
Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: August 20, 2021
Panel Meeting Date: September 13 – 14, 2021

The 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.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: August 20, 2021
Subject: Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics

Enclosed is the Draft Report of the Safety Assessment of Yeast-Derived Ingredients in Cosmetics (*yeast092021rep*). The following 8 ingredients are reviewed in this report:

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

Because the term “yeast” pertains to a wide variety of species, it is unknown which species are being referred to in cosmetic ingredient manufacturing. Based on the known use Yeast in food products as a fermentation agent, the species *Saccharomyces cerevisiae* was evaluated for the purposes of this report. However, to date, no clarification of the species used in cosmetic products with “Yeast” on the label has been provided. The Panel could choose to cite this lack of clarification as a data insufficiency. Alternatively, the Panel could choose to limit their report conclusion to uses of “Yeast,” wherein the ingredient exclusively comprises *Saccharomyces cerevisiae* (i.e., use of other yeast species would not be covered by this report).

This is the first time the Expert Panel is reviewing this ingredient group. The Scientific Literature Review (SLR) was announced on June 9, 2021. Since the issuing of the SLR, the following unpublished data were received.

- Summary manufacturing and physical/chemical properties data on a *Saccharomyces Cerevisiae* Extract (*yeast092021data1*)
- Manufacturing, physical properties, and heavy metal specifications data on Yeast Extract Beta-Glucan (*yeast092021data2*)
- Manufacturing, composition, and impurities data on several *Saccharomyces Cerevisiae* Extracts (*yeast092021data3*)

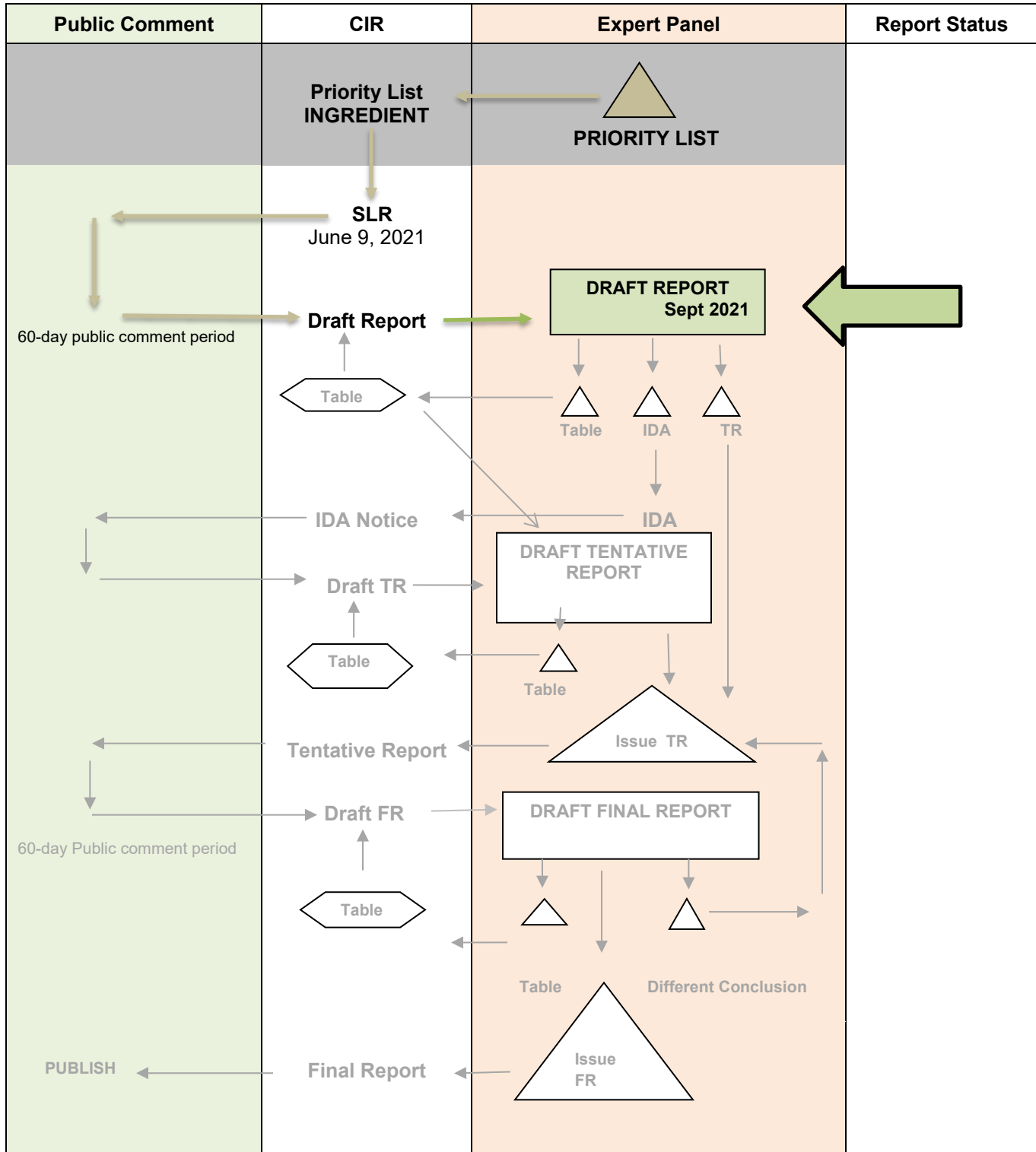
Included in this packet are concentration of use data (*yeast092021data4*), 2021 VCRP frequency of use data (*yeast092021FDA*), a report history (*yeast092021hist*), a data profile (*yeast092021prof*), the search strategy (*yeast092021strat*), and flow chart (*yeast092021flow*). In addition, comments on the SLR were provided from Council (*yeast092021pcpc*), and have been addressed.

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, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Yeast-derived ingredients

MEETING September 2021



Yeast-Derived Ingredients History

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

September 2021

- Expert Panel reviews Draft Report

Yeast-derived ingredients Profile – September 2021 – Writer, Priya Cherian

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

* “X” indicates that data were available in a category for the ingredient

Yeast-Derived Ingredients – September 2021 – Writer, Priva Cherian

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Hydrolyzed Yeast Extract									✓								
Hydrolyzed Yeast		✓							✓								✓
Hydrolyzed Yeast Protein	100684-36-4; 227025-31-2	✓							✓								✓
Yeast	68876-77-7	✓	✓						✓								✓
Yeast Beta-Glucan		✓							✓								✓
Yeast Extract																	
Yeast Polysaccharides		✓							✓								✓
Saccharomyces Cerevisiae Extract	84604-16-0	✓	✓						✓	✓							✓

Search Strategy

- All search terms were used in PubMed and ToxNet
- Genus and species, INCI names, and CAS numbers were searched in the “Pertinent Websites” listed below

Typical Search Terms

- INCI names
- Genus and species name: *Saccharomyces cerevisiae*, *Saccharomyces cerevisiae* extract, *Saccharomyces cerevisiae* beta-glucan, *Saccharomyces cerevisiae* polysaccharides, *Saccharomyces cerevisiae* protein, hydrolyzed *Saccharomyces cerevisiae*
- Baker’s yeast
- CAS numbers
- chemical/technical names
- Search terms:
 - Allergy
 - Sensitization
 - Irritation
 - Metabolism
 - Manufacturing
 - Production
 - Synthesis
 - Fungal
 - Fungemia
 - Dermal
 - Skin
 - Respiratory
 - Reproduction
 - Maternal
 - Dermal penetration
 - Absorption
 - Ocular
 - Eye
 - Clinical
 - Toxicity
 - Carcinogenicity
 - Mutagenicity

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/ingredientpackaginglabeling/gras/default.htm>
- SCOGS database: <http://www.fda.gov/food/ingredientpackaginglabeling/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/opthpv/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

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ABBREVIATIONS

α -MSH	α -melanocyte-stimulating hormone
BAL	bronchoalveolar lavage
B16F10	melanocytes
Caco-2	adenocarcinoma of the colon
CAS	Chemical Abstracts Service
CFR	Code of Federal Regulations
CIR	Cosmetic Ingredient Review
CL	chemiluminescence
Council	Personal Care Products Council
DART	Developmental and Reproductive Toxicity
DLD1	adenocarcinoma of the colon
DPM	disintegrations per minute
<i>Dictionary</i>	<i>International Cosmetic Ingredient Dictionary and Handbook</i>
ECHA	European Chemicals Agency
EP-2	natural yeast extract isolated by ethanol precipitation
FDA	Food and Drug Administration
GRAS	generally recognized as safe
HCC70	non-metastatic breast cancer cell line
HCT116	adenocarcinoma of the colon
HaCaT	human keratinocytes
HeLa	human cervical cancer cells
HSCAS	hydrated sodium calcium aluminosilicate
ICU	intensive care unit
IgA	immunoglobulin A
IgE	immunoglobulin E
IFN	interferon
IgG	immunoglobulin G
IL	interleukin
kDa	kilodaltons
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LD ₅₀	median lethal dose
LDH	lactate dehydrogenase
LLNA	local lymph node assay
MCF-7	human metastatic breast cancer cell line
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide
NOAEL	no-observable-adverse-effect-level
NR	not reported
OECD	Organisation for Economic Cooperation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBS	phosphate-buffered saline
PMN	polymorphonuclear leukocytes
RAST	radioallergosorbent
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
US	United States
VCRP	Voluntary Cosmetic Registration Program
ZR-75-1	human metastatic breast cancer cell line

INTRODUCTION

This assessment reviews the safety of the following 8 ingredients as used in cosmetic formulations:

Hydrolyzed Yeast	Yeast Beta-Glucan
Hydrolyzed Yeast Extract	Yeast Extract
Hydrolyzed Yeast Protein	Yeast Polysaccharides
Yeast	Saccharomyces Cerevisiae 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-conditioning agents – miscellaneous; other reported functions for this ingredient group include hair-conditioning agent, film former, skin protectant, and/or viscosity-increasing agent (Table 1).¹ The functions of Yeast and Saccharomyces Cerevisiae Extract are not reported.

The United States (US) Food and Drug Administration (FDA) has affirmed that *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]. *Saccharomyces cerevisiae* is also considered to be GRAS as a multipurpose additive [21CFR172.896]. In addition, glycan derived from the cell walls of *Saccharomyces cerevisiae* is approved as a direct food additive for human consumption [21CFR172.898]. For the ingredients that are affirmed GRAS, 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 of this safety assessment is topical exposure and local effects.

Because the term “yeast” pertains to a wide variety of species, it is unknown which species are being referred to in cosmetic ingredient manufacturing. Based on the definition of yeast in the *Dictionary*, and its known use in food products as a fermentation agent,² the species *Saccharomyces cerevisiae* was evaluated for the purposes of this report.

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 exhaustive search of the world’s literature. 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 was found on the European Chemicals Agency (ECHA) website.³ 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, 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, 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). Additionally, cosmetic ingredient names, according to the *Dictionary*, are written without italics. If it is not known whether the ingredient being discussed is a cosmetic ingredient, the test substance will be identified using generic terminology (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.

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. All ingredients reviewed in this report are derived from yeast.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.^{4,5} Yeasts are typically nomadic, highly adaptable, and are able to survive in a wide range of conditions. In addition, phenotypic characteristics of yeasts may vary dependent upon environment.⁶ 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.⁷ 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).⁸ ECHA registration dossier information indicate the water solubility of a *Saccharomyces cerevisiae* extract 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).³ Other properties of these yeast-derived ingredients can be found in Table 2.

Method of Manufacture

Saccharomyces Cerevisiae Extract

According to a supplier, *Saccharomyces Cerevisiae* Extract is prepared via an extraction using 1,2-propylene glycol.³ The extract is sterile filtered and combined with 0.35% potassium sorbate and 0.35% sodium benzoate for preservation. According to a different source, *Saccharomyces Cerevisiae* Extract is prepared by first concentrating or spray-drying a solution obtained via yeast autodigestion.⁹ The resulting solution is extracted with purified water, filtrated, 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.

In order to obtain a baker's yeast extract (*Saccharomyces cerevisiae*), dry baker's yeast (50 g) is ground using a mortar, and stirred overnight with water (100 ml).¹⁰ The mixture is then centrifuged for 30 min, filtered, dialyzed, and freeze-dried, ultimately obtaining approximately 1 g baker's yeast extract.

Yeast Beta-Glucan

In order to prepare Yeast Beta-Glucan, the strain of yeast is first selected and cultivated.¹¹ Molasses is used as the medium of cultivation, and is exposed to heat to remove impurities, followed by the addition of nitrogen and phosphorous for sterilization of the compounds. Yeast is developed via fermentation, followed by centrifugation, autolysis, and separation. The remaining substance is subjected to an acid-base treatment, spray-dried, and packaged. According to a different source, Yeast Beta-Glucan is prepared by first extracting the beta-glucan from *Saccharomyces cerevisiae* cell wall with 2% sodium hydroxide for 5 h.¹² The suspension is then cooled and centrifuged for 10 min. The resulting supernatant is neutralized with 2 M acetic acid and treated with 3 volumes of ethanol to precipitate beta-glucan.

Composition and Impurities

Hydrolyzed Yeast

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.¹³

Hydrolyzed Yeast Protein

The following data on a non-hydrolyzed yeast protein concentrate are included for inference purposes. According to a study, a yeast protein concentrate was reported to contain 78% protein, 2.26% ribonucleic acid, 1.13% ash (residual after pyrolysis), 2.65% soluble fiber, 0.49% insoluble fiber, 6.47% total lipids, and 9.10% total carbohydrates.¹⁴ Essential amino acids observed in this concentrate were as follows: lysine (8.78 g/100g protein), leucine (8.62 g/100g protein), isoleucine (5.09 g/100g protein), threonine (4.07 g/100g protein), tryptophan (1.39 g/100g protein), valine (5.91 g/100g protein), methionine-cystine (2.30 g/100g protein), phenylalanine-tyrosine (8.79 g/100g protein), and histidine (2.77 g/100g protein).

Saccharomyces Cerevisiae Extract

According to a supplier, *Saccharomyces Cerevisiae* Extract may not contain more than 20 ppm heavy metals or 2 ppm arsenic.⁹ 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, less than 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.¹⁵ 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.¹⁶ 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, monounsaturated, and polyunsaturated fatty acid composition of whole yeast cells was determined to be 42.71, 28.31, and 28.90% (of total fatty acids), respectively. The specific fatty acids observed can be found in Table 3.

The main classes of lipids observed in *Saccharomyces cerevisiae* extracts were determined to be glycerophospholipids, sphingolipids, sterols, and glycerolipids.¹⁷ 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.¹⁸ The inner layer of the cell wall contains (1 \rightarrow 3) β - and (1 \rightarrow 6) β -linked glucose residues, and chitin. The outer layer of the cell wall is mainly composed of α -mannan and glycoproteins.

Yeast

According to the Food Chemicals Codex, dried yeast (*Saccharomyces cerevisiae*) may not contain more than 1 mg/kg lead.⁷ In addition, dried yeast may not contain more than 8% ash.

Yeast Beta Glucan

According to supplier specifications, Yeast Beta-Glucan must contain $\geq 85\%$ (1 \rightarrow 3)- β /(1 \rightarrow 6)- β -glucan, ≤ 0.2 ppm lead, ≤ 0.2 ppm arsenic, ≤ 0.1 ppm cadmium, and ≤ 0.1 ppm mercury.¹⁹ In order for baker's yeast glycan (derived from dried cell walls of *Saccharomyces cerevisiae*) to meet GRAS specifications for food use, the ingredient must contain, on a dry weight basis, less than 0.4 ppm arsenic, 0.13 ppm cadmium, 0.2 ppm lead, 0.05 ppm mercury, 0.09 ppm selenium, and 10 ppm zinc [21CFR172.898]. According to a study, the cell wall of *Saccharomyces cerevisiae* contains beta-glucans composed of (1 \rightarrow 3) β - and (1 \rightarrow 6) β -linked glucose residues.²⁰

Yeast Polysaccharides

According to biochemical analyses, glucose represents approximately 80 - 90% of the polysaccharides found in the cell walls of *Saccharomyces cerevisiae*.²¹ Other polysaccharide components found in *Saccharomyces cerevisiae* cell walls include *N*-acetyl glucosamine and mannose residues, which represent 1 - 2%, and 10 - 20% of the total polysaccharides, respectively. In a different study, a yeast cell wall preparation was reported to contain 74% glucan and 7% mannan, as determined by a high performance liquid chromatography refractive index detector.²²

USE**Cosmetic**

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US FDA and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2021 VCRP survey data, Yeast Extract is reported to be used in 267 formulations (222 leave-on formulations and 45 rinse-off formulations; Table 4) and *Saccharomyces Cerevisiae* Extract is reported to be used in 74 formulations (73 leave-on formulations and 1 rinse-off formulations).²³ All other ingredients are reported to be used in 70 formulations or less. The results of the concentration of use survey conducted by the Council in 2020 indicate Yeast Polysaccharides has the highest maximum concentration of use in a leave-on formulation; it is used at up to 0.36% in face powders.²⁴

Incidental ingestion of these yeast-derived ingredients may occur due to use in lipsticks and mouthwashes/breath fresheners (e.g., Yeast Extract is used in lipsticks at up to 0.002%). In addition, several of these ingredients may result in incidental eye exposure as they are reported to be used in eye lotion (e.g., Yeast Extract and *Saccharomyces Cerevisiae* Extract at up to 0.15%), eye shadow (e.g., Yeast Beta-Glucan at up to 0.01%), eyeliner (Yeast Extract at up to 0.002%), eye makeup remover (e.g., Yeast Extract at up to 0.0048%), and mascara (Yeast Extract and Yeast Polysaccharides at up to 0.024%) formulations. Mucous membrane exposure may also occur as Yeast Extract is reported to be used in feminine hygiene deodorants at up to 0.038%.

Additionally, some of the yeast-derived ingredients are used in cosmetic sprays and could possibly be inhaled; for example, *Saccharomyces Cerevisiae* Extract is reported to be used in moisturizing spray products at up to 0.045%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $>10 \mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles $<10 \mu\text{m}$ compared with pump sprays.^{25,26} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{27,28} Several ingredients were reported to be used in face powder formulations and could possibly be inhaled, including *Saccharomyces Cerevisiae* Extract (concentration not reported), Yeast Extract (up to 0.021%) and Yeast Polysaccharides (up to 0.36%). Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.²⁹⁻³¹

The yeast-derived ingredients in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.³²

Non-Cosmetic

Yeasts are commonly used worldwide in the food and beverage industry, mainly in baking and alcohol production as a fermentative agent.¹⁴ Inactivated yeast cells are used for animal feed and in over-the-counter nutritional supplements for

humans. According to the US FDA, 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]. In addition, 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 also 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). Specifications required for these GRAS ingredients are described in the Composition and Impurities section of this report.

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Human

Oral

Yeast Beta-Glucan

A soluble branched yeast (1→3)-β-D-glucan derived from *Saccharomyces cerevisiae* was given to 18 healthy volunteers.³³ Groups of 6 individuals received the test substance, in water, in doses of either 100, 200, or 400 mg/d, for 4 consecutive days, followed by a non-treatment, 4-d follow-up period. The test substance was administered as a mouthwash for 2 min and then swallowed. The plasma concentration of (1→3)-β-D-glucan was measured on days 1 (before and 1 h after drug administration), 2, 5, and 8 using a commercial chromogenic assay. The concentration of (1→3)-β-D-glucan in subjects ranged from 0 to 20 pg/ml in plasma before treatment. The amount of (1→3)-β-D-glucan in the plasma never exceeded 20 pg/ml in samples obtained throughout the study. No significant differences between the concentrations on days 5 or 8 and the pre-study value were found. Repeated measurements of (1→3)-β-D-glucan in serum revealed no systemic absorption of the test substance. Data regarding the toxicity analysis performed in this study can be found in the Short-Term Toxicity section of this report.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Saccharomyces Cerevisiae Extract

An acute dermal toxicity assay was performed in Crl:WI (Han) rats (5/sex).³ A *Saccharomyces cerevisiae* extract in water (2000 mg/kg) was applied to an area of 25 cm² in males and 18 cm² in females, under an occlusive patch. After 24 h of application, patches were removed, and animals were observed each day, 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, and the dermal median lethal dose (LD₅₀) was determined to be > 2000 mg/kg bw.

Yeast Polysaccharides

A test article consisting of 90% yeast (*Saccharomyces cerevisiae*) cell wall (containing 24% glucan and 7% mannan) in 10% hydrated sodium calcium aluminosilicate (HSCAS) was evaluated in an acute dermal toxicity assay using Sprague-Dawley albino rats (5/sex/group).²² A 55% dilution of the test article (2000 mg/kg bw; final test concentration of 49.5% yeast cell wall) was applied to a gauze pad and placed on the clipped, dorsal/trunk area of each animal. Pads were then wrapped to avoid dislocation and test substance loss. After the 24-h administration period, animals were observed for the following 14 d. No mortalities or signs or gross toxicity, dermal irritation, adverse pharmacological effects, or abnormal behaviors were noted. The acute dermal LD₅₀ of a 55% dilution of the test article was determined to be > 2000 mg/kg bw.

Oral

Hydrolyzed Yeast

Sprague-Dawley rats (5 rats/sex/group) were orally given a single dose of yeast hydrolysate (5000 mg/kg bw; obtained from *Saccharomyces cerevisiae*).¹³ The method of oral administration was not stated. Control animals were given water only. No signs of toxicity were observed throughout the study.

Yeast Beta-Glucan

A single-dose oral toxicity assay was performed in Fisher 344 rats (5/sex).³⁴ Animals were administered a beta-glucan extract (2000 mg/kg bw) derived from *Saccharomyces cerevisiae*, via gavage. Control animals received water only. Animals were observed for 14 d following treatment. No adverse effects were observed. The LD₅₀ was determined to be > 2000 mg/kg bw.

Yeast Polysaccharides

A test substance consisting of 90% yeast (*Saccharomyces cerevisiae*) cell wall (containing 24% glucan and 7% mannan) in 10% HSCAS was evaluated in an acute oral toxicity assay.²² A 25% dilution of the test substance (2000 mg/kg bw; final

test concentration of 22.5% yeast cell wall) in distilled water was given to Sprague-Dawley albino rats (5 animals/group) via gavage. Animals were observed for 14 d following administration, and necropsied after the 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.

Inhalation

Yeast Polysaccharides

The same test substance as indicated above was also evaluated for acute inhalation toxicity. This assay was performed according to Organisation for Economic Cooperation and Development test guidelines (OECD TG) 403.²² The test substance (undiluted) was ground in a ball mill and aerosolized before administration. Sprague Dawley albino rats (5/sex) were exposed to the aerosolized test substance, in a chamber, for 4 h. The gravimetric and nominal chamber concentrations were 2.09 and 5.81 mg/l, respectively. The mass median aerodynamic diameter was estimated to be 3.75 µm. Animals were observed for 14 d following exposure. Two males and two females exhibited irregular respiration and hypoactive behavior following exposure; however, these animals recovered by day 5. No other adverse effects were noted.

Short-Term Toxicity Studies

Animal

Oral

Hydrolyzed Yeast

A 14-d oral toxicity assay was performed using Sprague-Dawley rats (5 rats/sex/group).¹³ Animals were orally administered either the test substance (1000 mg/kg bw yeast hydrolysate obtained from *Saccharomyces cerevisiae*), or an equal volume of water. The method of oral administration was not stated. A satellite group was treated with the hydrolysate at the same dose, and 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.

Human

Oral

Yeast Beta-Glucan

A soluble branched yeast (1→3)-β-D-glucan derived from *Saccharomyces cerevisiae* was given to 18 healthy volunteers.³³ Groups of 6 individuals received the test substance, in water, in doses of either 100, 200, or 400 mg/d, for 4 consecutive days. The test substance was administered as a mouthwash for 2 min and then swallowed. Seventeen of the 18 volunteers completed the trial (reason for withdrawal was not stated). Abnormalities regarding hematological parameters and vital signs were evaluated. No adverse effects were noted that were attributable to the test substance. Inspection of the oral cavity revealed minor mucosal lesions in 7 subjects; however, these lesions were considered to be unrelated to the test substance. Data regarding the lack of absorption of the test material in blood serum are provided in the Toxicokinetic Studies section of this report.

Subchronic Toxicity Studies

Oral

Yeast Beta-Glucan

Specific pathogen free (SPF) Fischer-344 rats (10/sex/group) were given either 2, 33.3, or 100 mg/kg bw/d of a beta-glucan extract derived from *Saccharomyces cerevisiae*, in water, via gavage, once a day, for 91 d.³⁴ A control group was given water only. No mortality, clinical pathology, functional/behavioral, microscopic, or gross observations indicating toxicity were observed. In addition, no negative effects on animal weights or food consumption were noted. No dose-dependent hematological or biochemical toxicities were observed. A no-observed-adverse-effect level (NOAEL) of 100 mg/kg bw/d was established.

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

In Vitro

Yeast Polysaccharides

The potential genotoxicity of a test substance consisting of 90% yeast (*Saccharomyces cerevisiae*) cell wall (containing 24% glucan and 7% mannan) in 10% HSCAS was evaluated via an Ames assay.²² The test substance was evaluated at

concentrations of 0, 3.4, 10.3, 30.98, 92.6, 277.8, 833.3, and 2500 µg/plate, using *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA102, with and without metabolic activation. The test substance was not considered to be mutagenic.

In Vivo

Yeast Polysaccharides

A mammalian micronucleus test was performed in Swiss ICO OF1 mice according to OECD TG 474.²² Animals were given the same test substance as indicated above (at doses of 500, 1000, and 2000 mg/kg/d), via gavage, once a day, for 2 d. A negative and a positive control group were given 0.5% methylcellulose in purified water and cyclophosphamide in 0.9% saline, respectively. The number of micronucleated polychromatic erythrocytes per animal was determined following treatment. The test substance was not considered to be 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

Treatment with *Saccharomyces cerevisiae* resulted in the growth inhibition or apoptosis of several cancer cell types in multiple anti-carcinogenicity assays.³⁵⁻³⁸ 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). In addition, in an in vivo assay, yeast (1→3)-β-D-glucan (derived from *Saccharomyces cerevisiae*; up to 200 mg/kg) induced cell apoptosis in S180 tumor cells in Kunming SPF male mice.³⁹

OTHER RELEVANT STUDIES

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.

Saccharomyces Cerevisiae Extract

Forty-seven patients with inhalant allergy to fungi were tested for allergic sensitivity to baker's yeast (*Saccharomyces cerevisiae*).¹⁰ 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 (RAST) testing 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.⁴⁰ Skin prick tests were performed in duplicate, and the results were evaluated after 15 min. Serum samples were taken for total serum immunoglobulin E (IgE) determinations. Twenty percent of patients (92 subjects) 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 (*Pityosporum 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.⁴¹ 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 kDa 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.⁴² 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 five yeasts, and the 13-kDa band was shared by four 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* (18 patients had a response) and *Candida albicans* (responses were mainly against the mannans of these species). The corresponding patient numbers in IgA immunoblotting were 17 (*Candida albicans*), 7 (*Saccharomyces cerevisiae*), and 2 (*Cryptococcus albidus*). An IgA response to the 20-kDa band of *Saccharomyces cerevisiae* was observed in 12 subjects.

Yeast Beta-Glucan

The immunomodulatory effect of yeast beta-glucan derived from *Saccharomyces cerevisiae* (strain HII31) was evaluated in BALB/cMlac mice (6/group; sex not specified).⁴³ Animals were orally administered 100, 150, or 200 mg air-dried beta-glucan/kg bw, for 7 d. The method of oral administration was not stated. The control group was left untreated. After the 7-d treatment period, animals were killed, and cytokine levels (interleukin (IL)-6, IL-10, IL-17, interferon gamma (IFN- γ), and transforming growth factor beta (TGF- β)) were determined in the serum via an enzyme-linked immunosorbent assay. Treatment with low-dose beta-glucan (100 and 150 mg/kg bw) induced expression of select pro-inflammatory (IL-17 and IFN- γ) and anti-inflammatory (IL-10) cytokines in a statistically significant manner, compared to controls. High doses of beta-glucan were required to alter the IL-6 and TGF- β expression

The effect of yeast (1 \rightarrow 3)- β /(1 \rightarrow 6)- β -glucan derived from *Saccharomyces cerevisiae* on atopic dermatitis symptoms was evaluated in male ddY mice (10/group) or male Sprague-Dawley rats (10/group) in several assays.⁴⁴ Parameters measured include histamine, IgE, incidences of scratching behavior, and ear thickness. In all assays, atopic dermatitis was induced, and animals were orally treated with 0.2 ml of the test substance, each day, for 7 d. The method of oral administration was not stated. A positive control group consisting of animals with no disease-induction and no treatment, as well as a negative control group with disease induction and no treatment, were also used. Administration of β -1,3/1,6-glucan to atopic dermatitis-induced animals showed a significant reduction in vasodilation in the rat model, compared to the negative control ($p < 0.05$). In addition, pruritus, edema, and histamine were significantly reduced in mouse models ($p < 0.05$), compared to the negative control. The atopic dermatitis-induced negative control rats showed the highest level of serum IgE content, whereas treated groups showed significantly lower levels of IgE ($p < 0.05$).

Pulmonary Toxicity

The following studies are included in this report as they may be helpful in evaluating the inhalation toxicity potential of Yeast Beta-Glucan.

Yeast Beta-Glucan

Sodium hydroxide-soluble and sodium hydroxide-insoluble yeast (1 \rightarrow 3)- β -D-glucan derived from baker's yeast (*Saccharomyces cerevisiae*) were evaluated for acute pulmonary toxicity in male Sprague-Dawley rats (5/group).⁴⁵ Rats were anesthetized and administered an intratracheal instillation of either sodium hydroxide-soluble (1.6 mg/kg bw) or sodium hydroxide-insoluble (1.9 mg/kg bw) yeast (1 \rightarrow 3)- β -D-glucan. Control animals were given phosphate-buffered saline (PBS). Pulmonary responses to the test substance were measured 18 h post-instillation. Parameters measured include serum albumin concentration, lactate dehydrogenase activity (LDH) in acellular bronchoalveolar lavage fluid to evaluate lung damage, lavageable polymorphonuclear leukocytes (PMN) to evaluate inflammation, and breathing frequency increase to evaluate irritation. Oxidant production was evaluated via measuring nitric oxide levels and chemiluminescence (CL). Exposure to the sodium hydroxide-insoluble yeast (1 \rightarrow 3)- β -D-glucan produced a significant increase in all measured parameters, compared to control rats ($p < 0.05$). A statistically significant increase ($p < 0.05$) in LDH, PMN, and CL, were observed in animals treated with sodium hydroxide-soluble yeast (1 \rightarrow 3)- β -D-glucan, compared to control animals. These effects, however, were significantly less than with exposure to sodium hydroxide-insoluble yeast (1 \rightarrow 3)- β -D-glucan.

In a similar study, the same parameters evaluated above were studied using an aqueous suspension of yeast (1 \rightarrow 3)- β -D-glucan in saline derived from baker's yeast (*Saccharomyces cerevisiae*).⁴⁶ Male Sprague-Dawley rats were exposed to yeast (1 \rightarrow 3)- β -D-glucan (0-5 mg/kg bw) via intratracheal instillation. Control animals were instilled with sterile saline only. To evaluate dose-response, one group of animals was killed 1 d after instillation. To evaluate recovery, animals were killed 1, 2, 3, 4, or 7 d following instillation. The number of animals used was not stated. A dose-dependent, statistically significant

increase in all measurement parameters, excluding CL, was observed 1 d following exposure to the test substance, compared to control animals. All measured parameters showed significant recovery by day 7 post-exposure.

Effect on Melanogenesis

The following study is included in this report as it may be helpful in evaluating the potential anti-pigmentation effects of *Saccharomyces Cerevisiae* Extract.

Saccharomyces Cerevisiae Extract

The effect of a natural yeast extract (EP-2) isolated by ethanol precipitation from *Saccharomyces cerevisiae* on melanogenesis was evaluated in an in vitro assay.⁴⁷ To evaluate the melanin synthesis inhibition, B16F10 cells (melanocytes) were exposed to EP-2 (50, 100, and 200 µg/ml) for 72 h. EP-2 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 EP-2 (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 EP-2 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 EP-2 (50, 100, and 500 µg/ml), or the positive control, arbutin. EP-2 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

Details of irritation and sensitization studies summarized below are provided in Table 5.

The irritation potential of a powdered *Saccharomyces cerevisiae* extract (10 mg moistened with 5 µl water) was evaluated in an in vitro assay using a human epidermis model.³ The test substance was considered to be non-irritating following a 15-min exposure and 42-h recovery period. In an assay using 3 male New Zealand albino rabbits, the irritation potential of a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall (24% glucan and 7% mannan) in 10% HSCAS was evaluated.²² The test substance was diluted to 55% in water and applied under semi-occlusive conditions for 4 h. Slight irritation was noted 30 - 60 min after patch removal. In a human irritation assay (n = 28), a cosmetic formulation containing 1% *Saccharomyces cerevisiae* extract was applied to the skin, under an occlusive patch, for 48 h. No significant irritation was noted 15 min or 48 h after patch removal.

Several local lymph node assays (LLNAs) were performed in mice using *Saccharomyces cerevisiae* extract, at concentrations of up to 50%.³ In one assay, the test substance was considered to be sensitizing at concentrations greater than 10%; however, in four other assays performed according to the same procedures, the test substance was considered to be non-sensitizing. In a sensitization assay involving guinea pigs, a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall (24% glucan and 7% mannan) in 10% HSCAS was evaluated.²² The test substance was diluted to 55% in a vehicle of 2% carboxymethylcellulose (final test concentration of 49.5% yeast cell wall) in distilled water, and placed on the skin of guinea pigs, under occlusive conditions, once a week for 3 wk. A challenge patch was applied to a naïve site, under occlusive conditions, 27 d after the first induction dose. The test substance was considered to be non-sensitizing.

OCULAR IRRITATION STUDIES

In Vitro

Saccharomyces Cerevisiae Extract

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).³ 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.

Animal

Saccharomyces Cerevisiae Extract

A powdered *Saccharomyces cerevisiae* extract (59 mg) was placed, undiluted, in one eye of 3 male New Zealand White rabbits.³ 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.

Yeast Polysaccharides

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.²² 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***Saccharomyces Cerevisiae* Extract

A 29-yr-old American woman presented to the hospital with multiple severe anaphylactic reactions induced by food.⁴⁸ 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 25-yr-old woman was admitted to the hospital with a dry cough, low-grade fever, and focal patchy shadow of pulmonary infiltrates.⁴⁹ The patient had no previous history of atopic diseases. Because *Saccharomyces cerevisiae* was detected in patient sputum, eosinophilic 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.

In April of 2003, three patients in an intensive care unit (ICU) were diagnosed with *Saccharomyces cerevisiae*-induced fungemia.⁵⁰ Medical records for the 41 patients that were present in the ICU during this time period were reviewed and evaluated for *Clostridium difficile*-associated diarrhea, and use of a *Saccharomyces boulardii* probiotic. Feces and pharynx surveillance cultures for the patients in the ICU were also performed and were used to detect *Saccharomyces cerevisiae* carriage. Captures of the probiotic were obtained for culture. The three case patients were treated with the probiotic preparation via nasogastric administration prior to presenting with fungemia symptoms. The culture of probiotic capsules revealed heavy growth of a yeast similar to that recovered from the 3 fungemic patients. All yeasts were identified as *Saccharomyces cerevisiae*. No further cases of fungemia were detected after discontinuation of probiotic use in the ICU. According to the literature, *Saccharomyces cerevisiae* is responsible for 0.1 - 3.6% of all episodes of fungemia.

SUMMARY

The safety of 8 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 skin-conditioning agents. Other functions of this ingredient group include hair-conditioning agent, film former, skin protectant, and/or viscosity-increasing agent; the function in cosmetics is not reported for 2 ingredients. *Saccharomyces cerevisiae* is considered to be GRAS as a flavoring agent, adjuvant, and multipurpose additive in foods. In addition, glycan derived from the cell wall of *Saccharomyces cerevisiae* is considered GRAS as a direct food additive for human consumption. The species *Saccharomyces cerevisiae* was chosen for evaluation in this report based on the definition of yeast in the *Dictionary*, and its widespread use in food.

According to 2021 VCRP survey data, Yeast Extract is reported to be used in 267 formulations (222 leave-on formulations; 45 rinse-off formulations). *Saccharomyces Cerevisiae* Extract is reported to be used in 74 total formulations.

All other in-use ingredients are reported to be used in 70 formulations or less. The results of the concentration of use survey conducted by the Council indicate Yeast Polysaccharides has the highest concentration of use in a leave-on formulation; it is used at up to 0.36 in face powders.

The absorption of a soluble branched yeast (1→3)-β-D-glucan derived from *Saccharomyces cerevisiae* was evaluated in 18 healthy volunteers. The test substance was given in water to the subjects in doses of either 100, 200, or 400 mg/d for 4 consecutive days, followed by a 4-d follow-up. The test substance was administered as a mouthwash for 2 min and then swallowed. The amount of yeast (1→3)-β-D-glucan in the plasma never exceeded 20 pg/ml in samples obtained throughout the study. No signs of systemic absorption were observed.

The LD₅₀ in an acute dermal toxicity assay performed in Crl:WI (Han) rats using a *Saccharomyces cerevisiae* extract was determined to be > 2000 mg/kg bw. Similarly, an acute dermal toxicity assay was performed in Sprague-Dawley rats using a test article containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS. The acute dermal LD₅₀ of a 55% dilution of the test article was determined to be > 2000 mg/kg bw. In an acute oral toxicity assay, yeast hydrolysate obtained from *Saccharomyces cerevisiae* was given to Sprague-Dawley rats in a dose of 5000 mg/kg bw. No signs of toxicity were observed. Similarly, no adverse effects were observed when Fischer 344 rats were given a beta-glucan extract derived from *Saccharomyces cerevisiae* (2000 mg/kg bw), via gavage. A 25% dilution of a test substance consisting of 90% yeast (*Saccharomyces cerevisiae*) cell wall and 10% HSCAS (2000 mg/kg bw; final test concentration of 22.5% yeast cell wall) was given to Sprague-Dawley albino rats via gavage. Reversible reduced fecal volume was observed in one female. No adverse effects were noted. The same test substance, undiluted and aerosolized, was evaluated in an acute inhalation toxicity assay using Sprague-Dawley albino rats. Animals were exposed to the test substance for 4 h. Reversible irregular respiration and hypoactive behavior were noted. No other signs of toxicity were observed.

In a short-term toxicity assay, Sprague-Dawley rats were given an oral dose of 1000 mg/kg bw yeast hydrolysate obtained from *Saccharomyces cerevisiae*, each day, for 14 d. The method of oral administration was not stated. No adverse hematological effects, gross abnormalities, or histopathological changes were observed. In a human assay, soluble branched yeast (1→3)-β-D-glucan derived from *Saccharomyces cerevisiae* (up to 400 mg/d) was given to 18 healthy volunteers, each day, for 4 d. The test substance was administered as a mouthwash for 2 min and then swallowed. No test substance-related signs of toxicity were observed. In a subchronic toxicity assay, SPF Fischer 344 rats were given up to 100 mg/kg bw/d of a beta-glucan extract derived from *Saccharomyces cerevisiae*, in water, via gavage, once a day, for 91 d. An NOAEL of 100 mg/kg bw/d was established.

No mutagenicity was observed in an Ames assay performed using a test substance consisting of 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS (up to 2500 µg/plate; performed with and without metabolic activation), on *S. typhimurium* strains TA1535, TA1537, TA98, and TA102. In a mammalian micronucleus assay, Swiss ICO OF1 mice were given the same test substance as indicated above (up to 2000 mg/kg/d), via gavage, once a day, for 2 d. The test substance was not considered to be 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). In addition, in an in vivo assay, yeast (1→3)-β-D-glucan (derived from *Saccharomyces cerevisiae*) induced cell apoptosis in S180 tumor cells in Kunming SPF male mice.

Skin prick tests were performed in 47 individuals with an inhalant allergy to fungi (10 non-allergic subjects 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 for 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, twenty 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 immunomodulatory effect of yeast beta-glucan derived from *Saccharomyces cerevisiae* (strain HII31) was evaluated in BALB/cMlac mice. Mice were orally administered air-dried beta-glucan in doses of up to 200 mg/kg bw, for 7 d. Animals were killed following the treatment period and cytokine levels were observed. Treatment with low-dose beta-glucan (100 and 150 mg/kg bw) induced expression of select pro-inflammatory (IL-17 and IFN- γ) and anti-inflammatory (IL-10) cytokines in a statistically significant manner, compared to controls.

The effect of yeast (1 \rightarrow 3)- β /(1 \rightarrow 6)- β -glucan derived from *Saccharomyces cerevisiae* on atopic dermatitis symptoms was evaluated in male ddY mice or male Sprague-Dawley rats in several assays. Vasodilation, pruritus, edema, and histamine levels were decreased in atopic-dermatitis induced animals following a 7-d oral treatment with the test substance. The atopic dermatitis-induced negative control rats showed the highest level of serum IgE content, whereas treated groups showed significantly lower levels of IgE ($p < 0.05$).

The effect of sodium hydroxide-soluble and sodium hydroxide-insoluble yeast (1 \rightarrow 3)- β -D-glucan derived from baker's yeast (*Saccharomyces cerevisiae*) was evaluated in male Sprague-Dawley rats. Rats were administered an intratracheal instillation of either sodium hydroxide-soluble (1.6 mg/kg bw) or sodium hydroxide-insoluble (1.9 mg/kg bw) yeast (1 \rightarrow 3)- β -D-glucan, and evaluated 18-h post-instillation. Serum albumin concentration, LDH, PMN, breathing frequency, nitric oxide, and CL was evaluated. Exposure to the sodium hydroxide-insoluble yeast (1 \rightarrow 3)- β -D-glucan produced a significant increase in all measured parameters, compared to untreated control rats ($p < 0.05$). Rats exposed to the sodium hydroxide-soluble fraction exhibited a statistically significant increase ($p < 0.05$) in LDH, PMN, and CL, compared to control animals. The same parameters evaluated above were studied using an aqueous suspension of yeast (1 \rightarrow 3)- β -D-glucan saline derived from baker's yeast (*Saccharomyces cerevisiae*) in male Sprague-Dawley rats. A dose-dependent, statistically significant increase in all measurement parameters, excluding CL was observed 1 d following exposure to the test substance, compared to control animals.

The inhibitory effects of a *Saccharomyces cerevisiae* extract on melanogenesis was evaluated in B16F10 cells (melanocytes), alone, at doses of up to 200 μ g/ml, and in melanocytes co-cultured with human keratinocytes, at doses of up to 500 μ g/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 μ g/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.

The irritation potential of a powdered *Saccharomyces cerevisiae* extract (10 mg moistened with 5 μ l water) was evaluated in an in vitro assay using a human epidermis model. The test substance was considered to be non-irritating following a 15-min exposure and 42-h recovery period. In an in vivo assay, a mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS was evaluated in 3 male New Zealand albino rabbits. The test substance was diluted to 55% in water and applied under semi-occlusive conditions for 4 h. Slight irritation was noted 30-60 min after patch removal. In a human irritation assay ($n = 28$), a cosmetic formulation containing 1% *Saccharomyces cerevisiae* extract was applied to the skin, under an occlusive patch, for 48 h. No significant irritation was noted 15 min or 48 h after patch removal.

Several LLNAs were performed in mice using a *Saccharomyces cerevisiae* extract (up to 50%). In one assay, the test substance was considered to be sensitizing at concentrations greater than 10%, however, in four other assays performed according to the same procedures, the test substance was considered to be non-sensitizing. A mixture containing 90% yeast (*Saccharomyces cerevisiae*) cell wall in 10% HSCAS was evaluated for potential sensitization in male Hartley guinea pigs. The test substance was diluted to 55% in a vehicle of 2% carboxymethylcellulose in distilled water (final test concentration of 49.5% yeast cell wall), and placed on the skin of guinea pigs, under occlusive conditions, once a week for 3 wk. A challenge patch was applied to a naïve site, under occlusive conditions, 27 d after the first induction dose. The test substance was considered to be non-sensitizing.

The ocular irritation potential of a powdered *Saccharomyces cerevisiae* extract (750 μ l; 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. 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.

In a case report, a 29-yr-old American 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*). 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. In April 2003, three patients in an ICU presented with *Saccharomyces cerevisiae*-induced fungemia. All three

patients were treated with a nasogastric administration of a *Saccharomyces boulardii* probiotic before presenting with symptoms. Cultures of probiotic capsules revealed heavy growth of *Saccharomyces cerevisiae*, which was also observed in feces and pharynx cultures of patients. No further cases of fungemia were detected after discontinuation of probiotic use in the ICU.

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 assessment¹**

Ingredient (CAS No.)	Definition	Function
Hydrolyzed Yeast	Hydrolyzed Yeast is the hydrolysate of yeast derived by acid, enzyme or other method of hydrolysis.	hair-conditioning agents; skin-conditioning agents - misc
Hydrolyzed Yeast Extract	Hydrolyzed Yeast Extract is the hydrolysate of Yeast Extract derived by acid, enzyme or other method of hydrolysis.	skin-conditioning agents - misc
Hydrolyzed Yeast Protein [100684-36-4; 227025-31-2]	Hydrolyzed Yeast Protein is the hydrolysate of yeast protein derived by acid, enzyme or other method of hydrolysis.	hair-conditioning agents; skin-conditioning agents - misc
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 Beta-Glucan	Yeast Beta-Glucan is a carbohydrate fraction obtained from the hydrolysis of Yeast.	film formers; skin-conditioning agents - misc; viscosity-increasing agents - aq
Yeast Extract [68876-77-7; 8013-01-2]	Yeast Extract is the extract of Yeast.	skin protectants; skin-conditioning agents - misc
Yeast Polysaccharides	Yeast Polysaccharides is the polysaccharide fraction derived from the cell walls of Yeast.	film formers; skin-conditioning agents - misc; viscosity-increasing agents- aq
Saccharomyces Cerevisiae Extract [84604-16-0]	Saccharomyces Cerevisiae Extract is the extract of the yeast cells of <i>Saccharomyces cerevisiae</i> .	not reported

Table 2. Chemical properties of yeast-derived ingredients

Property	Value	Reference
Saccharomyces Cerevisiae Extract		
Physical Form	liquid	8
Color	clear-yellow	8
Odor	faint	8
Density/Specific Gravity (@ 20°C)	1.035 – 1.055	8
Vapor pressure (mmHg @ 105°C)	3.83	3
Refraction Index (RIU (@ 20°C))	1.035 – 1.055	8
Yeast		
Physical Form	powder, granules, or flakes	7
Color	light brown - buff	7
Yeast Beta-Glucan		
Physical Form	powder	19
Color	off-white	19
Odor	characteristic	19
Water Solubility (mg/ml)	1	19

Table 3. Fatty acid composition of whole yeast cells (*Saccharomyces cerevisiae*)¹⁶

Fatty acid	Amount identified (% of total)
caprylic (C8:0)	2.01
capric (C10:0)	0.73
hundeconoic (C11:0)	0.33
lauric (C12:0)	2.03
myristic (C14:0)	0.97
pentadecanoic (C15:0)	0.33
palmitic (C16:0)	24.60
palmitoleic (C16:1 ω7)	5.77
margaric (C17:0)	nd
cis-10-heptadecenoic	nd
stearic (C18:0)	9.03
elaidic (C18:1 ω9T)	0.57
oleic (C18:1 ω9)	22.47
trans-linoleic (C18:2 ω6T)	nd
linoleic (C18:2 ω6)	29.90
α-linolenic (C18:3 ω3α)	0.53
arachidic (C20:0)	5.03
behenic (C22:0)	nd
arachidonic (C20:4 ω6)	nd
eicosapentaenoic (C20:5 ω3)	nd
docosahexaenoic (C20:5 ω3)	nd

nd = not detected

Table 4. 2021 Frequency and concentration of use according to duration and exposure^{23,24}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Hydrolyzed Yeast		Hydrolyzed Yeast Extract		Hydrolyzed Yeast Protein	
Totals*	4	0.00038 – 0.004	22	0.000018 – 0.035	70	0.000038 – 0.19
Duration of Use						
Leave-On	1	0.00038 – 0.004	21	0.00003 – 0.035	60	0.000038 – 0.19
Rinse-Off	3	NR	1	0.000018 – 0.0011	10	0.00025 – 0.005
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	0.0005	2	NR	9	0.0005 – 0.0036
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1 ^a	NR	8 ^a ; 11 ^b	0.00043 – 0.0035 ^a	13 ^a ; 29 ^b	NR
Incidental Inhalation-Powder	NR	0.0005 ^c	11 ^b	0.02 ^c	29 ^b	0.0005 – 0.19 ^c
Dermal Contact	4	0.00038 – 0.004	22	0.00003 – 0.02	68	0.000038 – 0.19
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	0.000035 – 0.035	2	0.00025 – 0.005
Hair-Coloring	NR	NR	NR	0.000018 – 0.000035	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Saccharomyces Cerevisiae Extract		Yeast		Yeast Beta-Glucan	
Totals*	74	0.0001 – 0.3	8	NR	52	0.01
Duration of Use						
Leave-On	73	0.001 – 0.18	6	NR	29	0.01
Rinse Off	1	0.0001 – 0.3	2	NR	23	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	18	0.00083 – 0.15	NR	NR	3	0.01
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	16 ^a ; 30 ^b	0.045; 0.1 ^a	3 ^b	NR	6 ^a ; 19 ^b	NR
Incidental Inhalation-Powder	2; 30 ^b	0.001 – 0.18 ^c	3 ^b	NR	19 ^b	NR
Dermal Contact	72	0.00083 – 0.3	8	NR	52	0.01
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	0.0001 – 0.001	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	2	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Yeast Extract		Yeast Polysaccharides			
Totals*	267	0.0000036 – 0.16	2	0.0001 – 0.36		
Duration of Use						
Leave-On	222	0.0000036 – 0.16	2	0.017 – 0.36		
Rinse Off	45	0.0001 – 0.01	NR	0.0001		
Diluted for (Bath) Use	NR	NR	NR	NR		
Exposure Type						
Eye Area	14	0.001 – 0.15	NR	0.024		
Incidental Ingestion	2	0.00072 – 0.002	NR	NR		
Incidental Inhalation-Spray	2; 78 ^a ; 77 ^b	0.065; 0.00001 – 0.03 ^a ; 0.038 ^b	1 ^a	NR		
Incidental Inhalation-Powder	77 ^b	0.0000036 – 0.021; 0.038 ^b ; 0.0036 – 0.16 ^c	NR	0.36		
Dermal Contact	224	0.0000036 – 0.16	2	0.0001 – 0.36		
Deodorant (underarm)	NR	NR	NR	NR		
Hair - Non-Coloring	40	0.0001 – 0.03	NR	NR		
Hair-Coloring	NR	NR	NR	NR		
Nail	1	NR	NR	NR		
Mucous Membrane	3	0.0007 – 0.038	NR	NR		
Baby Products	NR	NR	NR	NR		

*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.

^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

NR – not reported

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Irritation					
IN VITRO					
Powdered <i>Saccharomyces cerevisiae</i> extract	100%; 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	³
ANIMAL					
Mixture containing 90% yeast (<i>Saccharomyces cerevisiae</i>) 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	²²
HUMAN					
Cosmetic formulation containing 1% <i>Saccharomyces cerevisiae</i> extract	100%	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 hr after patch removal	Slight erythema noted in one volunteer 15 min after patch removal, however, no reaction was noted 48 h after patch removal	⁵¹
Sensitization					
ANIMAL					
<i>Saccharomyces cerevisiae</i> 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.	³
<i>Saccharomyces cerevisiae</i> 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.	³
<i>Saccharomyces cerevisiae</i> 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.	³
<i>Saccharomyces cerevisiae</i> 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.	³
<i>Saccharomyces cerevisiae</i> 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.	³

Table 5. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Mixture containing 90% yeast (<i>Saccharomyces cerevisiae</i>) 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. 27 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	²²

DPM = disintegrations per minute; HSCAS = hydrated sodium calcium aluminosilicate; 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

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2021 FDA VCRP Data – Yeast-derived ingredients**Hydrolyzed Yeast Extract – Total: 22**

Other Eye Makeup Preparations	2
Cleansing	1
Face and Neck (exc shave)	8
Body and Hand (exc shave)	3
Moisturizing	7
Skin Fresheners	1

Hydrolyzed Yeast – Total: 4

Moisturizing	1
Paste Masks (mud packs)	3

Hydrolyzed Yeast Protein – Total: 70

Eye Lotion	6
Other Eye Makeup Preparations	3
Hair Conditioner	1
Other Hair Preparations	1
Aftershave Lotion	1
Other Shaving Preparation Products	1
Cleansing	4
Face and Neck (exc shave)	26
Body and Hand (exc shave)	3
Moisturizing	11
Paste Masks (mud packs)	4
Skin Fresheners	2
Other Skin Care Preps	7

Yeast – Total: 8

Face and Neck (exc shave)	2
Body and Hand (exc shave)	1
Paste Masks (mud packs)	2
Other Skin Care Preps	3

Yeast Beta-Glucan – Total: 52

Other Eye Makeup Preparations	3
Face and Neck (exc shave)	13
Body and Hand (exc shave)	6
Moisturizing	2
Night	4

Paste Masks (mud packs)	23
Other Skin Care Preps	1

Yeast Extract – Total: 267

Eye Shadow	1
Eye Lotion	6
Other Eye Makeup Preparations	7
Hair Conditioner	11
Hair Spray (aerosol fixatives)	2
Shampoos (non-coloring)	9
Tonics, Dressings, and Other Hair Grooming Aids	12
Other Hair Preparations	6
Blushers (all types)	1
Foundations	13
Lipstick	1
Makeup Bases	6
Other Makeup Preparations	3
Other Manicuring Preparations	1
Mouthwashes and Breath Fresheners	1
Bath Soaps and Detergents	1
Shaving Cream	1
Other Shaving Preparation Products	2
Cleansing	12
Face and Neck (exc shave)	58
Body and Hand (exc shave)	19
Moisturizing	46
Night	14
Paste Masks (mud packs)	8
Skin Fresheners	5
Other Skin Care Preps	21

Yeast Polysaccharides – Total: 2

Moisturizing	1
Other Skin Care Preps	1

Saccharomyces Cerevisiae Extract – Total: 74

Eye Lotion	9
Other Eye Makeup Preparations	9
Face Powders	2
Lipstick	2
Makeup Bases	1
Other Makeup Preparations	2
Aftershave Lotion	1
Shaving Cream	1

Face and Neck (exc shave)	28
Body and Hand (exc shave)	2
Moisturizing	14
Night	2
Other Skin Care Preps	1



Memorandum

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

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

DATE: June 25, 2021

SUBJECT: Saccharomyces Cerevisiae Extract

Anonymous. 2021. Summary information Saccharomyces Cerevisiae Extract.

Summary Information - Saccharomyces Cerevisiae Extract

Botanical name: *Saccharomyces cerevisiae*

INCI name (EU/USA): Propylene Glycol 75 – 100 %

Saccharomyces Cerevisiae Extract 10 – 25 %

Parts used: Dried yeast inactive

Plant composition: - Carbohydrates - Proteins - Purines - Acids
- Glutathione - Nucleotides - Nucleosides - Choline
- Methionine - Carnitine - Squalene - Lipoids
- Ferments - Vitamins - Sterins - Inosit

Plant properties: - free radical scavenger - moisturizing - light protective effect
- wound healing - antiphlogistic - smoothing - tonic
- elasticizing - antiseptic - anti-irritant

Manufacturing

Solvent of extraction: 1,2-Propylene glycol

Preservatives: 0.35 % Potassium sorbate

0.35 % Sodium benzoate

Incidental ingredients: 0.1 – 1 % Lactic acid (pH-regulation)

Process: The plant material is extracted at considerate temperatures during a fixed time and sterile filtered at the end of the fabrication.

Analytical Data

Aspect: clear, yellow coloured liquid

Odour: faint odour

pH-value: 4.0 – 5.0

Proof of identity. HPLC

Bacteriological control: max. 100 germs / ml

Refraction index: 1.425 – 1.445 (20°C)

Density: 1.035 – 1.055 (20°C)

Colour number: 2 – 6 (Lovibond)

This is a natural product which can change in colour during age.

Solubility: in water faint cloudy



Memorandum

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

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

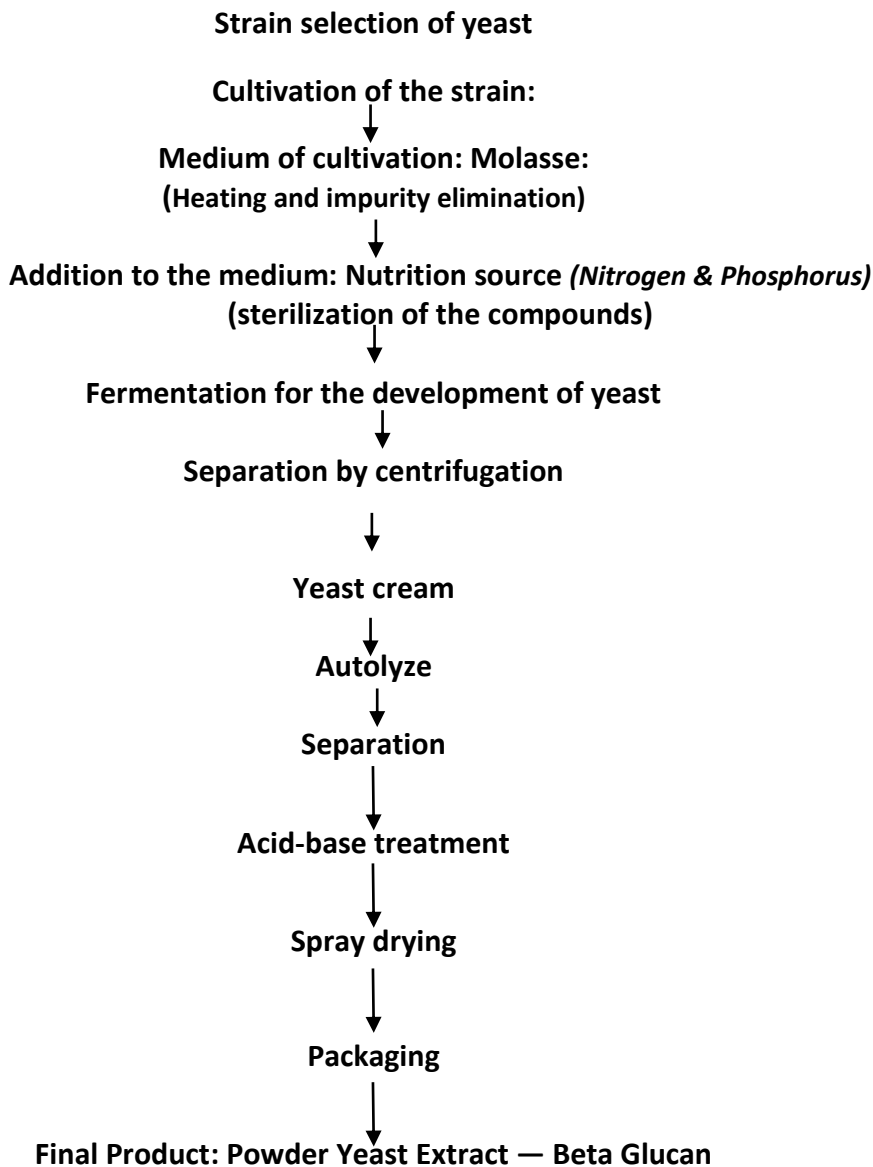
DATE: June 29, 2021

SUBJECT: Yeast Beta-Glucan

Lucas Meyer Cosmetics. 2021. Flow chart water soluble yeast extract-beta-glucan.

Lucas Meyer Cosmetics. 2021. Water soluble yeast extract - Beta Glucan - Specification criteria.

Flow chart Water Soluble Yeast Extract — Beta Glucan



June 02th, 2021

Date

Anne-Valérie CORNET (ex. SERGENT), Ing.
Regulatory Affairs Manager
IFF Lucas Meyer Cosmetics France & Canada

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Water Soluble Yeast Extract — Beta Glucan – SPECIFICATION CRITERIA
SP-WSYE-3

DEFINITION Non-GMO *Saccharomyces cerevisiae* extract, soluble in water
 PRESERVATIVE(S) None
 APPLICATION Cosmetic ingredient
 COUNTRY OF ORIGIN China

ORGANOLEPTIC CHARACTERISTICS	METHODS	SPECIFICATIONS
APPEARANCE	VISUAL	POWDER
COLOUR	VISUAL	OFF-WHITE
ODOUR	OLFACTIVE	CHARACTERISTIC
PHYSICOCHEMICAL CHARACTERISTICS	METHODS	SPECIFICATIONS
SOLUBILITY IN WATER	VISUAL	1 MG/ML
BETA-1,3 / 1,6-GLUCAN CONTENT	QB/T4572-2013	≥ 85%
LOSS ON DRYING	GB 5009.3	≤ 8%
ASH CONTENT	GB 5009.4	≤ 3%
PROTEIN	GB 5009.5	≤ 3.5%
FAT	GB 5009.6	≤ 3.0%
HEAVY METALS	METHODS	SPECIFICATIONS
LEAD	GB 5009.12	≤ 0.2 MG/KG
ARSENIC	GB 5009.11	≤ 0.2 MG/KG
CADMIUM	GB 5009.15	≤ 0.1 MG/KG
MERCURY	GB 5009.17	≤ 0.1 MG/KG
MICROBIOLOGY	METHODS	SPECIFICATIONS
TOTAL PLATE COUNT	GB 4789.2	< 100 CFU/G
YEASTS & MOLDS	GB 4789.15	< 50 CFU/G
<i>E. COLI</i>	GB 4789.38	ABSENCE
<i>S. AUREUS</i>	GB 4789.10	ABSENCE
<i>SALMONELLA</i> SPP.	GB 4789.4	ABSENCE
STORAGE		
Store the containers in a dry place, away from light, keep at room temperature Shelf life : 24 months		

Quality Assurance Manager
 Lucas Meyer Cosmetics Canada Inc.

April 16, 2021

Date

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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: July 21, 2021

SUBJECT: Saccharomyces Cerevisiae Extract

Anonymous. 2021. Saccharomyces Cerevisiae Extract as Yeast Extract, Yeast Extract BG and Yeast Extract BGN.

July 2021

Saccharomyces Cerevisiae Extract as Yeast Extract, Yeast Extract BG and Yeast Extract BGN

1. Clarification on which yeast species are used in cosmetic formulations

Trade name	Yeast species
Yeast Extract	Saccharomyces cerevisiae
Yeast Extract BG	
Yeast Extract BGN	

2. Method of manufacturing data, specific to use of these ingredients in cosmetics

Trade name	The method of manufacture
Yeast Extract	Digested solution obtained by yeast autodigestion ⇒concentration or spray-drying⇒extract with purified water ⇒filtrate⇒evaporate⇒add ethanol⇒sedimentation⇒filtrate ⇒add 50 vol% ethanolic solution⇒packaging
Yeast Extract BG	Digested solution obtained by yeast autodigestion ⇒concentration or spray-drying⇒extract with purified water ⇒filtrate⇒evaporate⇒add 1,3-butylene glycol ⇒sedimentation ⇒filtrate⇒add50 vol% 1,3-butylene glycolic solution⇒packaging
Yeast Extract BGN	

3. Composition and impurities data, specific to use of these ingredients in cosmetics

Trade name	The chemical characterization
Yeast Extract	<Composition> Amino acid and Saccharides < Impurities > Heavy metals: not more than 20ppm Arsenic: not more than 2ppm
Yeast Extract BG	
Yeast Extract BGN	

Concentration of Use by FDA Product Category – Yeast-Derived Ingredients*

Hydrolyzed Yeast Extract
 Hydrolyzed Yeast
 Hydrolyzed Yeast Protein
 Yeast

Yeast Beta-Glucan
 Yeast Extract
 Yeast Polysaccharides
 Saccharomyces Cerevisiae Extract

Ingredient	Product Category	Maximum Concentration of Use
Hydrolyzed Yeast Extract	Hair conditioners	0.0011%
Hydrolyzed Yeast Extract	Shampoos (noncoloring)	0.000035%
Hydrolyzed Yeast Extract	Tonics, dressings, and other hair grooming aids	0.00043-0.0035%
Hydrolyzed Yeast Extract	Other hair preparations (noncoloring)	0.035%
Hydrolyzed Yeast Extract	Hair dyes and colors	0.000018%
Hydrolyzed Yeast Extract	Hair rinses (coloring)	0.000035%
Hydrolyzed Yeast Extract	Face and neck products Not spray	0.02%
Hydrolyzed Yeast Extract	Other skin care preparations	0.00003%
Hydrolyzed Yeast	Eye lotions	0.0005%
Hydrolyzed Yeast	Foundations	0.00038%
Hydrolyzed Yeast	Face and neck products Not spray	0.0005%
Hydrolyzed Yeast	Other skin care preparations	0.004%
Hydrolyzed Yeast Protein	Eye lotions	0.0005-0.0036%
Hydrolyzed Yeast Protein	Hair conditioners	0.005%
Hydrolyzed Yeast Protein	Shampoos (noncoloring)	0.00025%
Hydrolyzed Yeast Protein	Other hair preparations (noncoloring)	0.005%
Hydrolyzed Yeast Protein	Foundations	0.000038%
Hydrolyzed Yeast Protein	Face and neck products Not spray	0.0005-0.12%
Hydrolyzed Yeast Protein	Body and hand products Not spray	0.19%
Hydrolyzed Yeast Protein	Night products Not spray	0.002%
Yeast Beta-Glucan	Eye shadows	0.01%
Yeast Beta-Glucan	Moisturizing products Not spray	0.01%
Yeast Extract	Eyeliners	0.002%
Yeast Extract	Eye shadows	0.001-0.002%
Yeast Extract	Eye lotions	0.038-0.15%
Yeast Extract	Eye makeup removers	0.0048%
Yeast Extract	Mascaras	0.024%
Yeast Extract	Colognes and toilet waters	0.065%
Yeast Extract	Hair conditioners	0.0001%
Yeast Extract	Permanent waves	0.01%
Yeast Extract	Shampoos (noncoloring)	0.002-0.005%

Yeast Extract	Tonics, dressings, and other hair grooming aids	0.009-0.03%
Yeast Extract	Other hair preparations (noncoloring)	0.01%
Yeast Extract	Face powders	0.0000036-0.021%
Yeast Extract	Foundations	0.0014-0.038%
Yeast Extract	Lipstick	0.00072-0.002%
Yeast Extract	Bath soaps and detergents	0.0007%
Yeast Extract	Feminine hygiene deodorants	0.038%
Yeast Extract	Other personal cleanliness products	0.01%
Yeast Extract	Aftershave lotions	0.025%
Yeast Extract	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.0007-0.0036%
Yeast Extract	Face and neck products Not spray	0.0036-0.16%
Yeast Extract	Body and hand products Not spray	0.0074-0.042%
Yeast Extract	Moisturizing products Not spray	0.0002-0.002%
Yeast Extract	Skin fresheners	0.00001-0.0036%
Yeast Extract	Other skin care preparations	0.0036-0.14%
Yeast Polysaccharides	Mascaras	0.024%
Yeast Polysaccharides	Face powders	0.36%
Yeast Polysaccharides	Foundations	0.024%
Yeast Polysaccharides	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.0001%
Yeast Polysaccharides	Other skin care preparations	0.017%
Saccharomyces Cerevisiae Extract	Eye lotions	0.001-0.15%
Saccharomyces Cerevisiae Extract	Eye makeup removers	0.00083%
Saccharomyces Cerevisiae Extract	Hair conditioners	0.001%
Saccharomyces Cerevisiae Extract	Shampoos (noncoloring)	0.0001%
Saccharomyces Cerevisiae Extract	Aftershave lotions	0.025%
Saccharomyces Cerevisiae Extract	Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.3%
Saccharomyces Cerevisiae Extract	Face and neck products Not spray	0.001-0.18%
Saccharomyces Cerevisiae Extract	Body and hand products Not spray	0.01%
Saccharomyces Cerevisiae Extract	Moisturizing products Spray	0.045%
Saccharomyces Cerevisiae Extract	Night products Not spray	0.045%
Saccharomyces Cerevisiae Extract	Skin fresheners	0.1%
Saccharomyces Cerevisiae Extract	Other skin care preparations	0.09%

*Ingredients found in the title of the table but not in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2020; Table prepared: January 5, 2021



Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: July 7, 2021

SUBJECT: Scientific Literature Review: Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics (release date June 9, 2021)

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Yeast-Derived Ingredients as Used in Cosmetics.

Key Issue

Although focusing on *Saccharomyces cerevisiae* is an appropriate approach for this report, it would be helpful if other yeast species used in food were noted in the Introduction or Non-Cosmetic Use section. As many original INCI names came from the food industry, please check the *Food Chemical Codex* to see how it defines yeast and yeast-derived ingredients.

Additional Considerations

Composition and Impurities, Yeast Polysaccharides – N-Acetyl glucosamine and mannose should not be called “other polysaccharides”, they are other components of polysaccharides.

Cosmetic Use; Summary – Please add “%” after “0.36”.

Short-Term Toxicity Studies, Human – Since beta-glucan was not absorbed, it would be helpful to state: “Data regarding the lack of absorption of the test material....”

Anti-Carcinogenicity – It would be helpful to include some indication of the concentrations tested in this section.

Pulmonary Toxicity – It is not clear what is meant by “1→3-β-glucan saline” (perhaps the word “in” is missing before saline).

Dermal Irritation and Sensitization – Please correct “In an assay using in 3 male New Zealand albino rabbits....”

Summary – Please make it clear that the sentence describing the GRAS uses is about use in food.

Summary – “reversible reduced fecal volume” should not be called an “adverse” effect.

Table 4, Irritation, reference 45 – In the Procedure column, rather than stating: “skin irritation noted 15 min after patch removal, and also 48 h after patch removal, if a positive reaction was observed”, it would be clearer to state: “skin was evaluated for irritation 15 min and 48 hr after patch removal”

Table 4, Sensitization, LLNA Procedure – The description of the Procedure should state the radioactive compound injected (probably thymidine in the phosphate-buffered saline).