes; however, this irritation was completely resolved within 48 h for all animals.

The ocular irritation potential of a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall (24% glucan and 7% mannan) in 10% HSCAS was evaluated in 3 male New Zealand albino rabbits.[4] (These data may be relevant to the ingredient Hydrolyzed Saccharomyces Cell Wall, when derived from *Saccharomyces cerevisiae*.) One eye of each animal was anesthetized, and 0.09 g of the test substance was instilled into the conjunctival sac. Irritation was evaluated using a high-intensity white light at 1, 24, 48, and 72 h post-instillation. No corneal opacity or iritis was observed in any treated eye during the study. One h following test substance administration, all treated eyes exhibited positive conjunctivitis. The severity of irritation decreased with time, with no irritation noted 72 h after instillation. The test substance was considered to be mildly irritating.

CLINICAL STUDIES

Case Reports

Case reports were found in the literature describing infection relating to several of the yeast species reviewed in this report.[55-78] These reports, however, were found in immunocompromised or post-surgical patients; therefore, their relevancy to cosmetic safety is unlikely.

Saccharomyces cerevisiae

A 29-yr-old woman presented to the hospital with multiple severe anaphylactic reactions induced by food.[79] The patient reported a pollen and animal dander allergy, and previous anaphylactic reactions after exposure to contrast media, beer, wine, spaghetti Bolognese sauce, pasta, and bread. Skin prick tests revealed positive results for soya, various nuts and seeds, anthocyanin, and beer malt containing barley. The next anaphylactic reaction took place following ingestion of a meal consisting of industrial-made olive sauce, pasta, and feta cheese. The patient experienced severe allergic symptoms including angioedema of the throat, difficulty breathing, and near loss of consciousness, and was treated in the emergency department. Three wk after the reaction, the patient was examined using skin prick tests and serum allergen-specific IgE/inhibition tests. Various yeasts and molds were tested as well as 2 pasta sauces, individual sauce ingredients, commercial yeast extract preparations, and wines. Skin prick and serum IgE test results were positive to several molds (*Cladosporium herbarum*, *Alternaria alternata*, *Aspergillus fumigatus*, and *Penicillium notatum*), baker's yeast (*Saccharomyces cerevisiae*), *Malassezia furfur*, champignon and the 2 pasta sauces, the yeast ingredient, and a food-quality yeast extract.

A 33-yr-old with a history of allergic rhinoconjunctivitis with exercise-induced asthma reported experiencing episodes of anaphylaxis with no associated exercise over a period of 3 yr.[80] These reactions were successfully treated with epinephrine. The patient related the episodes to ingestion to beer, chips, olives, and wine. Skin prick tests with common aeroallergens, beer extracts, wine, yeast (including several *Saccharomyces cerevisiae* extracts), cereal extracts, and fruits were performed. Results were positive with beer extract, *Saccharomyces cerevisiae* extracts, *Pencillium nalgiovense*, and mushrooms. A sodium dodecyl sulfate-polyacrylamide gel electrophoresis immunoblotting assay was performed with several beer extracts, *Saccharomyces cerevisiae* extract, and the patient's serum. The main IgE-reactive bands detected in the beer extracts were 97 kDa, 80 kDa, 55 kDa, 40 kDa, 32 kDa, and 17 kDa. In the *Saccharomyces cerevisiae* extract, a high intensity IgE-binding zone was observed between 100 kDa and 29 kDa, and a band around 17 kDa. In order to determine whether *Saccharomyces cerevisiae* was the allergenic source of IgE-reactive proteins detected in beer extracts, an immunoblotting-inhibition assay was performed using a trappist style beer extract in the solid phase and beer extracts and *Saccharomyces cerevisiae* extracts as inhibitors. Both beer extracts and Saccharomyces cerevisiae extracts produced total inhibition of IgE-binding in the trappist style beer extract.

A 25-yr-old woman was admitted to the hospital with a dry cough, low-grade fever, and focal patchy shadow of pulmonary infiltrates.[81] The patient had no previous history of atopic diseases. Because *Saccharomyces cerevisiae* was detected in patient sputum, eosinic bronchitis caused by *Saccharomyces cerevisiae* was suspected. Fungal antigenic solutions were prepared by culturing fungus on medium containing 0.5% yeast extract. Skin tests with the fungal antigens were performed via intradermal injection of the antigen solution (1 mg/ml). Reactions to the injections were observed 15 min and 48 h post-administration. The patient displayed an immediate positive skin reaction to *Saccharomyces cerevisiae*, but both the immediate and delayed skin reactions were negative for *Penicillin janthinellum* as a control. After 7 d of beclomethasone dipropionate inhalation therapy, the patient's symptoms improved, and *Saccharomyces cerevisiae* was no longer present in sputum. Three mo later, the patient was readmitted for bronchoprovocation testing using *Saccharomyces cerevisiae* and *Penicillin janthinellum* antigens. Antigen solutions were administered via a nebulizer. Test results were negative following *Penicillin janthinellum* antigen exposure, but positive following *Saccharomyces cerevisiae* exposure. The patient exhibited a coughing attack, high fever, and ticklish throat within 15 min of exposure. Serum C-reactive protein and sputum eosinophils were increased on the day after provocation testing with *Saccharomyces cerevisiae* antigen. Symptoms disappeared 3 d after testing.

SUMMARY

The safety of 56 yeast-derived ingredients as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, the majority of these ingredients are reported to function in cosmetics as skin protectants or skin conditioning agents. Several of the species reviewed in this report are used in foods (e.g., *Saccharomyces cerevisiae* is GRAS as a flavoring agent and adjuvant at a level not to exceed 5% in food [21CFR184.1983]).

According to 2023 VCRP survey data, Yeast Extract is reported to be used in 398 formulations (343 leave-on formulations and 55 rinse-off formulations). All other in-use ingredients are reported to be used in 81 formulations or less. The results of a concentration of use survey conducted by the Council indicate Galactomyces Ferment Filtrate has the highest concentration of use in a leave on formulation; it is used at up to 90.7% in moisturizing products.

Several in vitro dermal absorption assays were performed using 30% emulsions of Metschnikowia Agaves Extract, Pichia Anomala Extract, Pichia Heedii Extract, Pichia Minuta Extract, a Yeast Extract derived from *Candida saitoana*, and a Yeast Extract derived from *Metschnikowia reukaufii*. Dermal absorption in these studies ranged from 0.2 to 4.6% of the

applied dose 24 h after application. When the dissemination of live *Pichia pastoris* cells was evaluated in female mice, clearance was achieved by day 6 post-administration in all organs.

An LD_{50} of > 2000 mg/kg was determined in acute dermal toxicity assays using 49.5% *Saccharomyces cerevisiae* cell wall (in hydrated sodium calcium aluminosilicate) and a *Saccharomyces cerevisiae* extract (in water). No signs of toxicity were observed in an acute oral toxicity assay in which rats were given 2000 mg/kg fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water). No toxicity was observed in an acute oral toxicity assay performed in rats using yeast hydrolysate obtained from *Saccharomyces cerevisiae* (5000 mg/kg bw) or in an assay where rats were given 2000 mg/kg fermentate powder derived from *Saccharomyces cerevisiae*. No serious adverse effects were observed in acute oral toxicity assay performed in rats using 49.5% *Saccharomyces cerevisiae* cell wall (in hydrated sodium calcium aluminosilicate and water). The same test substance (at gravimetric chamber concentrations of 2.09 mg/l) was used in an acute inhalation assay performed in rats. The LC_{50} was determined to be > 2.09 mg/l. No adverse effects were observed in acute toxicity assay performed in mice inoculated with live *Pichia pastoris* cells (in saline; 1×10^6 CFU).

No significant adverse effects were noted in a 14-d assay in which rats were orally administered 1000 mg/kg bw/d yeast hydrolysate derived from *Saccharomyces cerevisiae*. In a different 14-d study, *Kluyveromyces marxianus* extracts (strains A4 and A5; 1.0 x 10^6 CFU/ml or 1.0 x 10^8 CFU/ml; in sterilized saline) were orally administered to female mice. Statistically significant lower spleen to body ratios and liver to body ratios were noted in mice treated with the high concentration of the A5 strain, and the low concentration of the A4 strain, respectively. *Phaffia rhodozyma* extract (up to 1000 mg/kg) in corn oil was given to rats, via gavage, for 28 d. The NOAEL was determined to be > 1000 mg/kg. Fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water) was given to rats (20/sex/group) in a 90-d oral toxicity study (rats given up to 1500 mg/kg bw/d), and a 1-yr oral toxicity study (rats given up to 800 mg/kg bw/d). The NOAELs for the 90-d and 1-yr study were determined to be 1500 mg/kg bw/d and 800 mg/kg bw/d, respectively.

Negative results were obtained for Ames assays performed on *Phaffia rhodozyma* extract (in acetone; up to 5000 µg/plate), fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water; up to 5000 µg/plate), and 90% yeast (*Saccharomyces cerevisiae*) cell wall (in hydrated sodium calcium aluminosilicate; up to 3500 µg/plate). Negative results were also obtained in mammalian cell gene mutation assay performed using a fermentate powder derived from *Saccharomyces cerevisiae* (in methylcellulose and water; up to 5000 µg/plate). Mammalian bone marrow chromosomal assays were performed using a *Phaffia rhodozyma* extract (in corn oil; up to 2000 mg/kg bw/d; performed in male mice) and 90% yeast (*Saccharomyces cerevisiae*) cell wall (in hydrated sodium calcium aluminosilicate; up to 2000 mg/kg bw/d; performed in mice). Both test substances were considered to be non-clastogenic.

Treatment with *Saccharomyces cerevisiae* resulted in the growth inhibition or apoptosis of several cancer cell types in multiple anti-carcinogenicity assays. Cell lines that were inhibited by *Saccharomyces cerevisiae* include human metastatic breast cancer cells (MCF-7 and ZR-75-1), non-metastatic breast cancer cells (HCC70), squamous cell carcinoma of the tongue (SCC-4), adenocarcinomas of the colon (Caco-2, DLD1, and HCT116), and cervical cancer cells (HeLa).

The anti-inflammatory properties of a dried *Saccharomyces cerevisiae* fermentate was evaluated in 23 subjects. Inflammation was induced via histamine scratches in all subjects (saline used as control). Treatment with the fermentate resulted in faster and more effective inflammation reduction compared to the control.

The immunological cross-reactivity of several yeast species (including *Candida psuedotropicalis* (synonymous to *Kluyveromyces fragilis*), *Geotrichum candidum* (synonymous to *Galactomyces candidus*), and *Saccharomyces cerevisiae*) was evaluated in vitro. Significant cross-reactivity was only observed between *Candida* species. When skin prick tests were performed in 67 atopic patients using whole cell and disrupted cell extracts several yeast species including *Saccharomyces cerevisiae*, whole cell and disrupted cell extracts of *Saccharomyces cerevisiae* resulted in positive results in 41 and 31% of patients, respectively.

A delayed-type hypersensitivity test was performed in female mice using *Pichia pastoris* cells (in saline) on stratum corneum-removed skin. One control group was exposed to the same test substance on regular, intact, shaved skin, and another control group received saline only, on stratum corneum-removed skin. Seven days after administration, ear thickness was measured. Delayed type hypersensitivity was evaluated by inoculating ears with heat-killed *Pichia pastoris* cells. Results between control, vehicle-control, and *Pichia pastoris*-treated groups were similar.

Skin prick tests were performed in 47 individuals with an inhalant allergy to fungi; 10 non-allergic subjects were used as controls. Tests were performed using baker's yeast (*Saccharomyces cerevisiae*) extract and purified enolase obtained from baker's yeast. Clear reactions to the baker's yeast extract were noted in all fungi-allergic patients. Twenty-three patients showed a reaction to the baker's yeast enolase. No reactions were noted for either test substance in control subjects. Skin prick tests using a *Saccharomyces cerevisiae* extract were also performed in a different study, using 449 patients (229 with atopic dermatitis, 50 with allergic rhinitis and/or asthma, and 173 nonatopic controls). Ninety-two patients had positive skin prick tests to the extract. Patients with moderate to severe dermatitis displayed positive skin prick test reactions significantly more frequently than allergic rhinitis/asthma patients or nonatopic controls ($p < 0.001$). A significant correlation between total serum IgE and positive skin prick test results with *Saccharomyces cerevisiae* was seen ($r = 0.53$, $p < 0.001$).

Allergens of *Saccharomyces cerevisiae* were evaluated via an IgE-immunoblotting assay performed on 83 patients (70 atopic patients, 13 non-atopic controls). Forty-one atopic patients were positive in the IgE immunoblotting assay, revealing 22 IgE stained bands. Non-atopic serum and sera from atopic patients with negative skin prick tests to *Saccharomyces cerevisiae* were IgE negative in this experiment. In a similar assay, 20 patients (16 atopic, 4 non-atopic controls) were evaluated for IgE, IgA, and IgG responses to several common yeasts including *Saccharomyces cerevisiae*. Immunoblotting assays revealed IgE binding in all species (5 IgE binding bands in *Saccharomyces cerevisiae*). Prominent IgE binding was seen to a 46-kDa band of several species, including *Saccharomyces cerevisiae*. In addition, IgA and IgG responses were observed against *Saccharomyces cerevisiae*.

The cause of allergic alveolitis was evaluated in 12 Australian patients after a home evaluation for fungal growth. Twelve fungal species, including *Geotrichum candidum (*synonymous to *Galactomyces candidus*) was found in homes. When a precipitin test was performed on the subjects using freeze-dried fungal extracts and other allergens, 2 displayed positive reactions to *Geotrichum candidum* extract. Skin prick tests performed in the same patients resulted in one positive reaction to *Geotrichum candidum* extract. In an inhalation test performed in 6 of these patients, positive late responses were observed in 2 patients.

Normal human melanocytes treated with Galactomyces Ferment Filtrate (at concentrations of 20% or greater) exhibited a reduction in cell viability. Galactomyces Ferment Filtrate (5 and 10%) resulted in a reduction in melanin in human melanoma cells and normal human melanocytes. When the mechanism of action of Galactomyces Ferment Filtrate was evaluated, it was observed that 10% Galactomyces Ferment Filtrate increases the expression of Nrf2 and GST in human melanoma cells. The hyperpigmentation-reversal potential of Galactomyces Ferment Filtrate-containing skin care products was evaluated in 86 volunteers after a 1 yr treatment period. Treatment with Galactomyces Ferment Filtrate-containing products resulted in significant age-induced hyperpigmentation reversal.

The inhibitory effects of a *Saccharomyces cerevisiae* extract on melanogenesis were evaluated in B16F10 cells (melanocytes), alone, at doses of up to 200 µg/ml, and in melanocytes co-cultured with human keratinocytes, at doses of up to 500 µg/ml. Melanin synthesis decreased in a dose-dependent manner in melanocytes cultured with and without human keratinocytes. The inhibitory effect of *Saccharomyces cerevisiae* extract (up to 500 µg/ml) on tyrosinase was examined by a cell-free tyrosinase assay with mushroom tyrosinase, and by an intracellular tyrosinase assay in B16F10 cells. The test substance decreased the activity of intracellular tyrosinase in a dose-dependent manner, but had no direct inhibitory effect on tyrosinase itself.

All in vitro dermal irritation assays yielded negative results (performed using a powdered *Saccharomyces cerevisiae* extract (tested neat), a Yeast Extract derived from *Metschnikowia reukaufii* (tested neat) a trade name mixture containing 1.25% Saccharomyces Cerevisiae Extract (tested neat), and a trade name mixture containing 4% Saccharomyces Cerevisiae Extract (concentration tested not stated). Slight irritation was observed in an irritation assay performed in rabbits using a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% hydrated sodium calcium aluminosilicate (tested at 55% in water under semi-occlusive conditions). All test substances were considered to be non-irritating in patch tests performed in humans using Metschnikowia Agaves Extract (15% in water), Pichia Anomala Extract (15% in water), Pichia Heedii Extract (15% in water), Pichia Minuta Extract (15% in water), a cosmetic formulation containing 1% *Saccharomyces cerevisiae* extract (tested neat), a Yeast Extract derived from *Candida mangoliae* (15% in water), a Yeast Extract derived from *Candida saitoana* (15% in water), a Yeast Extract derived from *Metschnikowia pulcherrima* (15% in water), and a Yeast Extract derived from *Metschnikowia reukaufii* (15% in water).

Several LLNAs were performed in mice using *Saccharomyces cerevisiae* extract, at concentrations of up to 50%. In one assay, the test substance was considered to be sensitizing at concentrations > 10%; however, in four other assays performed according to the same procedures, the test substance was considered to be non-sensitizing. No sensitization was observed in an assay performed in guinea pigs using a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS (tested at 49.5% in water and carboxymethylcellulose). HRIPTs were negative in assays performed using Metschnikowia Agaves Extract (15% in water), Pichia Anomala Extract (15% in water), Pichia Heedii Extract (15% in water), Pichia Minuta Extract (15% in water), a Yeast Extract derived from *Candida saitoana* (15% in water), and a Yeast Extract derived from *Metschnikowia reukaufii* (15% in water).

The ocular irritation potential of a powdered *Saccharomyces cerevisiae* extract (750 µl; 20% in physiological saline) was evaluated in isolated bovine corneas. The test substance resulted in a mean irritancy score of 3.3, and was not considered to be a severe irritant or corrosive. No irritation was noted in an EpiOcular™ assay performed on a trade name mixture containing 1.25% Yeast Extract (derived from *Saccharomyces cerevisiae*). Mild irritation was noted in an Irritection® assay performed on a trade name mixture containing 4.5% Yeast Extract (derived from *Saccharomyces cerevisiae*). The ocular irritation potential of a powdered *Saccharomyces cerevisiae* extract (59 mg) was also evaluated in male New Zealand White rabbits. Irritation of the conjunctivae was noted; however, all effects were fully resolved within 48 h. The ocular irritation potential of a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS was evaluated in male New Zealand albino rabbits. The test substance was considered to be mildly irritating.

A 29-yr-old woman suffered from multiple severe anaphylactic reactions following a meal of olive sauce, pasta, and feta cheese. Skin prick and serum IgE tests revealed were positive to several molds including baker's yeast (*Saccharomyces*

cerevisiae). A 33-yr-old woman with a history of allergies and asthma reported anaphylaxis episodes that were related to ingestion of beer, chips, olive, and wine. An immunoblotting assay revealed a high-intensity IgE-binding zone, when evaluating *Saccharomyces cerevisiae* extract, between 100 kDa and 29 kDa, and a band around 17 kDa. In a different case report, a 25-yr-old woman was admitted to the hospital with a dry cough, low-grade fever, and focal patchy shadow of pulmonary infiltrates. Skin prick tests were positive to *Saccharomyces cerevisiae*. Bronchoprovocation testing performed 3 mo later using *Saccharomyces cerevisiae* antigens yielded positive results, and the patient exhibited a coughing attack, high fever, and ticklish throat within 15 min of exposure. Serum C-reactive protein and sputum eosinophils were increased on the day after provocation testing with *Saccharomyces cerevisiae* antigen.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. INCI names, definitions, and reported functions of the yeast-derived ingredients in this safety assessment[1]

Ingredient (CAS No.)	Definition	Function
Galactomyces Ferment Filtrate	Galactomyces Ferment Filtrate is a filtrate of the product obtained by the fermentation of a growth media by the microorganism, *Galactomyces candidus*, *Galactomyces fermentans*, or *Galactomyces reessii*.	Skin-Conditioning agents - Humectant
Hydrolyzed Candida Bombicola Extract	Hydrolyzed Candida Bombicola Extract is the hydrolysate of an extract of *Candida bombicola* obtained by acid, enzyme or other method of hydrolysis.	Surfactants – Cleansing Agents
Hydrolyzed Candida Saitoana Extract	Hydrolyzed Candida Saitoana Extract is the hydrolysate of an extract of *Candida saitoana* derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Hydrolyzed Kluyveromyces Extract	Hydrolyzed Kluyveromyces Extract is the hydrolysate of Kluyveromyces Extract derived by acid, enzyme or other method of hydrolysis.	Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Metschnikowia Agaves Extract [1309127-75-0]	Hydrolyzed Metschnikowia Agaves Extract is the hydrolysate of an extract of the yeast, *Metschinikowia agaves* derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Hydrolyzed Mestchnikowia Reukaufii Extract	Hydrolyzed Metschnikowia Reukaufii Extract is the extract of the hydrolysate of Metschnikowia Reukaufii Lysate Extract derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Hydrolyzed Mestchnikowia Shanxiensis Extract	Hydrolyzed Metschnikowia Shanxiensis Extract is the hydrolysate of an extract of the microorganism, *Metschnikowia shanxiensis.*	Skin Protectants
Hydrolyzed Saccharomyces Cell Wall	Hydrolyzed Saccharomyces Cell Wall is the hydrolysate of the cell walls of *Saccharomyces* derived by acid, enzyme or other method of hydrolysis.	Film Formers Hair Conditioning Agents Skin-Conditioning Agents - Humectant Slip Modifiers
Hydrolyzed Saccharomyces Extract	Hydrolyzed Saccharomyces Extract is the hydrolysate of an extract of Saccharomyces derived by acid, enzyme or other method of hydrolysis.	Skin-Conditioning Agents - Emollient
Hydrolyzed Saccharomyces Lysate Extract	Hydrolyzed Saccharomyces Lysate Extract is the extract of the product obtained by the hydrolysis of Saccharomyces Lysate Extract.	Skin-Conditioning Agents - Humectant
Hydrolyzed Torulaspora Delbrueckii Extract	Hydrolyzed Torulaspora Delbrueckii Extract is the hydrolysate of an extract of *Torulaspora delbrueckii* derived by acid, enzyme or other method of hydrolysis.	Skin Protectants
Hydrolyzed Yeast	Hydrolyzed Yeast is the hydrolysate of yeast derived by acid, enzyme or other method of hydrolysis.	Hair-Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Hydrolyzed Yeast Extract	Hydrolyzed Yeast Extract is the hydrolysate of Yeast Extract derived by acid, enzyme or other method of hydrolysis.	Skin-Conditioning Agents - Miscellaneous
Kluyveromyces Extract	Kluyveromyces Extract is the extract of *Kluyveromyces lactis* or *Kluyveromyces fragilis*.	Skin-Conditioning Agents - Humectant
Lactic Yeasts [68876-77-7]	Lactic Yeasts is a Yeast obtained from milk.	Not Reported
Lipomyces Lipid Bodies	Lipomyces Lipid Bodies are the lipid-rich organelles produced through fermentation by *Lipomyces*.	Skin-Conditioning Agents - Emollient
Lipomyces Oil	Lipomyces Oil is the oil produced through fermentation by the fungus, *Lipomyces starkeyi*.	Hair-Conditioning Agents; Skin-Conditioning Agents – Humectant; Surfactants-Cleansing Agents; Surfactants-Emulsifying Agents
Lipomyces Oil Extract	Lipomyces Oil Extract is the extract of Lipomyces Oil	Skin-Conditioning Agents - Emollient
Metschnikowia Agaves Extract	Metschnikowia Agaves Extract is the extract of the yeast, *Metschnikowia agaves*.	Skin Protectants
Metschnikowia Henanesis Extract	Metschnikowia Henanensis Extract is the extract of the fungus, *Metschnikowia henanensis.*	Skin-Conditioning Agents - Humectants
Metschnikowia Reukaufii Lysate Extract	Metschnikowia Reukaufii Lysate Extract is the extract of a lysate of the cultured cells of *Metschnikowia reukaufii.*	Skin Protectants
Metschnikowia Viticola Extract	Metschnikowia Viticola Extract is the extract of the yeast, *Metschnikowia viticola.*	Skin-Conditioning Agents - Humectant
Pichia Caribbica Ferment	Pichia Caribbica Ferment is the product obtained by the fermentation of *Pichia caribbica*.	Skin-Conditioning Agents - Humectant
Pichia Extract	Pichia Extract is the extract of various species of the microorganism, *Pichia.*	Skin Protectants
Pichia Ferment Extract Filtrate	Pichia Ferment Extract Filtrate is a filtrate of an extract of the product obtained through fermentation by the microorganism, *Pichia pastoris.*	Skin Protectants; Skin-Conditioning Agents – Emollient; Skin-Conditioning Agents - Humectant
Pichia Ferment Lysate Filtrate	Pichia Ferment Lysate Filtrate is a filtrate of a lysate of the product obtained by the fermentation of *Pichia pastoris*, *Pichia populi* or *Pichia stipitis.*	Humectants; Skin Protectants; Skin-Conditioning Agents – Miscellaneous

Table 1. INCI names, definitions, and reported functions of the yeast-derived ingredients in this safety assessment[1]

Ingredient (CAS No.)	Definition	Function
Pichia Pastoris Ferment Filtrate	Pichia Pastoris Ferment Filtrate is a filtrate of the product obtained by the fermentation of a growth media by the microorganism, *Pichia pastoris*.	Skin-Conditioning Agents – Miscellaneous
Phaffia Rhodozyma Extract	Phaffia Rhodozyma Extract is the extract of the microorganism, *Phaffia rhodozyma*.	Hair-Conditioning Agents; Skin-Conditioning Agents - Miscellaneous
Phaffia Rhodozyma Ferment Extract	Phaffia Rhodozyma Ferment Extract is the extract of the fermentation product of *Phaffia rhodozyma*.	Antioxidants; Colorants; Skin-Conditioning Agents - Emollient
Pichia Anomala Extract [1033319-29-7]	Pichia Anomala Extract is the extract of the yeast, *Pichia anomala*.	Skin Protectants
Pichia Heedii Extract [1801269-82-8]	Pichia Heedii Extract is the extract of the yeast, *Pichia heedii*.	Skin Protectants
Pichia Minuta Extract [2009239-94-3]	Pichia Minuta Extract is the extract of the microorganism, *Pichia minuta.*	Skin Protectants
Saccharomyces	Saccharomyces is one or more species of the microorganism, *Saccharomyces*	Anti-Acne Agents; Anti-Microbial Agents; Binders; Skin Protectants
Saccharomyces Cerevisiae Extract [84604-16-0]	Saccharomyces Cerevisiae Extract is the extract of the yeast cells of *Saccharomyces cerevisiae.*	
Saccharomyces Extract	Saccharomyces Extract is the extract of Saccharomyces	Antioxidants; Hair-Conditioning Agents; Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Saccharomyces Ferment	Saccharomyces Ferment is the product obtained through fermentation by the microorganism, *Saccharomyces*.	Not Reported
Saccharomyces Ferment Extract	Saccharomyces Ferment Extract is the extract of the product obtained by the fermentation of media by *Saccharomyces*.	Flavoring Agents Fragrance Ingredients
Saccharomyces Ferment Extract Lysate Filtrate	Saccharomyces Ferment Extract Lysate Filtrate is the filtrate of the product obtained after the lysis of the cultured cells of the microorganism, *Saccharomyces*.	Skin Protectants
Saccharomyces Ferment Filtrate	Saccharomyces Ferment Filtrate is a filtrate of the product obtained by the fermentation of a growth media by the microorganism, *Saccharomyces*.	Skin-Conditioning Agents - Humectant
Saccharomyces Ferment Lysate Extract	Saccharomyces Ferment Lysate Extract is the extract of the lysed cells of *Saccharomyces* grown in culture.	Skin Protectants
Saccharomyces Ferment Lysate Filtrate	Saccharomyces Ferment Lysate Filtrate is the filtrate of a lysate of the product obtained by the fermentation of *Saccharomyces*.	Skin Protectants
Saccharomyces Lysate [8013-01-2]	Saccharomyces Lysate is a lysate of the product obtained by the fermentation of *Saccharomyces*.	Not Reported
Saccharomyces Lysate Extract [8013-01-2]	Saccharomyces Lysate Extract is the extract of Saccharomyces Lysate	Skin-Conditioning Agents – Humectant; Skin-Conditioning Agents - Miscellaneous
Saccharomyces Lysate Extract Filtrate	Saccharomyces Lysate Extract Filtrate is a filtrate of the extract of the product obtained by the lysis of *Saccharomyces* cells.	Skin-Conditioning Agents - Miscellaneous
Saccharomyces Lysate Filtrate	Saccharomyces Lysate Filtrate is a filtrate of lysed *Saccharomyces* grown in culture.	Hair-Conditioning Agents; Skin Protectants
Schizosaccharomyces Ferment Extract Filtrate	Schizosaccharomyces Ferment Extract Filtrate is a filtrate of an extract obtained by the fermentation of *Schizosaccharomyces*.	Humectants; Skin-Conditioning Agents - Miscellaneous
Schizosaccharomyces Ferment Filtrate	Schizosaccharomyces Ferment Filtrate is a filtrate of the product obtained by the fermentation of a growth media by the microorganism, *Schizosaccharomyces*.	Hair-Conditioning Agents; Humectants; Skin-Conditioning Agents – Miscellaneous
Schizosaccharomyces Pombe Extract	Schizosaccharomyces Pombe Extract is the extract of the yeast, *Schizosaccharomyces pombe*.	Skin-Conditioning Agents – Miscellaneous
Torulaspora Delbrueckii Extract [1291071-26-5]	Torulaspora Delbrueckii Extract is the extract of the yeast, *Torulaspora delbrueckii*.	Skin Protectants
Torulaspora Delbrueckii Ferment [1291071-26-5]	Torulaspora Delbrueckii Ferment is the product obtained by the fermentation of *Torulaspora delbrueckii*.	Skin-Conditioning Agents - Miscellaneous
Yarrowia Lipolytica Extract	Yarrowia Lipolytica Extract is the extract of the microorganism, *Yarrowia lipolytica* obtained through fermentation.	Skin-Conditioning Agents - Humectant
Yarrowia Lipolytica Ferment Lysate	Yarrowia Lipolytica Ferment Lysate is the product obtained after the lysis of the cultured cells of the microorganism, *Yarrowia lipolytica.*	Skin-Conditioning Agent – Humectant
Yarrowia Lipolytica Oil	Yarrowia Lipolytica Oil is the oil derived from the fermentation of the fungus, *Yarrowia lipolytica* grown in culture.	Skin-Conditioning Agent - Emollient
Yeast [68876-77-7]	Yeast is a class of microorganisms (Saccharomycetes) characterized by their lack of photosynthetic ability, existence as unicellular or simple irregular filaments, and reproduction by budding or direct division.	Not Reported
Yeast Extract [68876-77-7; 8013-01-2]	Yeast Extract is the extract of Yeast.	Skin Protectants; Skin-Conditioning Agents - Miscellaneous
Yeast Ferment Extract	Yeast Ferment Extract is the extract of the product obtained by the fermentation of *Saccharomyces cerevisiae*.	Skin-Conditioning Agents – Miscellaneous

Table 2. Chemical properties of yeast-derived cosmetic ingredients

Property	Value	Reference
Saccharomyces Cerevisiae Extract		
Physical Form	liquid	10
Color	clear-yellow	10
Odor	faint	10
Specific Gravity (@ 20ºC)	1.035 – 1.055	10
Vapor pressure (mmHg @ 105ºC)	3.83	2
Refraction Index (RIU (@ 20°C))	1.035 – 1.055	10
Yeast		
Physical Form	powder, granules, or flakes	9
Color	light brown - buff	9
Yeast Extract*		
Physical Form	liquid	17
Color	clear-pale yellow	17
Odor	characteristic	17
Water Solubility	soluble	17
Specific Gravity (@ 25ºC)	1.05 – 1.15	17
Refraction Index (RIU (@ 25°C))	1.3920 – 1.5000	17

*derived from *Saccharomyces cerevisiae*

Table 3. Taxonomy of yeast-derived ingredients[1,82]

INCI Ingredient	Class	Order	Family	Genus	Associated Genus and Species/Synonyms	Synonyms**
Galactomyces Ferment Filtrate*	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Geotrichum*	*Galactomyces candidus*	*Dipodascus geotrichum* *Endomyces geotrichum* *Galactomyces geotrichum* *Geotrichum candidum*
	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Dipoascus*	*Galactomyces fermentans*	-
	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Galactomyces*	*Galactomyces reessii*	*Endomyces reessii* *Dipodascus reessii*
Hydrolyzed Candida Bombicola Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetales*	*Starmerella*	*Candida bombicola*	*Starmerella bombicola*
Hydrolyzed Candida Saitoana Extract	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Candida*	*Candida saitoana*	-
Hydrolyzed Kluyveromyces Extract*	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Kluyveromyces*	*Kluyveromyces fragilis*	*Candida kefyr* *Candida pseudotropicalis* *Dekkeromyces marxianus* *Guilliermondella marxiana* *Kluyveromyces cicerisporus* *Kluyveromyces marxianus* *Saccharomyces marxianus* *Zygofabospora marxiana* *Zygorenospora marxiana* *Zygosaccharomyces marxianus*
	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Kluyveromyces*	*Kluyveromyces lactis*	*Torulaspora lactis* *Saccharomyces lactis* *Kluyveromyces drosophilarum* *Candida sphaerica*
Hydrolyzed Metschnikowia Agaves Extract	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia agaves*	-
Hydrolyzed Mestchnikowia Reukaufii Extract	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia reukaufii*	*Candida reukaufii*
Hydrolyzed Metschnikowia Shanxiensis	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia shanxiensis*	-
Hydrolyzed Saccharomyces Cell Wall	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Hydrolyzed Saccharomyces Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Hydrolyzed Saccharomyces Lysate Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Hydrolyzed Torulaspora Delbrueckii Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Torulaspora*	*Torulaspora delbrueckii*	*Saccharomyces delbrueckii* *Saccharomyces fermentati* *Saccharomyces rosei* *Candida colliculosa*
Hydrolyzed Yeast	Saccharomycetes	-	-	-	-	-
Hydrolyzed Yeast Extract	Saccharomycetes	-	-	-	-	-
Kluyveromyces Extract*	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Kluyveromyces*	*Kluyveromyces fragilis*	*Candida kefyr* *Candida pseudotropicalis* *Dekkeromyces marxianus*

Table 3. Taxonomy of yeast-derived ingredients[1,82]

INCI Ingredient	Class	Order	Family	Genus	Associated Genus and Species/Synonyms	Synonyms**
						Guilliermondella marxiana *Kluyveromyces cicerisporus* *Kluyveromyces marxianus* *Saccharomyces marxianus* *Zygofabospora marxiana* *Zygorenospora marxiana* *Zygosaccharomyces marxianus*
	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Kluyveromyces*	*Kluyveromyces lactis*	*Torulaspora lactis* *Saccharomyces lactis* *Kluyveromyces drosophilarum* *Candida sphaerica*
Lactic Yeasts	Saccharomycetes	-	-	-	-	-
Lipomyces Lipid Bodies	Saccharomycetes	Saccharomycetales	*Lipomycetaceae*	*Lipomyces*	*Lipomyces sp.*	-
Lipomyces Oil	Saccharomycetes	Saccharomycetales	*Lipomycetaceae*	*Lipomyces*	*Lipomyces starkeyi*	-
Lipomyces Oil Extract	Saccharomycetes	Saccharomycetales	*Lipomycetaceae*	*Lipomyces*	*Lipomyces starkeyi*	-
Metschnikowia Agaves Extract	Saccharomycetes	Saccharomycetales	*Metschnikowiaceae*	*Metschnikowia*	*Metschnikowia agaves*	-
Metschnikowia Henanensis Extract	Saccharomycetes	Saccharomycetales	*Metschnikowiaceae*	*Metschnikowia*	*Metschnikowia henanensis*	-
Metschnikowia Reukaufii Lysate Extract	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia reukaufii*	*Candida reukaufii*
Mestchnikowia Viticola Extract	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia viticola*	-
Pichia Anomala Extract	Saccharomycetes	Saccharomycetales	*Phaffomycetaceae*	*Wickerhamomyces*	*Pichia anomala*	*Whickerhamomyces anomalus* *Saccharomyces anomalus* *Endomyces anomalus* *Hansenula anomala* *Pichia anomalus* *Willia anomala*
Pichia Caribbica Ferment	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Meyerozyma*	*Pichia caribbica*	*Meyerozyma caribbica* *Candida fermentati* *Torula fermentati*
Pichia Extract	Saccharomycetes	Saccharomycetales	*Pichiaceae*	-	-	-
Pichia Ferment Extract Filtrate	Saccharomycetes	Saccharomycetales	*Phaffomycetaceae*	*Komagatella*	*Pichia pastoris*	*Komagataella pastoris* *Zygosaccharomyces pastoris*
Pichia Ferment Lysate Filtrate*	Saccharomycetes	Saccharomycetales	*Phaffomycetaceae*	*Barnettozyma*	*Pichia populi*	*Barnettozyma populi* *Hansenula populi*
Pichia Ferment Lysate Filtrate*	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Scheffersomyces*	*Pichia stipitis*	*Scheffersomyces stipitis* *Yamadazyma stipitis*
Pichia Heedii Extract	Saccharomycetes	Saccharomycetales	*Pichiaceae*	*Pichia*	*Pichia heedii*	-
Pichia Minuta Extract	Saccharomycetes	Saccharomycetales	*Pichiaceae*	*Ogataea*	*Pichia minuta*	*Ogataea minuta* *Hansenula minuta* *Candida methanolovescens* *Torulopsis methanolovescens*
Pichia Pastoris Ferment Filtrate	Saccharomycetes	Saccharomycetales	*Phaffomycetaceae*	*Komagatella*	*Pichia pastoris*	*Komagataella pastoris* *Zygosaccharomyces pastoris*
Phaffia Rhodozyma Extract	Tremellomycetes	Cystofilobasidales	*Mrakiaceae*	*Phaffia*	*Phaffia rhodozyma*	*Cryptococcus rhodozymus* *Rhodomyces dendrorhous*

Table 3. Taxonomy of yeast-derived ingredients[1,82]

INCI Ingredient	Class	Order	Family	Genus	Associated Genus and Species/Synonyms	Synonyms**
						Xanthophyllomyces dendrorhous
Phaffia Rhodozyma Ferment Extract	Tremellomycetes	Cystofilobasidales	*Mrakiaceae*	*Phaffia*	*Phaffia rhodozyma*	*Cryptococcus rhodozymus* *Rhodomyces dendrorhous* *Xanthophyllomyces dendrorhous*
Saccharomyces	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Cerevisiae Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	*Saccharomyces cerevisiae*	*Mycoderma cerevisiae* *Candida robusta* *Saccharomyces capensis* *Saccharomyces italicus* *Saccharomyces oviformis* *Saccharomyces uvarum var. melibiosus*
Saccharomyces Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment Extract Lysate Filtrate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment Filtrate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment Lysate Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Ferment Lysate Filtrate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Lysate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Lysate Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Lysate Extract Filtrate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Saccharomyces Lysate Filtrate	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	-	-
Schizosaccharomyces Ferment Extract Filtrate	Schizosaccharomycetes	Schizosaccharomycetales	*Schizosaccharomycetaceae*	*Schizosaccharomyes*	-	-
Schizosaccharomyces Ferment Filtrate	Schizosaccharomycetes	Schizosaccharomycetales	*Schizosaccharomycetaceae*	*Schizosaccharomyes*	-	-
Schizosaccharomyces Pombe Extract	Schizosaccharomycetes	Schizosaccharomycetales	*Schizosaccharomycetaceae*	*Schizosaccharomyes*	*Schizosaccharomyces pombe*	*Schizosaccharomyces malidevorans*
Torulaspora Delbrueckii Extract	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Torulaspora*	*Torulapora delbrueckii*	*Saccharomyces delbrueckii* *Saccharomyces fermentati* *Saccharomyces rosei* *Candida colliculosa*
Torulaspora Delbrueckii Ferment	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Torulaspora*	*Torulapora delbrueckii*	*Saccharomyces delbrueckii* *Saccharomyces fermentati* *Saccharomyces rosei* *Candida colliculosa*
Yarrowia Lipolytica Extract	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Yarrowia*	*Yarrowia lipolytica*	*Endomycopsis lipolytica* *Mycotorula lipolytica* *Candida lipolytica*

Table 3. Taxonomy of yeast-derived ingredients[1,82]

INCI Ingredient	Class	Order	Family	Genus	Associated Genus and Species/Synonyms	Synonyms**
Yarrowia Lipolytica Ferment Lysate	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Yarrowia*	*Yarrowia lipolytica*	*Endomycopsis lipolytica* *Mycotorula lipolytica* *Candida lipolytica*
Yarrowia Lipolytica Oil	Saccharomycetes	Saccharomycetales	*Dipodascaceae*	*Yarrowia*	*Yarrowia lipolytica*	*Endomycopsis lipolytica* *Mycotorula lipolytica* *Candida lipolytica*
Yeast	Saccharomycetes	-	-	-	-	-
Yeast Extract***	Saccharomycetes	-	-	-	-	-
	Saccharomycetes	Saccharomycetales	*NR*	*Starmerella*	*Candida magnoliae*	*Starmarella magnolia* *Torulopsis magnoliae*
	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Kurtzmaniella*	*Candida oleophila*	-
	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Candida*	*Candida saitoana*	-
	Saccharomycetes	Saccharomycetales	*Debaryomycetaceae*	*Debaryomyces*	*Debaryomyces nepalensis*	-
	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Mestchnikowia agaves*	-
	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Metschnikowia*	*Metschnikowia reukaufii*	*Candida reukaufii*
	Saccharomycetes	Saccharomycetales	*Mestchnikowiaceae*	*Mestchnikowia*	*Metschnikowia pulcherrima*	*Candida pulcherrima*
	Saccharomycetes	Saccharomycetales	*Phaffomycetaceae*	*Wickerhamomyces*	*Pichia anomala*	*Whickerhamomyces anomalus* *Saccharomyces anomalus* *Endomyces anomalus* *Hansenula anomala* *Pichia anomalus* *Willia anomala*
	Saccharomycetes	Saccharomycetales	*Pichiaceae*	*Pichia*	*Pichia heedii*	-
	Saccharomycetes	Saccharomycetales	*Pichiaceae*	*Ogataea*	*Pichia minuta*	*Ogataea minuta* *Hansenula minuta* *Candida methanolovescens* *Torulopsis methanolovescens*
	Saccharomycetes	Saccharomycetales	*Pichiaceae*	*Ogataea*	*Pichia naganishii*	*Ogataea naganishii*
	Saccharomycetes	Saccharomycetales	*Saccharomycetaceae*	*Saccharomyces*	*Saccharomyces cerevisiae*	*Mycoderma cerevisiae* *Candida robusta* *Saccharomyces capensis* *Saccharomyces italicus* *Saccharomyces oviformis* *Saccharomyces uvarum var. melibiosus*
Yeast Ferment Extract	Saccharomycetes	-	-	-	-	-

*ingredient has more than one associated genus and species according to the *Dictionary*, and therefore has multiple entries in this table

**synonyms include heterotypic synonyms, homotypic synonyms, and basionyms

***although this is a generic yeast ingredient, several species have been identified in unpublished literature[17,18] that correspond to "Yeast Extract"; it is unknown whether or not these species are the only species used in the formulation of Yeast Extract

NR = not reported

Table 4. Fatty acid composition of several yeast species (measured as % of total fatty acids)[19]

Fatty acid	*Candida kefyr* (synonymous to *Kluyveromyces fragilis*)	*Candida lipolytica* (synonymous to *Yarrowia lipolytica*)	*Saccharomyces cerevisiae*
decanoic (C10:0)	0.06 ± 0.01	-	6.15 ± 1.18
lauric (C12:0)	0.22 ± 0.02	-	7.59 ± 1.35
myristic (C14:0)	2.05 ± 0.13	-	1.90 ± 0.05
myristoleic (C14:1)	0.24 ± 0.05	-	0.98 ± 0.04
pentadecanoic (C15:0)	0.25 ± 0.06	0.87 ± 0.11	-
palmitic (C16:0)	20.06 ± 1.55	11.99 ± 2.23	12.72 ± 1.45
palmitoleic (C16:1)	27.46 ± 2.48	17.22 ± 1.12	51.21 ± 2.25
heptadecanoic (C17:1)	0.08 ± 0.01	2.71 ± 0.43	-
stearic (C18:0)	1.15 ± 0.04	0.77 ± 0.02	0.95 ± 0.02
cis-9-octadecanoic (C18:1(9))	24.61 ± 2.38	42.85 ± 3.65	18.50 ± 1.33
cis-11-octadecanoic (C18:1(11))	0.40 ± 0.02	0.58 ± 0.04	-
linoleic (C18:2)	19.41 ± 2.13	23.01 ± 2.15	-
linolenic (C18:3)	4.01 ± 0.66	-	-

Table 5. Nutrient, amino acid, and mineral composition of *Saccharomyces cerevisiae* and *Yarrowia lipolytica*[83]

Nutrient (%)	*Yarrowia lipolytica*	*Saccharomyces cerevisiae*
crude protein	45.5	40.34
crude fat	1.47	0.51
dry matter	97.30	97.44
ash	7.71	8.03
Amino acids (g/kg dry matter)		
lysine	30.5	7.71
methionine	6.94	6.01
threonine	15.85	13.21
tryptophan	4.01	3.98
cysteine	4.23	4.66
leucine	28.0	24.55
isoleucine	18.9	14.77
histidine	9.78	8.98
arginine	17.51	20.98
phenylalanine	18.53	19.31
Minerals (g/kg)		
calcium	4.11	2.98
phosphorous	4.87	9.44
magnesium	1.77	1.69
iron	0.111	0.099
zinc	0.071	0.066
copper	0.01	0.012

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Galactomyces Ferment Filtrate		Hydrolyzed Candida Saitoana Extract		Hydrolyzed Yeast		Hydrolyzed Yeast Extract	
Totals*	**77**	**0.072 – 90.7**	**10**	**0.02 – 3.8**	**2**	**0.00038 – 0.004**	**26**	**0.000018 – 0.035**
summarized by likely duration and exposure**								
Duration of Use								
Leave-On	*70*	*0.072 – 90.7*	*9*	*0.02 – 3.8*	*2*	*0.00038 – 0.004*	*25*	*0.00003 – 0.035*
Rinse-Off	*7*	*5*	*1*	*NR*	*NR*	*NR*	*1*	*0.000018 – 0.0011*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type*								
Eye Area	5	0.072 – 37.5	2	0.02	NR	0.0005	1	NR
Incidental Ingestion	NR	NR	NR	NR	1	NR	NR	NR
Incidental Inhalation-Spray	31[a]; 24[b]	NR	2[a]; 4[b]	NR	1[a]	NR	10[a]; 13[b]	0.00043 – 0.0035[a]
Incidental Inhalation-Powder	24[b]	1.1	4[b]	3.8[c]	NR	0.0005[c]	13[b]	0.02[c]
Dermal Contact	76	1.1 – 90.7	10	0.02 – 3.8	1	0.00038 – 0.004	26	0.00003 – 0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	NR	NR	NR	NR	NR	0.000035 – 0.035
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	0.000018 – 0.000035
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	NR	NR	NR	1	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Eye Makeup Preparations								
Eyeliner								
Eye Shadow								
Eye Lotion	4	37.5	1	0.02	NR	0.0005		
Eye Makeup Remover								
Mascara	NR	0.072						
Other Eye Makeup Preparations	1	NR	1	NR			1	NR
Fragrance Preparations								
Cologne and Toilet Water								
Hair Preparations (non-coloring)								
Hair Conditioner							NR	0.0011
Hair Spray (aerosol fixatives)								
Permanent Waves								
Shampoos (non-coloring)	1	NR					NR	0.000035
Tonics, Dressings, and Other Hair Grooming Aids							NR	0.00043 – 0.0035
Wave Sets								
Other Hair Preparations							NR	0.035
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)							NR	0.000018
Hair Rinses (coloring)							NR	0.000035
Makeup Preparations								
Blushers (all types)								
Face Powders	NR	1.1						
Foundations	NR	17.6			NR	0.00038		
Lipstick					1	NR		
Makeup Bases								

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Rouges								
Makeup Fixatives								
Other Makeup Preparations	1	NR						
Manicuring Preparations (Nail)								
Other Manicuring Preparations								
Oral Hygiene Products								
Dentifrices								
Personal Cleanliness Products								
Bath Soaps and Detergents	1	NR						
Deodorants (underarm)								
Feminine Deodorants	1	NR						
Other Personal Cleanliness Products	1	NR						
Shaving Preparations								
Aftershave Lotion								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing	4	5	1	NR			1	NR
Depilatories								
Face and Neck (exc shave)	23	NR	4	3.8 (not spray)	NR	0.0005 (not spray)	10	0.02 (not spray)
Body and Hand (exc shave)							3	NR
Moisturizing	24	90.7 (not spray)	1	0.02 (not spray)	1	NR	7	NR
Night		83.1 (not spray)	1	NR			1	NR
Paste Masks (mud packs)								
Skin Fresheners	7	NR					2	NR
Other Skin Care Preparations	9	NR	1	0.02	NR	0.004	1	0.00003
Suntan Preparations								
Suntan Gels, Creams, and Liquids								
	Kluyveromyces Extract		**Pichia Anomala Extract**		**Pichia Ferment Lysate Filtrate**		**Saccharomyces Cerevisiae Extract**	
Totals*	**5**	**NR**	**2**	**0.5 – 0.1**	**3**	**NR**	**56**	**0.0001 – 0.3**
summarized by likely duration and exposure**								
Duration of Use								
Leave-On	*5*	*NR*	*2*	*0.05 – 0.1*	*3*	*NR*	*50*	*0.001 – 0.18*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*6*	*0.0001 – 0.3*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	1	NR	NR	NR	NR	NR	16	0.00083 – 0.15
Incidental Ingestion	NR	NR	NR	NR	NR	NR	1	NR
Incidental Inhalation-Spray	1[a]; 1[b]	NR	2[a]	NR	1[a]; 2[b]	NR	11[a]; 18[b]	0.045; 0.1[a]
Incidental Inhalation-Powder	1[a]	NR	NR	NR	2[b]	NR	2; 18[b]	0.001 – 0.18[c]
Dermal Contact	5	NR	2	0.05 – 0.1	3	NR	50	0.00083 – 0.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	4	0.0001 – 0.001
Hair-Coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Eye Makeup Preparations								
Eyeliner								
Eye Shadow								
Eye Lotion	9	0.0005 – 0.0036					6	0.001 – 0.15
Eye Makeup Remover								0.00083
Mascara								
Other Eye Makeup Preparations	6	NR	1	NR			10	NR
Fragrance Preparations								
Cologne and Toilet Water								
Hair Preparations (non-coloring)								
Hair Conditioner	4	0.005					NR	0.001
Hair Spray (aerosol fixatives)								
Permanent Waves								
Shampoos (non-coloring)	2	0.00025					4	0.0001
Tonics, Dressings, and Other Hair Grooming Aids	2	NR						
Wave Sets								
Other Hair Preparations	1	0.005						
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)							1	NR
Hair Rinses (coloring)								
Makeup Preparations								
Blushers (all types)								
Face Powders							2	NR
Foundations	NR	0.000038						
Lipstick							1	NR
Makeup Bases								
Rouges								
Makeup Fixatives								
Other Makeup Preparations							1	NR
Manicuring Preparations (Nail)								
Other Manicuring Preparations								
Oral Hygiene Products								
Dentifrices								
Personal Cleanliness Products								
Bath Soaps and Detergents								
Deodorants (underarm)								
Feminine Deodorants								
Other Personal Cleanliness Products								
Shaving Preparations								
Aftershave Lotion	1	NR					NR	0.025
Other Shaving Preparations	1	NR						
Skin Care Preparations								
Cleansing	4	NR					1	0.3
Depilatories								
Face and Neck (exc shave)	40	0.0005 – 0.12 (not spray)	1	NR			18	0.001 – 0.18 (not spray)

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Body and Hand (exc shave)	3	0.19 (not spray)					NR	0.01 (not spray)
Moisturizing	19	NR			2	0.1 (not spray)	9	0.045 (spray)
Night	4	0.002 (not spray)	1	NR	NR	0.05 (not spray)	2	0.045 (not spray)
Paste Masks (mud packs)								
Skin Fresheners	2	NR					NR	0.1
Other Skin Care Preparations	11	NR	2	NR			1	0.09
Suntan Preparations								
Suntan Gels, Creams, and Liquids								
	Saccharomyces Ferment		**Saccharomyces Ferment Filtrate**		**Saccharomyces Ferment Lysate Filtrate**		**Saccharomyces Lysate**	
Totals*	**42**	**0.00013 – 1.2**	**48**	**0.01 – 8**	**38**	**0.0035**	**14**	**NR**
summarized by likely duration and exposure**								
Duration of Use								
Leave-On	*38*	*0.00013 – 1.2*	*39*	*0.03 – 0.065*	*37*	*0.0035*	*8*	*NR*
Rinse-Off	*4*	*0.002*	*9*	*0.01 – 8*	*1*	*0.0035*	*6*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	3	NR	NR	NR	6	NR	1	NR
Incidental Ingestion	NR	0.00013	NR	NR	NR	NR	6	NR
Incidental Inhalation-Spray	20[a]; 1[b]	NR	16[a]; 12[b]	0.065; 0.03[a]; 0.038[b]	2; 12[a]; 14[b]	NR	3[a]; 3[b]	NR
Incidental Inhalation-Powder	1[b]	NR	1; 12[b]	0.038[b]	14[b]	NR	3[b]	NR
Dermal Contact	41	0.72 – 1.2	48	0.01 – 2.1	36	0.0035	8	NR
Deodorant (underarm)	8[a]	NR	4[a]	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	0.002	NR	0.03 – 8	2	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	0.00013	2	0.01 – 0.038	NR	NR	6	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Eye Makeup Preparations								
Eyeliner								
Eye Shadow					1	NR		
Eye Lotion	2	NR			3	NR		
Eye Makeup Remover								
Mascara								
Other Eye Makeup Preparations	1	NR			2	NR	1	NR
Fragrance Preparations								
Cologne and Toilet Water			NR	0.065				
Hair Preparations (non-coloring)								
Hair Conditioner	NR	0.002	NR	8				
Hair Spray (aerosol fixatives)					2	NR		
Permanent Waves								
Shampoos (non-coloring)	1	NR						
Tonics, Dressings, and Other Hair Grooming Aids			NR	0.03				
Wave Sets								
Other Hair Preparations								

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)								
Hair Rinses (coloring)								
Makeup Preparations								
Blushers (all types)	NR	1.2						
Face Powders			1	NR				
Foundations			NR	0.045				
Lipstick	NR	0.00013						
Makeup Bases								
Rouges					1	NR		
Makeup Fixatives								
Other Makeup Preparations					1	NR		
Manicuring Preparations (Nail)								
Other Manicuring Preparations								
Oral Hygiene Products								
Dentifrices							6	NR
Personal Cleanliness Products								
Bath Soaps and Detergents	8	NR						
Deodorants (underarm)			4	NR				
Feminine Deodorants			NR	0.038				
Other Personal Cleanliness Products	1	NR	2	0.01				
Shaving Preparations								
Aftershave Lotion								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing	2	NR	5	2.1	1	0.0035		
Depilatories								
Face and Neck (exc shave)			11	NR	13	NR	3	NR
Body and Hand (exc shave)	1	NR	1	NR	1	NR		
Moisturizing	19	NR			12	NR	3	NR
Night			15	NR				
Paste Masks (mud packs)								
Skin Fresheners			2	NR				
Other Skin Care Preparations	6	0.72	6	NR	1	NR	1	NR
Suntan Preparations								
Suntan Gels, Creams, and Liquids	1	NR	1	NR				

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Saccharomyces Lysate Extract		Schizosaccharomyces Ferment Filtrate		Yeast		Yeast Extract	
Totals*	**81**	**0.0007 – 0.71**	**5**	**NR**	**11**	**NR**	**398**	**0.0000036 – 0.16**
summarized by likely duration and exposure**								
Duration of Use								
Leave-On	*76*	*0.01 – 0.71*	*5*	*NR*	*10*	*NR*	*343*	*0.0000036 – 0.16*
Rinse-Off	*5*	*0.0007 – 0.0025*	*NR*	*NR*	*1*	*NR*	*55*	*0.0001 – 0.01*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	10	0.013 – 0.67	NR	NR	NR	NR	25	0.001 – 0.15
Incidental Ingestion	NR	NR	NR	NR	NR	NR	1	0.00072 – 0.002
Incidental Inhalation-Spray	20[a]; 26[b]	NR	2[a]; 1[b]	NR	1[b]	NR	2; 125[a]; 133[b]	0.065; 0.00001 – 0.03[a]; 0.038[b]
Incidental Inhalation-Powder	26[b]	0.01 – 0.71[c]	1[b]	NR	1[b]	NR	133[b]	0.0000036 – 0.021; 0.038[b]; 0.0036 – 0.16[c]
Dermal Contact	78	0.0023 – 0.71	5	NR	11	NR	334	0.0000036 – 0.16
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	3	0.0007 – 0.002	NR	NR	NR	NR	62	0.0001 – 0.03
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	1	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	1	0.0007 – 0.038
Baby Products	NR	0.067	NR	NR	NR	NR	NR	NR
as reported by product category								
Baby Products								
Baby Lotions/Oils/Powders/Creams	NR	0.067						
Eye Makeup Preparations								
Eyeliner							NR	0.002
Eye Shadow							NR	0.001 – 0.002
Eye Lotion	1	0.013 – 0.67					12	0.038 – 0.15
Eye Makeup Remover							NR	0.0048 – 0.0048
Mascara							NR	0.024
Other Eye Makeup Preparations	9	NR					13	NR
Fragrance Preparations								
Cologne and Toilet Water							NR	0.065
Hair Preparations (non-coloring)								
Hair Conditioner	1	0.0007 – 0.002					22	0.0001
Hair Spray (aerosol fixatives)							2	NR
Permanent Waves							NR	0.01
Shampoos (non-coloring)	1	0.0007 – 0.002						
Tonics, Dressings, and Other Hair Grooming Aids	1	NR					13	0.009 – 0.03
Wave Sets								
Other Hair Preparations							11	0.01
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)								
Hair Rinses (coloring)								
Makeup Preparations								
Blushers (all types)								
Face Powders							NR	0.0000036 – 0.021
Foundations	1	NR					5	0.0014 – 0.038
Lipstick							NR	0.00072 – 0.002

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Makeup Bases	1	NR					6	NR
Rouges								
Makeup Fixatives	1	NR					1	NR
Other Makeup Preparations	1	0.23					4	NR
Manicuring Preparations (Nail)								
Other Manicuring Preparations							1	NR
Oral Hygiene Products								
Dentifrices								
Personal Cleanliness Products								
Bath Soaps and Detergents							NR	0.0007
Deodorants (underarm)								
Feminine Deodorants							NR	0.038
Other Personal Cleanliness Products							NR	0.01
Shaving Preparations								
Aftershave Lotion	1	NR					NR	0.025
Other Shaving Preparations	2	NR					1	NR
Skin Care Preparations								
Cleansing	NR	0.0023 – 0.0025					12	0.0007 – 0.0036
Depilatories								
Face and Neck (exc shave)	25	0.18 – 0.71 (not spray)	1	NR	1	NR	117	0.0036 – 0.16 (not spray)
Body and Hand (exc shave)	1	0.01 (not spray)					16	0.0074 – 0.042 (not spray)
Moisturizing	15	0.025 (not spray)	2	NR			83	NR
Night	3	NR					22	NR
Paste Masks (mud packs)	1	NR			1	NR	5	NR
Skin Fresheners	1	NR					6	0.00001 – 0.0036
Other Skin Care Preparations	15	NR	2	NR	9	NR	31	0.0036 – 0.14
Suntan Preparations								
Suntan Gels, Creams, and Liquids								
	Yeast Ferment Extract							
Totals*	**15**	**NR**						
summarized by likely duration and exposure**								
Duration of Use								
Leave-On	*12*	*NR*						
Rinse-Off	*3*	*NR*						
Diluted for (Bath) Use	*NR*	*NR*						
Exposure Type								
Eye Area	NR	NR						
Incidental Ingestion	NR	NR						
Incidental Inhalation-Spray	6[a]; 4[b]	NR						
Incidental Inhalation-Powder	4[b]	NR						
Dermal Contact	14	NR						
Deodorant (underarm)	NR	NR						
Hair - Non-Coloring	1	NR						
Hair-Coloring	NR	NR						
Nail	NR	NR						
Mucous Membrane	1	NR						
Baby Products	NR	NR						

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Baby Products								
Baby Lotions/Oils/Powders/Creams								
Eye Makeup Preparations								
Eyeliner								
Eye Shadow								
Eye Lotion								
Eye Makeup Remover								
Mascara								
Other Eye Makeup Preparations								
Fragrance Preparations								
Cologne and Toilet Water								
Hair Preparations (non-coloring)								
Hair Conditioner								
Hair Spray (aerosol fixatives)								
Permanent Waves								
Rinses (non-coloring)								
Tonics, Dressings, and Other Hair Grooming Aids								
Wave Sets								
Other Hair Preparations	1	NR						
Hair Coloring Preparations								
Hair Dyes/Colors (all types requiring caution statements and patch tests)								
Hair Rinses (coloring)								
Makeup Preparations								
Blushers (all types)								
Face Powders								
Foundations								
Lipstick								
Makeup Bases								
Rouges								
Makeup Fixatives								
Other Makeup Preparations								
Manicuring Preparations (Nail)								
Other Manicuring Preparations								
Oral Hygiene Products								
Dentifrices								
Personal Cleanliness Products								
Bath Soaps and Detergents	1	NR						
Deodorants (underarm)								
Feminine Deodorants								
Other Personal Cleanliness Products								
Shaving Preparations								
Aftershave Lotion								
Other Shaving Preparations								
Skin Care Preparations								
Cleansing	2	NR						
Depilatories								
Face and Neck (exc shave)	4	NR						

Table 6. Frequency (2023)[32] and concentration (2021/2023)[33,84] of use according to likely duration and exposure and by product category

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
Body and Hand (exc shave)								
Moisturizing	6	NR						
Night								
Paste Masks (mud packs)								
Skin Fresheners								
Other Skin Care Preparations	1	NR						
Suntan Preparations								
Suntan Gels, Creams, and Liquids								

NR – not reported

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

**likely duration and exposure is derived based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

Table 7. Yeast-derived not reported to be use according to 2023 frequency of use and 2021/2023 concentration of use data

Hydrolyzed Candida Bombicola Extract	Pichia Heedii Extract
Hydrolyzed Kluyveromyces Extract	Pichia Minuta Extract
Hydrolyzed Metschnikowia Agaves Extract	Pichia Pastoris Ferment Filtrate
Hydrolyzed Metschnikowia Reukaufii Extract	Phaffia Rhodozyma Extract
Hydrolyzed Metschnikowia Shanxiensis Extract	Phaffia Rhodozyma Ferment Extract
Hydrolyzed Saccharomyces Cell Wall	Saccharomyces
Hydrolyzed Saccharomyces Extract	Saccharomyces Extract
Hydrolyzed Saccharomyces Lysate Extract	Saccharomyces Ferment Extract
Hydrolyzed Torulaspora Delbruekii Extract	Saccharomyces Ferment Extract Lysate Filtrate
Lactic Yeasts	Saccharomyces Ferment Lysate Extract
Lipomyces Lipid Bodies	Saccharomyces Lysate Extract Filtrate
Lipomyces Oil	Saccharomyces Lysate Filtrate
Lipomyces Oil Extract	Schizosaccharomyces Ferment Extract Filtrate
Metschnikowia Agaves Extract	Schizosaccharomyces Pombe Extract
Metschnikowia Henanensis Extract	Torulaspora Delbrueckii Extract
Metschnikowia Reukaufii Lysate Extract	Torulaspora Delbrueckii Ferment
Metschnikowia Viticola Extract	Yarrowia Lipolytica Extract
Pichia Caribbica Ferment	Yarrowia Lipolytica Ferment Lysate
Pichia Extract	Yarrowia Lipolytica Oil
Pichia Ferment Extract Filtrate	

Table 8. Food use/presence and non-cosmetic uses of yeast species

Associated Ingredients	Food Use/Presence	Other Non-Cosmetic Uses	Reference
Galactomyces Ferment Filtrate	*Geotrichum candidum* is used as an adjunct culture in the maturation of cheese *Galactomyces geotrichum* is found in alcohols and dairy products	*Galactomyces geotrichum* is used in biodegradation and bioremediation processes	85,86
Hydrolyzed Candida Bombicola Extract	*Starmerella bombicola* is naturally present in concentrated grape juice and in high-sugar fermented vegetables and honey	*Candida bombicola* produces sophorolipids which may be used as a biosurfactant in food, pharmaceutical, and cleaning industries	87
Hydrolyzed Candida Saitoana Extract	-	*Candida saitoana* is used as a biocontrol treatment of post-harvest disease in apples and citrus fruit	88
Hydrolyzed Kluyveromyces Extract Kluyveromyces Extract	*Kluyveromyces marxianus* is present in Korean kefir and other dairy products Lactase enzyme preparation from *Kluyveromyces lactis* is GRAS for use in hydrolyzing lactose in milk [21CFR184] Rennet and chymosin preparation from *Kluyveromyces marxianus* to coagulate milk in cheeses and other dairy products is considered GRAS [21CFR184]	*Kluyveromyces marxianus* is used in biotechnological (e.g., native enzyme production, inulinase production) and environmental applications (e.g., heavy metal recovery from agricultural industry waste water) *Kluyveromyces marxianus* may be used as a probiotic	38,89-91
Hydrolyzed Metschnikowia Agaves Extract Metschnikowia Agaves Extract	*Metschnikowia agaves* can be found in blue agave used to make tequila	-	92
Hydrolyzed Torulaspora Delbrueckii Extract Torulaspora Delbrueckii Extract Torulaspora Delbrueckii Ferment	*Torulaspora delbrueckii* is used in the production of breads/bakery products, chocolate, coffee, and fermented beverages *Torulaspora delbrueckii* may be present in cheese	-	93-95
Pichia Anomala Extract	*Wickerhamomyces anomalus* is used in Chinese liquor production and soy sauce *Pichia anomala* is commonly found in fermented food and beverages and may be used as a food-flavoring agent	*Pichia anomala* may be used as a biopreservative	96-99
Pichia Ferment Extract Filtrate Pichia Pastoris Ferment Filtrate	The following substances are considered GRAS: -Pepsin A enzyme preparation produced by *Pichia pastoris* to overexpress the gene encoding pepsin A -Myoglobin preparation from a strain of *Pichia pastoris* expressing the myoglobin gene from *Bos taurus* -Soy leghemoglobin preparation from a strain of *Pichia pastoris* -Soybean leghemoglobin from *Pichia pastoris* -Phospholipase C enzyme preparation from *Pichia pastoris* expressing a heterologous phospholipase C gene	-	100
Phaffia Rhodozyma Extract Phaffia Rhodozyma Ferment Extract	-	Astaxanthin-rich *Phaffia rhodozyma* may be used in feed for salmon and trout	101
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* is used in baking and alcohol production as a fermentative agent Baker's yeast extract (mechanically ruptured cells of *Saccharomyces cerevisiae*) is GRAS as a flavoring agent and adjuvant at a level not to exceed 5% in food [21CFR184.1983] Dried yeast (*Saccharomyces cerevisiae*) is considered to be GRAS as a multipurpose food additive [21CFR172.896] Baker's yeast glycan (derived from dried cell walls of *Saccharomyces cerevisiae*) is approved as a direct food additive for human consumption when used as described in 21CFR172.898 (e.g., not to exceed a concentration of 5% in finished salad dressing)	Inactivated yeast (*Saccharomyces cerevisiae*) cells are used in animal feed and over-the-counter nutritional supplements	35

Table 8. Food use/presence and non-cosmetic uses of yeast species

Associated Ingredients	Food Use/Presence	Other Non-Cosmetic Uses	Reference
Schizosaccharomyces Pombe Extract	*Schizosaccharomyces pombe* is used in cachaça (alcoholic beverage made from fermented sugarcane juice) and kombucha		[93]
Yarrowia Lipolytica Extract Yarrowia Lipolytica Ferment Lysate Yarrowia Lipolytica Oil	*Yarrowia lipolytica* has been found in a variety of different cheeses; predominantly ewe, goat, and buffalo cheese *Yarrowia lipolytica* is also found in other fermented dairy (e.g., yogurt) and meat (e.g., salami) products EPA-rich triglyceride oil *from Yarrowia lipolytica* is considered GRAS at a maximum intake of 3.0 g per person per day EPA and not to be combined or augmented with any other food ingredient containing EPA and/or another omega-3 fatty acid, docosahexaenoic acid [21 CFR 184.1472] *Yarrowia lipolytica* is GRAS for commercial production of food grade citric acid [21 CFR 173.165]	*Yarrowia lipolytica* is used in livestock feed, a biotechnological production host for organic acids or hydrophobic substances or carotenoids, a heterologous production host for pharmaceutical and industrial proteins and enzymes, for the mass production of biofuels, and for bioremediation purposes Oil produced by *Yarrowia lipolytica* may be used in the agro-alimentary, pharmaceutical, and bioenergy industry	[102,103]

EPA = eicosapentaenoic acid; GRAS = generally recognized as safe

Table 9. In vitro dermal absorption studies

Ingredient	Test Article	Concentration/Dose	Protocol	Results	References
Metschnikowia Agaves Extract	Emulsion containing Metschnikowia Agaves Extract	30%	OECD TG 428	Absorption of 2.4% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Pichia Anomala Extract	Emulsion containing Pichia Anomala Extract	30%	OECD TG 428	Absorption of 0.7% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Pichia Anomala Extract	Emulsion containing Pichia Anomala Extract	30%	OECD TG 428	Absorption of 0.41% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Pichia Heedii Extract	Emulsion containing Pichia Heedii Extract	30%	OECD TG 428	Absorption of 0.2% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Pichia Minuta Extract	Emulsion containing Pichia Minuta Extract	30%	OECD TG 428	Absorption of 0.6% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Yeast Extract (may also be chemically similar to Hydrolyzed Candida Saitoana Extract)	Emulsion containing Yeast Extract derived from *Candida saitoana*	30%	OECD TG 428	Absorption of 1.1% of the total quantity applied to the surface of the epidermis after 24 h	[18]
Yeast Extract (may also be chemically similar to Hydrolyzed Metschnikowia Reukaufii Extract)	Emulsion containing Yeast Extract derived from *Metschnikowia reukaufii*	30%	OECD TG 428	Absorption of 4.6% of the total quantity applied to the surface of the epidermis after 24 h	[18]

NR = not reported; OECD TG = Organisation for Economic Co-operation and Development test guidelines

Table 10. Acute toxicity studies*

Ingredient	Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL							
Hydrolyzed Saccharomyces Cell Wall	90% *Saccharomyces cerevisiae* cell wall (containing 24% glucan and 7% mannan)	10% Hydrated sodium calcium aluminosilicate	Sprague-Dawley rats (5/sex/group)	2000 mg/kg bw; 55% dilution (final test concentration of 49.5% yeast cell wall)	Test article applied to gauze pad and placed on clipped, dorsal/trunk area of animal; pads wrapped; 24-h administration period; 14-d evaluation period	No mortalities or signs or gross toxicity, dermal irritation, adverse pharmacological effects, or abnormal behaviors were noted. The acute dermal LD_{50} of a 55% dilution of the test article was determined to be > 2000 mg/kg bw.	4
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	Water	Crl:WI (Han) rats (5/sex/)	2000 mg/kg	OECD TG 402; occlusive conditions; 24 h administration period; observation for 14 d	Two males and two females showed chromodacryorrhoea on day 1 (24 h after treatment). In addition, one male showed hunched posture on day 1. Two females had scales or focal erythema in the treated skin area during the observation period. No other abnormalities were noted; LD_{50} was determined to be > 2000 mg/kg bw.	2
ORAL							
Hydrolyzed Yeast	Yeast hydrolysate obtained from *Saccharomyces cerevisiae*	NR	Sprague-Dawley rats (5/sex/group)	5000 mg/kg bw	OECD TG 420; gavage administration; 14-d observation period	No mortality or adverse effects observed.	28
Hydrolyzed Saccharomyces Cell Wall	90% *Saccharomyces cerevisiae* cell wall (containing 24% glucan and 7% mannan)	10% Hydrated sodium calcium aluminosilicate and distilled water	Sprague-Dawley rats (5/sex/group)	2000 mg/kg bw; 55% dilution (final test concentration of 49.5% yeast cell wall)	Administration via gavage; 14-d observation period	No mortalities were observed throughout the study. One female exhibited reduced fecal volume, however, this animal recovered by day 2. No other signs of toxicity were noted.	4
Saccharomyces Ferment	Fermentate powder derived from *Saccharomyces cerevisiae*	Methylcellulose and water	Sprague-Dawley rats (10/sex/group)	2000 mg/kg bw	OECD TG 423; gavage administration; 14-d observation period	No signs of toxicity observed.	37
INHALATION							
Hydrolyzed Saccharomyces Cell Wall	90% *Saccharomyces cerevisiae* cell wall (containing 24% glucan and 7% mannan)	10% Hydrated sodium calcium aluminosilicate and distilled water	Sprague-Dawley rats (5/sex/group)	Gravimetric and nominal chamber concentrations were 2.09 and 5.81 mg/l, respectively	OECD TG 403; mass median aerodynamic diameter estimated to be 3.75 µm; 14-d observation period	Two males and 2 females exhibited irregular respiration and hypoactive behavior following exposure; however, these animals recovered by day 5. No gross abnormalities were observed upon necropsy, and no other adverse effects were noted; LC_{50} was determined to be > 2.09 mg/l in male and female rats.	4
PARENTERAL							
Pichia Ferment Extract Filtrate and Pichia Pastoris Ferment Filtrate	Live *Pichia pastoris* cells	Sterile saline	Female BALB/c mice (20/group)	1×10^6 CFU	Intravenous administration of the test substance via the lateral tail vein; control group one received inoculation with saline; control group two was left untreated; body weight and behavior monitored; 5 mice/group were euthanized at 4, 24, and 48 h and 6 d post-administration; samples of sera and tissues (kidney, liver, brain, spleen, heart, and lung) were collected	Results were similar among control and treated groups (no adverse effects relating to body weight, survival, or locomotion changes); no adverse effects related to pathology in tissues were noted	36

CFU = colony-forming units; LC_{50} = median lethal concentration; LD_{50} = median lethal dose; NR = not reported; OECD TG = Organisation for Economic Co-operation and Development test guidelines
*It should be noted that the test articles evaluated in these studies may not be identical to the wINCI ingredients reviewed in this report; however, as they may be similar, both test articles and potentially-related wINCI ingredients have been included in the table

Table 11. Repeated dose oral toxicity studies*

Ingredient	Test Article	Vehicle	Animals/Group	Study Duration	Dose/Concentration	Protocol	Results	Reference
Hydrolyzed Yeast	Yeast hydrolysate obtained from *Saccharomyces cerevisiae*	NR	Sprague-Dawley rats (5/sex/group)	14 d	1000 mg/kg bw/d	OECD TG 407; animals administered test substance orally (method of oral administration not stated); animals killed after treatment period; control animals given water; satellite group treated with the test substance, at the same dose, at the same time period, and kept for another 14 d post-treatment for observation	No significant differences in organ weights between control and treated groups were noted. No adverse hematological effects, gross abnormalities, or histopathological changes were observed. Treatment with the test substance induced significant increases in body weight compared to the control group ($p < 0.05$).	[28]
Kluyveromyces Extract	*Kluyveromyces marxianus* strains A4 and A5	Sterilized saline	Female SPF BALB/c mice (6/group)	14 d	1.0 x 10^6 CFU/ml or 1.0 x 10^8 CFU/ml	Animals were orally administered the test substance (method of oral administration not stated); negative control group left untreated; another negative control group treated with saline only	No adverse effects relating to body weight or food and water intake were observed. The spleen to body ratio of the A5 strain (high concentration)-treated group was significantly lower than that of the untreated negative control group ($p < 0.05$). The liver to body weight ration of the A4 strain (low concentration)-treated group was significantly lower than that of the untreated negative control group ($p < 0.05$). All blood parameters and cytokine parameters (interleukin-1β and tumor necrosis factor-α) were comparable between treated and negative control groups.	[38]
Phaffia Rhodozyma Extract and Phaffia Rhodozyma Ferment Extract	*Phaffia rhodozyma* extract	Corn oil	Sprague-Dawley rats (6/sex/group)	28 d	3 ml/kg; 500 and 1000 mg/kg	OECD TG 407; gavage administration 6 d/wk; control group given corn oil	Decreased body weight was observed in females in the 1000 mg/kg treated group; increased ALT levels and relative liver weights were observed in females in the 1000 mg/kg group ($p < 0.05$); absolute and relative thymus weights tended to increase in males of the 1000 mg/kg group; no other toxicologically-relevant adverse effects were observed; NOAEL > 1000 mg/kg	[39]
Saccharomyces Ferment	Fermentate powder derived from *Saccharomyces cerevisiae*	Methylcellulose and water	Sprague-Dawley rats (20/sex/group)	90 d	30, 200, and 1500 mg/kg bw/d	OECD TG 408; gavage treatment once per day; control group used, however, details regarding treatment not provided	No treatment-related toxicity was observed regarding general state, behavior, external appearance, body weight, ophthalmologic changes, urine analysis, organ weights, or histopathology. A dose-related slight decrease in total cholesterol was observed in male rats of the high-dose (not observed in females); NOAEL = 1500 mg/kg bw/d	[37]
Saccharomyces Ferment	Fermentate powder derived from *Saccharomyces cerevisiae*	Methylcellulose and water	Sprague-Dawley rats (20/sex/group)	1 yr	20, 200, and 800 mg/kg bw/d	OECD TG 408 and 452; gavage administration; control group used, however, details regarding treatment not provided	No macroscopic or microscopic, serum chemistry, hematological, urinary, or histological adverse effects were observed to be of clinical significance. A statistically significant decrease in water consumption over nonconsecutive weeks was observed in the highest dose group; NOAEL = 800 mg/kg bw/d	[37]

ALT = alanine aminotransferase; CFU = colony-forming units; NOAEL = no-observed-adverse-effect level; OECD TG = Organisation for Economic Co-operation and Development test guidelines

*It should be noted that the test articles evaluated in these studies may not be identical to the wINCI ingredients reviewed in this report; however, as they may be similar, both test articles and potentially related wINCI ingredients have been included in the table

Table 12. Genotoxicity studies*

Ingredient	Test Article	Vehicle	Concentration/Dose	Test System	Procedure	Results	Reference
				IN VITRO			
Phaffia Rhodozyma Extract and Phaffia Rhodozyma Ferment Extract	*Phaffia rhodozyma* extract	Acetone	25 µl; 1.22 – 5000 µg/ plate	*S. typhimurium* strains TA 98 and TA100	Ames assay; OECD TG 471; performed with and without metabolic activation; vehicle used as negative control; positive controls: AF-2 and 2-AA	Non-genotoxic; controls gave expected results	[39]
Saccharomyces Ferment	Fermentate powder derived from *Saccharomyces cerevisiae*	Methylcellulose and water	5, 10, 50, 100, 500, 1000, 2500, and 5000 µg/plate	*S. typhimurium* strains TA97a, TA98, TA100, and TA1535; *E. coli* WP2 *urvA*	Ames assay; OECD TG 471; performed with and without metabolic activation; negative control: sterile water	Non-genotoxic; controls gave expected results	[37]
Saccharomyces Ferment	Fermentate powder derived from *Saccharomyces cerevisiae*	Methylcellulose and water	up to 5000 µg/ml (specific concentrations tested not stated)	Mouse lymphoma L5178Y cell line	Mammalian cell gene mutation assay; OECD TG 476; positive controls: methyl methanesulphonate and cyclophosphamide	Non-genotoxic; controls gave expected results	[37]
Hydrolyzed Saccharomyces Cell Wall	90% yeast (*Saccharomyces cerevisiae*) cell wall (containing 24% glucan and 7% mannan)	Hydrated sodium calcium aluminosilicate	3.4, 10.3, 30.98, 92.6, 277.8, 833.3, and 2500 µg/plate	*S. typhimurium* strains TA1535, TA1537, TA98, and TA102	Ames assay; OECD TG 471; performed with and without metabolic activation; vehicle used as negative control; positive controls: sodium azide, 9-aminoacridine, 2-nitro fluorene, mitomycin C, 2-anthramine, and benzo[a]pyrene	Non-genotoxic; controls gave expected results	[4]
				IN VIVO			
Phaffia Rhodozyma Extract and Phaffia Rhodozyma Ferment Extract	*Phaffia rhodozyma* extract	Corn oil	500, 1000, and 2000 mg/kg bw/d	Male ICR mice (3/group)	Mammalian bone marrow chromosomal aberration assay; OECD 475; negative control group received corn oil; positive control group received injection of mitomycin C	Non-clastogenic; controls gave expected results	[39]
Hydrolyzed Saccharomyces Cell Wall	90% yeast (*Saccharomyces cerevisiae*) cell wall (containing 24% glucan and 7% mannan)	Hydrated sodium calcium aluminosilicate	500, 1000, and 2000 mg/kg bw/d	Swiss ICO OF1 mice (28/sex/group)	Mammalian bone marrow chromosomal aberration assay; OECD TG 475; negative control: 0.5% methylcellulose in purified water; positive control group: cyclophosphamide in 0.9% saline	Non-clastogenic; controls gave expected results	[4]

2-AA = 2-aminoanthracene; AF-2 = 2-(2-furyl)-3-(5-nitro-2-furyl) acrylamide; NR = not reported; OECD TG = Organisation for Economic Co-operation and Development test guidelines

*It should be noted that the test articles evaluated in these studies may not be identical to the wINCI ingredients reviewed in this report; however, as they may be similar, both test articles and potentially related wINCI ingredients have been included in the table

Table 13. Dermal irritation and sensitization studies*

Ingredient	Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
IRRITATION						
In Vitro						
Saccharomyces Cerevisiae Extract	Powdered *Saccharomyces cerevisiae* extract	tested neat; 10 mg moistened with 5 µl water	human three dimensional epidermal model (EpiSkin™)	Human epidermis model; negative control of PBS; positive control of sodium dodecyl sulfate; 15 min exposure followed by 42-h recovery period; colorimetric measurement of MTT reduction was used as index of cell viability	Non-irritating	2
Saccharomyces Cerevisiae Extract	Trade name mixture containing 1.25% Saccharomyces Cerevisiae Extract	tested neat; 30 µl	reconstructed human epidermal model (EpiDerm™)	3 tissue inserts incubated with test substance for 60 min, followed by washing, re-plating, and MTT assay; negative control of PBS; positive control of sodium dodecyl sulfate	Non-irritating	53
Saccharomyces Cerevisiae Extract	Trade name mixture containing 4.5% Saccharomyces Cerevisiae Extract	25, 50, 75, 100, and 135 µl	Irritection® system**	Test substance applied to membrane for 24 h; irritancy measured via a spectrophotometer	Non-irritating	52
Yeast Extract (may also be chemically similar to Hydrolyzed Metschnikowia Reukaufii Extract)	Yeast Extract derived from *Metschnikowia reukaufii*	100%	NR	KeratinoSens; OECD TG 442D	No sensitization potential	18
Animal						
Hydrolyzed Saccharomyces Cell Wall	Mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall (24% glucan and 7% mannan) in 10% HSCAS	55%; moistened with distilled water	3 male New Zealand albino rabbits	Test substance mixture (0.91 g) was placed on gauze pad and applied to one 6 cm^2 dose site on each animal. The pad was wrapped under semi-occlusive conditions. Pads were kept on for 4 h. Erythema and edema were evaluated 30-60 min, 24, 48, and 72 h after patch removal. Sites were scored according to the Draize scoring system.	Slight erythema noted within 30-60 min after dressing removal; primary dermal irritation of 0.1; classified as slightly irritating	4
Human						
Metschnikowia Agaves Extract	Metschnikowia Agaves Extract	15% in water	11 subjects	Patch test; no other details provided	Non-irritating	18
Pichia Anomala Extract	Pichia Anomala Extract	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18
Pichia Anomala Extract	Pichia Anomala Extract	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18
Pichia Heedii Extract	Pichia Heedii Extract	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18
Pichia Minuta Extract	Pichia Minuta Extract	15% in water	11 subjects	Patch test; no other details provided	Non-irritating	18
Saccharomyces Cerevisiae Extract	cosmetic formulation containing 1% Saccharomyces Cerevisiae Extract	tested neat	28 subjects	20 µl were applied to the skin, under an occlusive patch, for 48 h; skin irritation was evaluated for irritation 15 min and 48 h after patch removal	Slight erythema noted in one volunteer 15 min after patch removal, however, no reaction was noted 48 h after patch removal	54
Yeast Extract	Yeast Extract derived from *Candida magnoliae*	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18
Yeast Extract (may also be chemically similar to Hydrolyzed Candida Saitoana Extract)	Yeast Extract derived from *Candida saitoana*	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18
Yeast Extract derived from *Metschnikowia pulcherrima*	Yeast Extract derived from *Metschnikowia pulcherrima*	15% in water	10 subjects	Patch test; no other details provided	Non-irritating	18

Table 13. Dermal irritation and sensitization studies*

Ingredient	Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Yeast Extract (may also be chemically similar to Hydrolyzed Metschnikowia Reukaufii Extract)	Yeast Extract derived from *Metschnikowia reukaufii*	15% in water	11 subjects	Patch test; no other details provided	Non-irritating	[18]
SENSITIZATION						
Animal						
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	0, 10, 25, and 50% in propylene glycol	female CBA/J mice (5/group)	LLNA; OECD TG 429; The dorsal surface of both ears were epidermally treated (25 µl/ear) with the test substance, once a day for 3 d. Control animals were treated with the vehicle only. On day 6, animals were injected via the tail vein with 0.25 ml PBS containing 3H-methyl thymidine, and 5 h later ,killed. The auricular lymph node was excised, evaluated, and drained. Radioactivity measurements were performed. The SI was evaluated for each group. The SI is the ratio of the DPM/group compared to DPM/vehicle control group. An SI ≥ 3 indicates potential skin sensitization.	SI values at the 10, 25, and 50% concentration levels were 2.1, 5, and 28.9, respectively. The estimated test substance concentration that would give an SI = 3 was calculated to be 14.7%. The test substance was considered to be sensitizing.	[2]
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	0, 10, 25, and 50% in propylene glycol	female CBA/J mice (5/group)	LLNA performed according to the same procedure as above	SI values at the 10, 25, and 50% concentration levels were 1.1, 2, and 1.7, respectively. The test substance was considered to be non-sensitizing.	[2]
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	0, 10, 25, and 50% in propylene glycol	female CBA/J mice (5/group)	LLNA performed according to the same procedure as above	SI values at the 10, 25, and 50% concentration levels were 2.5, 2.5, and 1.8, respectively. The test substance was considered to be non-sensitizing.	[2]
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	0, 10, 25, and 50% in propylene glycol	female CBA/J mice (5/group)	LLNA performed according to the same procedure as above	SI values at the 10, 25, and 50% concentration levels were 1.4, 1.7, and 2.6, respectively. The test substance was considered to be non-sensitizing.	[2]
Saccharomyces Cerevisiae Extract	*Saccharomyces cerevisiae* extract	0, 2.5, 5, 10, 25, and 50% in acetone and olive oil	female CBA mice (4/group)	LLNA performed according to the same procedure as above	SI values at the 2.5, 5, 10, 25, and 50% concentration levels were 0.87, 0.49, 1.36, 0.71, and 0.63, respectively. The test substance was considered to be non-sensitizing.	[2]
Hydrolyzed Saccharomyces Cell Wall	Mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall (24% glucan and 7% mannan) in 10% HSCAS	55%; vehicle of 2% carboxymethylcellulose in distilled water	male Hartley guinea pigs (20 test group, 10 control group)	OECD TG 406; Once each week for 3 wk, the test substance was applied to the animal's left side under an occlusive patch and left on for 6 h. Readings were made 24 and 48 h after each induction period. Twenty-seven d after the first induction dose, the test substance was applied, under an occlusive patch, on a naïve site on the right side of the animal as a challenge dose. Sites were evaluated for a sensitization response 24 and 48 h after challenge application. A control group was treated with HSCAS, only.	Non-irritating; Non-sensitizing	[4]

Table 13. Dermal irritation and sensitization studies*

Ingredient	Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			Human			
Metschnikowia Agaves Extract	Metschnikowia Agaves Extract	15% in water	112 subjects	HRIPT; no other details provided	Non-sensitizing	[18]
Pichia Anomala Extract	Pichia Anomala Extract	15% in water	104 subjects	HRIPT; no other details provided	Non-sensitizing	[18]
Pichia Anomala Extract	Pichia Anomala Extract	15% in water	100 subjects	HRIPT; no other details provided	Non-irritating; Non-sensitizing	[18]
Pichia Heedii Extract	Pichia Heedii Extract	15% in water	106 subjects	HRIPT; no other details provided	Non-irritating; Non-sensitizing	[18]
Pichia Minuta Extract	Pichia Minuta Extract	15% in water	107 subjects	HRIPT; no other details provided	Non-sensitizing	[18]
Yeast Extract (may also be chemically similar to Hydrolyzed Candida Saitoana Extract)	Yeast Extract derived from *Candida saitoana*	15% in water	112 subjects	HRIPT; no other details provided	Non-sensitizing	[18]
Yeast Extract (may also be chemically similar to Hydrolyzed Metschnikowia Reukaufii Extract)	Yeast Extract derived from *Metschnikowia reukaufii*	15% in water	104 subjects	HRIPT; no other details provided	Non-sensitizing	[18]

DPM = disintegrations per minute; HSCAS = hydrated sodium calcium aluminosilicate; HRIPT = human repeat insult patch test; LLNA = local lymph node assay; MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; OECD TG = Organisation for Economic Co-operation and Development test guidelines; PBS = phosphate-buffered saline; SI = stimulation index

*It should be noted that the test articles evaluated in these studies may not be identical to the wINCI ingredients reviewed in this report; however, as they may be similar, both test articles and potentially related wINCI ingredients have been included in the table

**the Irritection® system involved the use of a proprietary solution comprised of both proteins and macromolecules in a well that is covered by a membrane. The test material is applied to the membrane and diffuses into the well. The proteins and macromolecules within the well undergo conformational changes depending on the irritation potential of the test substance that mimic the biomolecular changes that occur when irritants are placed on the skin and eyes. The more turbid the solution becomes, the higher the irritancy level. Irritancy is measured using a spectrophotometer.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: October 5, 2021

SUBJECT: Yeast Extract (derived from *Saccharomyces cerevisiae*)

Active Concepts. 2020. Dermal and ocular irritation tests ABS Aloe Beta-Glucan (contains 1.25% Yeast Extract from *Saccharomyces cerevisiae*).

Active Concepts. 2006. AC Phytocoll irritation analysis (contains 4.50% Yeast Extract from *Saccharomyces cerevisiae*).

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

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Dermal and Ocular Irritation Tests

Tradename: ABS Aloe Beta-Glucan Contains 1.25% Yeast Extract Saccharomyces Cerevisiae

Code: 10221

CAS #: 7732-18-5 & 85507-69-3 & 8013-01-2

Test Request Form #: 6716

Lot #: 71670P

Sponsor: *Active Concepts, LLC; 107 Technology Drive Lincolnton, NC 28092*
Study Director: *Maureen Danaher*
Principle Investigator: *Michael Hovis*

Test Performed:
In Vitro EpiDerm™ Dermal Irritation Test (EPI-200-SIT)
EpiOcular™ Eye Irritation Test (OCL-200-EIT)

SUMMARY

In vitro dermal and ocular irritation studies were conducted to evaluate whether **ABS Aloe Beta-Glucan** would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays.

The product was tested according to the manufacture's protocol. The test article solution was found to be **non-irritating**. Reconstructed human epidermis and cornea epithelial model were incubated in growth media overnight to allow for tissue equilibration after shipping from MatTek Corporation, Ashland, MA. Test substances were applied to the tissue inserts and incubated for 60 minutes for liquid and solid substances in the EpiDerm™ assay and 30 minutes for liquid substances and 90 minutes for solid substances in the EpiOcular™ assay at 37°C, 5% CO_2, and 95% relative humidity (RH). Tissue inserts were thoroughly washed and transferred to fresh plates with growth media. After post substance dosing incubation is complete, the cell viability test begins. Cell viability is measured by dehydrogenase conversion of MTT [(*3-4,5-dimethyl thiazole 2-yl*)], present in the cell mitochondria, into blue formazan salt that is measured after extraction from the tissue. The irritation potential of the test chemical is dictated by the reduction in tissue viability of exposed tissues compared to the negative control.

Under the conditions of this assay, the test article was considered to be **non-irritant**. The negative and positive controls performed as anticipated.

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Dermal and Ocular Irritation Tests

I. Introduction

A. Purpose

In vitro dermal and ocular irritation studies were conducted to evaluate whether a test article would induce dermal or ocular irritation in the EpiDerm™ and EpiOcular™ model assays. MatTek Corporation's reconstructed human epidermal and human ocular models are becoming a standard in determining the irritancy potential of test substances. They are able to discriminate between irritants and non-irritants. The EpiDerm™ assay has accuracy for the prediction of UN GHS R38 skin irritating and no-label (non-skin irritating) test substances. The EpiOcular™ assay can differentiate chemicals that have been classified as R36 or R41 from the EU classifications based on Dangerous Substances Directive (DSD) or between the UN GHS Cat 1 and Cat 2 classifications.

II. Materials

A. Incubation Conditions:	37°C at 5% CO_2 and 95% relative humidity
B. Equipment:	Forma humidified incubator, ESCO biosafety laminar flow hood, Synergy HT Microplate reader; Pipettes
C. Media/Buffers:	DMEM based medium; DPBS; sterile deionized H_2O
D. Preparation:	Pre-incubate (37°C) tissue inserts in assay medium; Place assay medium and MTT diluent at 4°C, MTT concentrate at -20°C, and record lot numbers of kit components
E. Tissue Culture Plates:	Falcon flat bottom 96-well, 24-well, 12-well, and 6-well tissue culture plates
F. Reagents:	MTT (1.0mg/mL); Extraction Solution (Isopropanol); SDS (5%); Methyl Acetate
G. Other:	Nylon Mesh Circles (EPI-MESH); Cotton tip swabs; 1mL tuberculin syringes; Ted Pella micro-spatula; 220mL specimen containers; sterile disposable pipette tips; Parafilm

III. Test Assay

A. Test System

The reconstructed human epidermal model, EpiDerm™, and comea epithelial model, EpiOcular™, consist of normal human-derived epidermal keratinocytes which have been cultured to form a multilayer, highly differentiated model of the human epidermis and cornea epithelium. These models consist of organized basal, spinous, and granular layers, and the EpiDerm™ systems also contains a multilayer stratum comeum containing intercellular lamellar lipid layers that the EpiOcular™ system is lacking. Both the EpiDerm™ and EpiOcular™ tissues are cultured on specially prepared cell culture inserts.

B. Negative Control

Sterile DPBS and sterile deionized water are used as negative controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

C. Positive Control

Known dermal and eye imitants, 5% SDS solution and Methyl Acetate, were used as positive controls for the EpiDerm™ and EpiOcular™ assays, respectfully.

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D. Data Interpretation Procedure

a. EpiDerm™

An irritant is predicted if the mean relative tissue viability of the 3 tissues exposed to the test substance is reduced by 50% of the mean viability of the negative controls and a non-irritant's viability is > 50%.

b. EpiOcular™

An irritant is predicted if the mean relative tissue viability of the 2 tissues exposed to the test substance is reduced by 60% of the mean viability of the negative controls and a non-irritant's viability is > 40%.

IV. Method

A. Tissue Conditioning

Upon MatTek kit arrival at Active Concepts, LLC the tissue inserts are removed from their shipping medium and transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for 60 minutes. After those 60 minutes the inserts are transferred into fresh media and tissue culture plates and incubated at 37°C at 5% CO_2 and 95% relative humidity for an additional 18 to 21 hours.

B. Test Substance Exposure

a. EpiDerm™

30µL (liquid) or 25mg (solid) of the undiluted test substance is applied to 3 tissue inserts and allowed to incubate for 60 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

b. EpiOcular™

Each tissue is dosed with 20µL DPBS prior to test substance dosing. 50µL (liquid) or 50mg (solid) of the undiluted test substance is applied to 2 tissue inserts and allowed to incubate for 90 minutes in a humidified incubator (37°C, 5% CO_2, 95% RH).

C. Tissue Washing and Post Incubation

a. EpiDerm™

All tissue inserts are washed with DPBS, dried with cotton tipped swab, and transferred to fresh media and culture plates. After 24 hours the inserts are again transferred into fresh media and culture plates for an additional 18 to 20 hours.

b. EpiOcular™

Tissue inserts are washed with DPBS and immediately transferred into 5mL of assay medium for 12 to 14 minutes. After this soak the inserts are transferred into fresh media and tissue culture plates for 120 minutes for liquid substances and 18 hours for solid substances.

D. MTT Assay

Tissue inserts are transferred into 300µL MTT media in pre-filled plates and incubated for 3 hours at 37°C, 5% CO_2, and 95% RH. Inserts are then removed from the MTT medium and placed in 2mL of the extraction solution. The plate is sealed and incubated at room temperature in the dark for 24 hours. After extraction is complete the tissue inserts are pierced with forceps and 2 x 200µL aliquots of the blue formazan solution is transferred into a 96 well plate for Optical Density reading. The spectrophotometer reads the 96-well plate using a wavelength of 570 nm.

V. Acceptance Criterion

A. Negative Control

The results of this assay are acceptable if the mean negative control Optical Density (OD_{570}) is ≥ 1.0 and ≤ 2.5 (EpiDerm™) or ≥ 1.0 and ≤ 2.3 (EpiOcular™).

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B. Positive Control

a. EpiDerm™

The assay meets the acceptance criterion if the mean viability of positive control tissues expressed as a % of the negative control is ≤ 20%.

b. EpiOcular™

The assay meets the acceptance criterion if the mean viability of positive control tissues is < 60% of control viability.

C. Standard Deviation

Since each irritancy potential is predicted from the mean viability of 3 tissues for EpiDerm™ and 2 tissues for EpiOcular™, the variability of the replicates should be < 18% for EpiDerm™ and < 20% EpiOcular™.

VI. Results

A. Tissue Characteristics

The tissue inserts included in the MatTek EpiDerm™ and EpiOcular™ assay kits were in good condition, intact, and viable.

B. Tissue Viability Assay

The results are summarized in Figure 1. In no case was the tissue viability ≤ 50% for EpiDerm™ or ≤ 60% for EpiOcular™ in the presence of the test substance. The negative control mean exhibited acceptable relative tissue viability while the positive control exhibited substantial loss of tissue viability and cell death.

C. Test Validity

The data obtained from this study met criteria for a valid assay.

VII. Conclusion

Under the conditions of this assay, the test article substance was considered to be **non-irritating**. The negative and positive controls performed as anticipated.

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Dermal and Ocular Irritation Tests

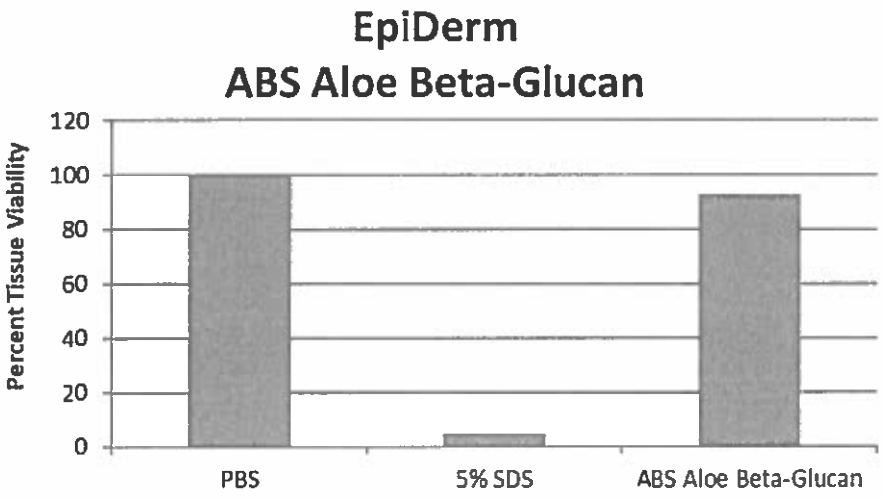


Figure 1: EpiDerm tissue viability

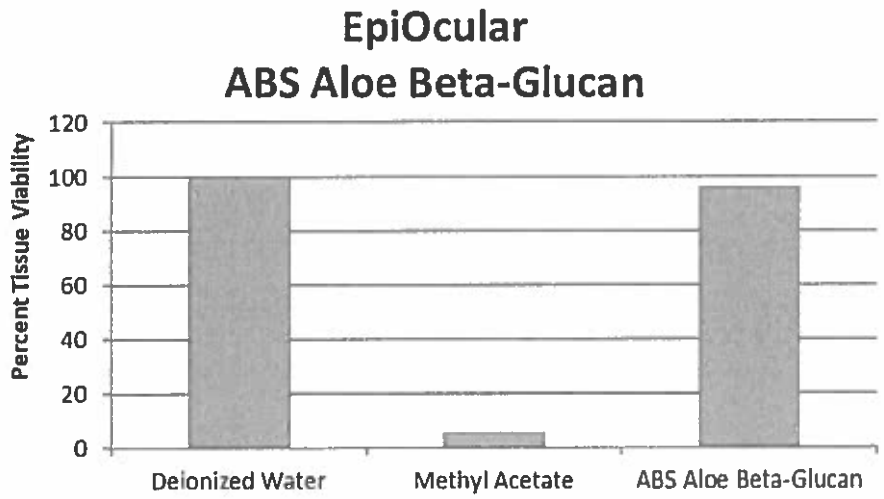


Figure 2: EpiOcular tissue viability

AC Phytocoll Irritation Analysis

info@activeconceptsllc.com • Phone: +1-704-276-7100 • Fax: +1-704-276-7101

Abstract:

Contains 4.5 C % Yeast Extract
Saccharomyces Cerevisiae

To confirm that **AC Phytocoll** is non-irritating, we used *in-vitro* dermal and ocular irritation assays.

The Irritection® assays purchased from InVitro International were used to determine the potential ocular and dermal irritancy of **AC Phytocoll**. The *in-vitro* system involves the use of a proprietary solution comprised of both proteins and macromolecules in a well that is covered by a membrane. Testing material is applied to the membrane and diffuses into the well. The proteins and macromolecules undergo conformational changes based on the irritancy of the diffused material, these changes are intended to mimic the biomolecular changes that occur when irritants are applied to both the eyes and skin. The conformational changes cause the solution to become turbid; there is a direct correlation between the irritancy level of the material and the solution's turbidity. Irritancy is quantitatively measured using a spectrophotometer.

Figure 1. The Ocular Irritection Model

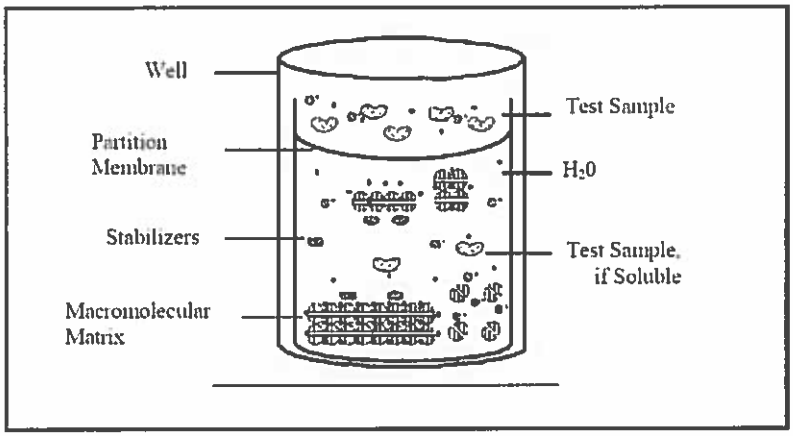
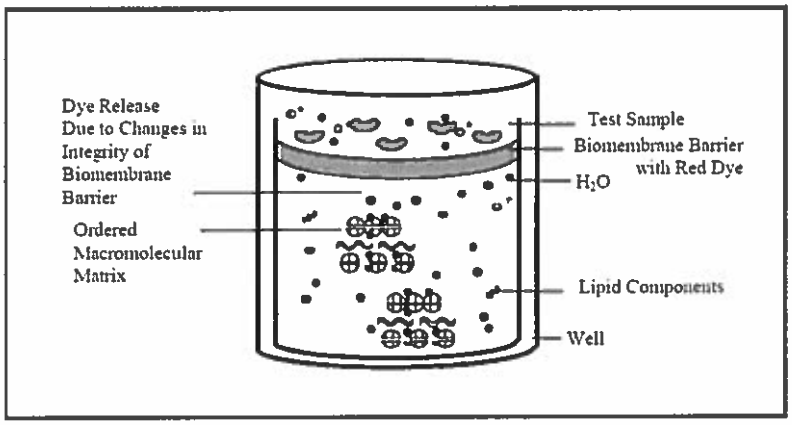


Figure 2. The Dermal Irritection Model



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AC Phytocoll Irritation Analysis

Materials and Methods:

For the ocular and dermal irritation assays, samples of **AC Phytocoll** were applied to Irritection® systems at concentrations of 25, 50, 75, 100 and 125 µl. The samples were left at room temperature for a period of 24 hours before they were analyzed with a spectrophotometer. The scales used to correlate the quantitative spectrophotometer value and potential irritancy for both ocular and dermal analysis follows.

Table 1. Ocular Irritancy Scale

Ocular Irritection Score	Ocular Irritancy Classification
0.0 – 12.5	Minimal Irritant
12.6 – 30.0	Mild Irritant
30.1 – 51.0	Moderate Irritant
51.1 – 80.0	Severe Irritant

Table 2. Dermal Irritancy Scale

Dermal Irritection Score	Dermal Irritancy Classification
0.0 – 0.90	Non-Irritant
0.91 – 1.20	Mild Irritant
1.21 – 5.00	Irritant

Results:

Ocular Assay:

Lot #	Sample	Dose (µl)	Irritection Score	Ocular Assay Classification
6482	AC Phytocoll	25	5.2	Minimal Irritant
		50	5.5	Minimal Irritant
		75	6.1	Minimal Irritant
		100	6.4	Minimal Irritant
		125	7.2	Minimal Irritant

Dermal Assay:

Lot #	Sample	Dose (µl)	Irritection Score	Dermal Assay Classification
6482	AC Phytocoll	25	0.29	Non-Irritant
		50	0.33	Non-Irritant
		75	0.42	Non-Irritant
		100	0.46	Non-Irritant
		125	0.51	Non-Irritant

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AC Phytocoll Irritation Analysis

Discussion:

Irritation is defined by the American Heritage Dictionary as a condition of inflammation, soreness or irritability of a bodily organ or part. Physical irritation is usually characterized with erythemia, dry flakey skin and watery eyes. Both the dermal and ocular assays reveal that **AC Phytocoll** is non-irritating and should not cause any of the aforementioned conditions. Although the Irritection® scores vary per dose, all the scores fall within the non-irritant range for the dermal assay, and the minimal irritant range for the ocular assay.

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: December 15, 2021

SUBJECT: Yeast Extract

Anonymous. 2021. Yeast Extract (derived from *Saccharomyces cerevisiae*) summary information.

- **Yeast Extract**

Manufacturing Process:

The **yeast (*Saccharomyces cerevisiae*)** is extracted with specified **eluent(s) under appropriate temperature conditions,** to yield a **concentrate**. The concentrate containing the phytochemical constituents is then blended with the desired diluent(s) and preservation system to produce the final ingredient. The ingredient is evaluated for physiochemical properties according to the specification requirements for the batch to be released. In addition, the concentrate is also evaluated for contaminants and physiochemical properties as needed.

Typical eluents include Water, Butylene Glycol, Glycerin, Propylene Glycol, and Carthamus Tinctorius (Safflower) Seed Oil.

Additional information:

- A typical product with the **Yeast Extract** prepared in Glycerin and Water has the following specifications:

Analysis:

	Specification	Range	Actual
	APPEARANCE	Clear to pale yellow liquid	PASS
	MICROBIAL PLATE COUNT	Less than 100 organisms per gram	PASS
	ODOR	Characteristic	PASS
	PH	4.0 - 6.5 at 25° C	4.7
	REFRACTIVE INDEX	1.3920 - 1.5000 at 25° C	1.3981
	SOLUBILITY	Soluble in any proportion in water	PASS
	SPECIFIC GRAVITY	1.05 - 1.15 at 25° C	1.13

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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 7, 2022

SUBJECT: Yeast Extract

Anonymous. 2022. Summary information - Yeast Extracts.

Summary Information - Yeast Extracts

February 2022

INCI name	Genus and species	Manufacturing process	Composition	Impurities	Dermal absorption and toxicological data
Yeast Extract	Candida saitoana belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars: 53% Mineral ashes: 39% Proteins: 7%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	OCDE 428 : Absorption of 1.1% of the total quantity applied to the surface of the epidermis after 24 hours – study made with an emulsion containing 30% of the ingredient Patch test (10 human volunteers): non irritant HRIPT (112 human volunteers): non sensitizing Studies made on the ingredient at 15% in water
Yeast Extract	Debaryomyces nepalensis belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars : 45%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	No data available
Yeast Extract	Metschnikowia reukaufii belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Proteins : 52% Mineral ashes : 38% Sugars : 10%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	OCDE 428 : Absorption of 4.6% of the total quantity applied to the surface of the epidermis after 24 hours - study made with an emulsion containing 30 % of the ingredient Patch test(11 human volunteers): non irritant

					HRIPT (104 human volunteers): non sensitizing Studies made on the ingredient at 15% in water KeratinoSens (OCDE 442D) : no sensitizing potential study made on the ingredient
Yeast Extract	Pichia naganishii belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Proteins : 35%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	No data available
Yeast Extract	Pichia anomala belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars: 58 % Proteins :29% Mineral ashes: 13%	The sum of heavy metals is lower than 15 ppm. [ICP-OES]	OCDE 428 : absorption of 0.41% of the total quantity applied to the surface of the epidermis after 24 hours - study made with an emulsion containing 30% of the ingredient Patch test (10 human volunteers): non irritant HRIPT (104 human volunteers): non sensitizing Studies made on the ingredient at 15% in water
Yeast Extract	Pichia anomala belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and	Proteins: 59% Mineral ashes: 35% Sugars: 6%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	OCDE 428 : Absorption of 0.7% of the total quantity applied to the surface of the epidermis after 24 hours - study

		insoluble phases, filtration and sterile filtration			made with an emulsion containing 30% of the ingredient Patch test (10 human volunteers): non irritant HRIPT(100 human volunteers) : non irritant and non sensitizing Studies made on the ingredient at 15% in water
Yeast Extract	Metschnikowia pulcherrima belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Proteins 30%	The sum of heavy metals is lower than 10 ppm. [ICP-OES]	Patch test (10 human volunteers): non irritant Studies made on the ingredient at 15% in water
Yeast Extract	Candida oleophila belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Proteins : 60%	No data available	No data available
Yeast Extract	Candida magnoliae belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars :53%	The sum of heavy metals is lower than 20 ppm. [ICP-OES]	Patch test (10 human volunteers): non irritant Studies made on the ingredient at 15 % in water

Yeast Extract	Metschnikowia agaves belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars : 54% Mineral ashes : 23% Proteins : 23%	The sum of heavy metals is lower than 20 ppm. [ICP-OES]	OCDE 428 : Absorption of 2.4% of the total quantity applied to the surface of the epidermis after 24 hours - study made with an emulsion containing 30% of the ingredient Patch test (11 human volunteers): non irritant HRIPT (112 human volunteers): non sensitizing Studies made on the ingredient at 15% in water
Yeast Extract	Pichia heedii belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration and sterile filtration	Sugars: 64% Mineral ashes: 26% Proteins: 10%	The sum of heavy metals is lower than 5 ppm. [ICP-OES]	OCDE 428 : Absorption of 0.2% of the total quantity applied to the surface of the epidermis after 24 hours - study made with an emulsion containing 30% of the ingredient Patch test (10 human volunteers): non irritant HRPIT (106 human volunteers): non irritant and non sensitizing Studies made on the ingredient at 15% in water
Yeast Extract	Pichia minuta belongs to the *Saccharomycetes* class	Solubilization of yeast in water, separation of soluble and insoluble phases, filtration	Sugars: 58% Proteins: 28% Mineral ashes: 14%	The sum of heavy metals is lower than 10 ppm. [ICP-OES]	OCDE 428 : Absorption of 0.6% of the total quantity applied to the surface of the epidermis after 24 hours - study made with an emulsion containing 30% of the ingredient

					Patch test (11 human volunteers): non irritant HRPIT (107 human volunteers): non sensitizing Studies made on the ingredient at 15% in water

Remark : The capacity of our cosmetic ingredients to pass through the skin barrier was studied ex vivo after depositing the ingredient on the surface skin according to OECD Guideline No. 428. The quantity of ingredient having penetrated was quantified by assaying fluorescence in the culture medium.