REPORT FOR THE
INTERNATIONAL COOPERATION ON COSMETICS REGULATION

MICROBIOME AND COSMETICS: SURVEY OF PRODUCTS, INGREDIENTS, TERMINOLOGIES AND REGULATORY APPROACHES [1]

Authors:

Julcemara Oliveira (1); Luciana Machado (1); Ioana Dobre (2); Magdalena Jurkiewicz (2); Georgios-Rizos Manikas (3); Petra Leroy Čadová (3); Ryo Iwase (4); Kenji Ohya (5); Otgonchimeg (Oti) Rentsendorj (6)#; Rinat Bachar (7); Rutie Elgozy (7); Momeena Omarjee (8); Seongjun Yang (9); Sunmi Lee (9); Chao-Hung Hung (10); Chia-Hsuan Lee (10); Meng-Ju Hsu (10); Siripen Charaslertrangsi (11); Ariadne Morais (12); Luciana Vasquez (12); Renata Amaral (12); Beta Montemayor (13); Lisa Harris (13); Colette Shortt (14); Elsa Dietrich (14); Gerald Renner (14); Sylvie Cupferman (14); Silvia Boracchi (15); Nakako Shibagaki (16); Ruka Suzuki (16); Shin Watanabe(16); Tetsuya Kambe (16); Carl Geffken (17); Jay Ansell (18)#; Joyce Lam (18); Nurit Harel (19); Dershana Valla (20); Susun An (21); Chien Yang (22); Wen-Chun Hsieh (22); Preecha Suvanaphen (23).

1. Brazilian Health Regulatory Agency (ANVISA), Brazil
2. Health Canada (HC), Canada
3. European Commission, Directorate-General Internal Market, Industry, Entrepreneurship and SMEs (DG GROW), Europe
4. Ministry Health Welfare and Labor (MHWL), Japan
5. National Institute of Health Sciences (NIHS), Japan
6. US Food and Drug Administration (US FDA), USA
7. Ministry of Health, Israel
8. South African Department of Health, South Africa
9. Ministry Food and Drug Safety (MFDS), South Korea
10. Taiwan Food and Drug Administration (TFDA), Taiwan
11. Thai Food and Drug Administration (Thai FDA), Thailand
12. Brazilian Association of the Cosmetic, Toiletry and Fragrance Industry (ABIPHEC), Brazil
13. Cosmetics Alliance Canada (CA Canada), Canada
14. Cosmetics Europe (CE), Europe
15. European Federation for Cosmetic Ingredients (EFfCI), Europe
16. Japan Cosmetic Industry Association (JCIA), Japan
17. Independent Cosmetic Manufactures and Distributors (ICMAD), USA
18. US Personal Care Products Council (PCPC), USA
19. Israeli Association of Cosmetic Manufacturers, Israel
20. Cosmetic Toiletry and Fragrance Association (CTFA), South Africa
21. Korea Cosmetic Association (KCA), South Korea
22. Taiwan Cosmetic Industry Association (TWCIA), Taiwan
23. Thai Cosmetic Manufacturers Association (TCMA), Thailand

Co-Chairs

[1] ICCR's focus is on cosmetics, the definition of which varies between jurisdictions. Due to these differences in legal definitions, some products that are considered cosmetics in one jurisdiction may be considered quasi-drugs, over-the counter (OTC) drugs or natural health products in another.

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1. SELECTED ABREVIATIONS AND DEFINITIONS

CLP Regulation	Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures
Cosing	European Commission database for information on cosmetic substances and ingredients
GI	Gastrointestinal
HMP	Human Microbiome Project
ICCR	International Cooperation on Cosmetics Regulation
JWG	Joint Regulator – Industry Working Group
NIH	National Institute of Health
REACH Regulation	Regulation (EC) No 1907/2006 on the Registration, Evaluation, Authorisation and Restriction of Chemicals
ToR	Terms of Reference

2. BACKGROUND

During the International Cooperation on Cosmetics Regulation (ICCR) 12th annual meeting (ICCR-12), from July 10-12, 2018, in Tokyo, Japan[2], the topic of cosmetics and the microbiome was discussed. It was agreed that technologies exploring the relationship between the human microbiome and healthy skin was an area of increasing interest, and the safety, quality, regulation, and potential development of international guidelines for products arising from these new concepts would be a worthwhile topic for the ICCR.

To that end, and with the full support of the Industry Associations, the ICCR Steering Committee agreed to create a new Joint Working Group (JWG) on the Microbiome as it relates to Cosmetics.

3. PURPOSE

The Joint Regulator – Industry Working Group (JWG) on the Microbiome was established to explore cosmetics that deliberately influence the human skin microbiome, including technologies and

[2] Meetings - International Cooperation on Cosmetics Regulation (iccr-cosmetics.org)

terminology, and to provide an overview of the current regulatory approaches in each jurisdiction. It is understood that a great number of products, including topical anti-microbials and drug products may affect various microbiomes, but this project will focus on products that are intentionally designed to work within the microbiome of human skin in order to achieve a cosmetic function. It is expected that these findings will increase regulators awareness and inform a path forward in this area.

To that end, the JWG was tasked with the following activities related to cosmetic products having a cosmetic effect on the microbiome:

I. *Survey and describe the terminology (i.e., probiotics, prebiotics, postbiotics, others, etc.)*
II. *Provide a summary of what products and approaches are being advanced within the ICCR jurisdictions.*
III. *Provide an overview of regulatory approaches in each jurisdiction governing cosmetic products.*

4. INTRODUCTION

Studies on the diversity of the human microbiome can be traced as far back as Antonie van Leewenhoek, who, in the early 1680s, compared his oral and fecal microbiota noting the striking differences in microbes between these two and between samples from individuals in different states of health and disease (Ursell *et al,* 2012). Today, more than three centuries later, the human microbiome has become the subject of extensive study. The term “microbiome”, as coined by Joshua Lederberg, signified the ecological community of commensal, symbiotic, and pathogenic microorganisms that share our body space and had been all but ignored as determinants of health and disease (Lederberg and McCray, 2001).

The human microbiome, consisting of the 10–100 trillion symbiotic microbial cells harbored by each person, primarily bacteria in the gastrointestinal (GI) tract, has been the subject of intensive study (Turnbaugh *et al,* 2007). However, this work primarily focused on the GI tract, as well as the use of pro- and pre-biotic ingredients, in food and dietary supplements.

More recently, the study of the microbiome has expanded to address broader aspects of human health. The National Institute of Health (NIH) Common Fund Human Microbiome Project (HMP) was established in 2008, with the mission of generating resources to enable the comprehensive characterization and analysis of the human microbiome by characterizing the microbial communities found at several different sites on the human body: nasal passages, oral cavity, skin, GI tract, and urogenital tract. The project has also been examining the role of the microbiota in human health and disease.

Within the decade, papers studying the effects on human health and disease skyrocketed. In 2016, the Human Microbiome, a new open-access journal, was launched, dedicated to publishing research on the impact of the microbiome on human health and disease (Human Microbiome Journal, 2016). Most studies; however, have focused on the microbiome of our GI tract.

Recently, researchers have turned their attention to other microbiomes, including that of the skin. However, the study of the skin microbiome and its role in the cosmetic realm is still in its infancy. In 2018, the Danish Environmental Protection Agency published the results of a survey of cosmetic products with "probiotic" or "prebiotic" claims, which provided some insight on pro- and pre-biotic cosmetics in Denmark as it relates to their ingredients, product types and market prevalence (The Danish Environmental Protection Agency, 2018).

The work undertaken by the ICCR JWG on the "Microbiome and Cosmetics" aims to build further awareness of the products and approaches advanced in the cosmetics industry which seek to leverage the skin microbiome to deliver a cosmetic effect.

Note: The two terms "microbiome" and "microbiota" are not synonymous (microbiota refers to the wide variety of microorganisms that live in a certain environment, but microbiome refers to the collective genomes of these microorganisms); however, in this report, the two terms were used interchangeably and mean the same thing.

5. RESULTS AND DISCUSSION

5.1 Terminology

In general, there are currently no available international guidelines on definitions or terminologies that are applicable to cosmetic ingredients that deliberatively work to influence the skin's microbiome.

The subject of the microbiome has been extensively studied and reported in the area of nutrition (Mills *et al*, 2019; Gottfried and Patno, 2020). Although some definitions exist at the World Health Organization level, there is still inconsistency in the use or interpretation of common terminology such as probiotics, prebiotics or postbiotics. It is not the intent of this report to enter a debate over the existing terms and definitions used in the scientific literature. However, for reporting consistency, the JWG found it important as part of Task I (and in preparation for Task II) to develop a set of categories and descriptors that could be used to cluster and categorize microbiome-related products, their

ingredients and other relevant approaches, in a cosmetically relevant context. The tasks are described below.

I. Survey and describe the terminology (i.e., probiotics, prebiotics, postbiotics, others, etc.)

II. Provide a summary of what products and approaches are being advanced within the ICCR jurisdictions.

It also became clear that it is premature and potentially uninstructive at this time to conduct an exhaustive survey of all individual products and ingredients available on the market of each participating jurisdiction. As a more useful and reasonable approach to undertake Task II, each jurisdiction was asked to provide illustrative examples of products and/or ingredients that fit within six preliminary categories as listed in Table 1.

The "other" category was included with the intention to capture anything that was missed from the first five categories. A product could be assigned to one or multiple categories depending on its featured ingredients. For example, a product that featured a prebiotic and a postbiotic ingredient, would be captured under two categories.

A reporting template using the six preliminary categories shown in Table 1, was developed and populated by the JWG members. The data supplied by each jurisdiction were gathered, collated, summarized and presented during the quarterly JWG meetings. Following a discussion of the results and reflecting on the survey findings, JWG members agreed to further streamline the initial categories and refine the descriptors when necessary. For example, it was found that the terms paraprobiotic and postbiotic are relatively new and not used consistently in cosmetic product representation.

The "paraprobiotics" have been referred to as "inactivated probiotics" or "ghost probiotics" in scientific literature, implying they are non-viable microorganism (Tsilingiri and Rescigno, 2013; Tsilingiri *et al.,* 2012). However, paraprobiotics may also refer to lysates or microbial fractions of non-viable microbial cells, which can be released upon inactivation through various methods including, but not limited to, thermal treatments, high pressure, ultra-violet rays, irradiation, or sonication (de Almada *et al.,* 2016). To avoid confusion and to address any areas of overlap, paraprobiotics (non-viable probiotic cells, their lysates or fractions) were added to the postbiotic ingredients (non-viable ingredients released by live microorganisms via fermentation processes or released after microbial lysis, such as ferments, extracts, lysates, filtrates, enzymes, peptides, etc.).

TABLE 1. PRELIMINARY PRODUCT / INGREDIENT CATEGORIES AND DESCRIPTORS

CATEGORIES	**DESCRIPTIONS**
Probiotic	Live or dormant micro-organisms (e.g. *Lactobacillus casei*, *Lactobacillus acidophillus*, *Nitrosomonas eutropha,* etc.)
Paraprobiotic (a)	Non-viable probiotic cells (intact or broken) or their crude cell extracts.
Prebiotic	Nutrients for probiotics or natural skin microbiota (e.g. niacinamide, minerals, thermal water, vitamins, oligosaccharides, natural oils, etc.)
Postbiotic	Soluble factors (products or metabolic by-products) secreted by live bacteria or released after bacterial lysis (e.g. *Bifida* ferment lysate, *Lactococcus* ferment lysate, *Bacillus coagulans* ferment, etc.)
Microbiome Friendly (or microbiota-friendly)	Does not interfere with the skin microbiome
Other	Not captured by the above groupings (e.g. microbiome-activated, or activated by skin microbiota, etc.)

(a) paraprobiotic subsequently combined with postbiotic category (see text)

As a revised approach, all surveyed product and ingredients were subsequently divided into two main categories based on viability: viable (live or dormant) – encompassing only probiotics (based on biological origin), and non-viable ingredients. The non-viable ingredients were further divided into two sub-categories: prebiotic (by their intended action on the skin microbiota) and postbiotic (based on their biological origin). It is acknowledged that the sub-categorization of ingredients combines principles of biological function and biological origin, which may create areas of overlap e.g. an ingredient classified as postbiotic based on its biological origin may also be classified as prebiotic based on the function it is claimed to have in a cosmetic product. In a limited number of cases, ingredients that did not fit within any of these categories and sub-categories were included under “Other”. The “Other” category was also used to capture other microbiome-related approaches that did not involve the use of pre-, pro- or post-biotic ingredients (microbiome-activated, or activated by skin microbiota, etc.).

The finalized consensus descriptors reached by the entire JWG for the purpose of the survey is presented in Table 2. A re-assessment of the survey results was conducted based on these revised categories and their descriptors.

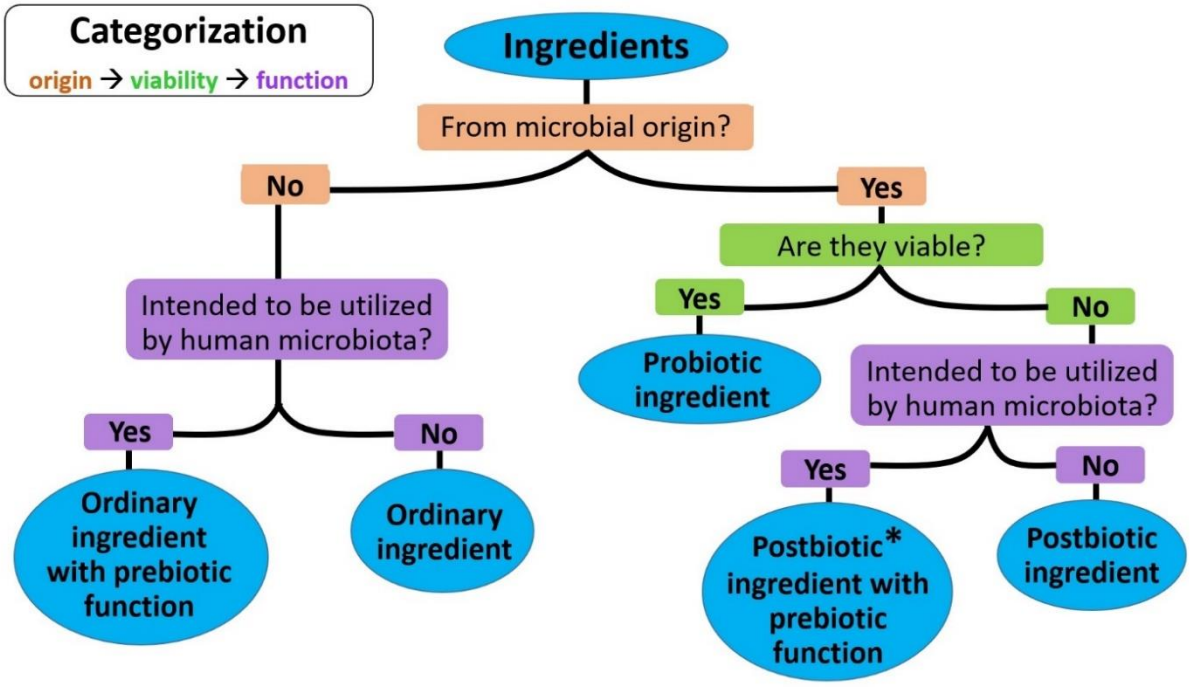
TABLE 2. REVISED PRODUCT / INGREDIENT CATEGORIES AND DESCRIPTORS

CATEGORIES	SUB CATEGORIES	DESCRIPTIONS
Viable Ingredients	Probiotic	Viable (live or dormant) microorganisms added to a cosmetic product in order to achieve a cosmetic benefit at the application site, either directly or via an effect on existing microbiota.
Non-Viable Ingredients	Prebiotic	Non-viable ingredients added to a cosmetic product with the intention of being actively used as nutrients by the microbiota of the application site in order to achieve a cosmetic benefit.
	Postbiotic	Non-viable ingredients comprised of inactivated microorganisms and/or soluble factors (products or metabolic by-products) released by live or inactivated microorganisms, added to a cosmetic product in order to achieve a cosmetic benefit at the application site, either directly or via an effect on the existing microbiota.
Other	Other	Not captured by the prebiotic, postbiotic and probiotic sub-groupings.

The JWG recognizes the survey was not an exhaustive data collection exercise and only reflects a narrow snapshot of microbiome products/ingredients available on the market internationally. Furthermore, the proposed descriptors for each category are not intended to set new definitions, but rather they were created for purposes of data gathering and reporting of the available microbiome-related products and approaches that exist at this time.

The reader is reminded that due to using cartesian or conceptual approaches in data collection and categorization (Table 2), some products/ingredients may belong to multiple sub-categories as a result of their biological nature (origin), viability, functions, or intended actions on the local microbiota. For example, postbiotic ingredients, especially byproducts of fermentation can also be prebiotics based on their alleged “nurturing” action on the skin microbiota (see Figure 1). Another example is paraprobiotics (“ghost” or “inactivated” probiotics) in cosmetics which eventually break down and release their intra-cellular content into the product. In that case, paraprobiotics may also offer prebiotic benefits to the host. Figure 1 shows a schematic description of how cosmetic ingredients were categorized by their biological origin, viability, and function.

FIGURE 1. A SCHEMATIC DESCRIPTION OF THE INGREDIENT CATEGORIZATION



* Note: If the ingredient is intended to be utilized by the skin microbiota, its function is "prebiotic".

5.2. Ingredients and Product Types

A summary of the survey results including descriptors' information, associated ingredients and products are presented below in sections 5.2.1 – 5.2.4. Ingredient types (e.g. pro-, pre-, and post-biotics) were further categorized in all sections to the extent it was possible.

5.2.1. Viable Ingredients - Probiotics

Description: Viable (live or dormant) microorganisms added to a cosmetic product in order to achieve a cosmetic benefit at the application site, either directly or via an effect on existing microbiota.

Viable probiotics appeared to account for the smallest portion of surveyed products. Products containing the descriptions "viable," "live," "active," or "probiotic" were assigned to this group. The assessment of viability relied largely on how the ingredient was represented in the context of the product. In the absence of further validation to confirm viability, it is possible that some non-viable ingredients were misrepresented as "probiotics" in the products' description.

Types of Probiotic Ingredients: There are three types of probiotic ingredients or approaches currently being used in cosmetics based on the observed survey responses:

- **Probiotics** (viable or likely viable): Survey data show a number of microorganisms and their identities mostly at the genus level (see Table 3).
- **Proprietary mixtures** (viable or likely viable): For example, Triclyst®, Lactospore®, Microbiotic Complex.
- **Undefined microorganism** (viable or likely viable): Yogurt, Yogurt powder.

Note: Strictly based on product description, it is not possible to confirm ingredient viability. In addition, some "probiotic" products are described generically as having "live lactic acid bacteria" or "34 live probiotics" with no further microbial identification or viability counts.

Further, probiotic ingredients (viable or likely viable) captured by the survey were arranged into three classes: lactic acid forming bacteria, non-lactic acid forming bacteria, and yeast (Table 3).

As shown in Table 3, the vast majority of products contain lactic acid forming bacteria, predominantly from genus *Lactobacillus*. Some of these lactic acid forming bacteria are natural inhabitants of the human body (commensal microbiome), primarily found in the GI microbiota. Among non-lactic acid forming bacteria, *Staphylococcus epidermidis* is a natural inhabitant of skin and mucosal microbiota.

When portrayed as live microorganisms in the product formulations, yeasts were also captured in the probiotic category of ingredients.

TABLE 3. EXAMPLES OF VIABLE OR LIKELY VIABLE MICROORGANISMS LISTED IN COSMETICS.

GENUS	SPECIES	NOTES
LACTIC ACID FORMING BACTERIA		
Lactobacillus	*L. rhamnosus, L. casei, L. acidophilus, L. bulgaricus, L. plantarum, L. paracasei*	Φ Naturally occurring in GI, urinary tract, oral and vaginal microbiota
Enterococcus	*E. faecium*	Φ Naturally occurring in GI microbiota.
Bifidobacterium	*B. longum*	Φ Naturally occurring in GI microbiota
Lactococcus	Unspecified	Not a natural inhabitant of human GI track. Used in dairy product fermentation.
Leuconostoc	Unspecified	Not a natural inhabitant of human gut. Involved in fermentation of food products (vegetables, dairy).

Bacillus	*B. coagulans*	Not a natural inhabitant of human gut. Used as oral probiotic in human and veterinary applications. Present in some fermented foods.
Pediococcus	*P. acidilactici* *P. pentosaceus*	Not a natural inhabitant of human gut. Found in some fermented foods. Potential use as oral supplement.
Streptococcus	*S. thermophilus*	Not a natural inhabitant of human gut. Found in probiotic supplements and fermented foods
NON-LACTIC ACID FORMING BACTERIA		
Staphylococcus	*S. epidermidis*	Φ Naturally occurring in skin and mucosal microflora.
Nitrosomonas	*N. eutropha*	Naturally occurring in strongly eutrophic env: municipal and industrial sewage disposal systems.
Rhodopseudomonas	*R. palustris*	Naturally occurring. Isolated from swine waste lagoons, earthworm droppings, pond water. Biotech appl: production of specific metabolites (e.g. antioxidants).
YEAST		
Saccharomyces	*S. cerevisiae*	Used in food product fermentation: winemaking, baking, brewing.
Hansenula	Unspecified	Production of biotech products (e.g. recombinant proteins, enzymes, vaccines, biopharmaceuticals.
Kloeckera	Unspecified	Involved in alcoholic fermentation.

ϕ: Commensal microbiome/microbiota.

When described in a nutritional context, probiotics are generally accepted as representing live microorganisms with health benefits (FAO/WHO, 2001). In agreement with this description, the microbial component in our surveyed products should be live or viable in order to align with the "probiotic" concept. In many cases, the identity of microorganisms was listed only at the genus level, considering different bacterial species of the same genus, or strains of the same species may show opposite biological functions (see *Lactobacillus, Leuconostoc, Hansenula,* or *Kloeckera* in Table 3).

Although "viable" or "likely viable" microorganisms in our survey were captured under the umbrella of "probiotics", it does not imply that the ICCR's Microbiome Cosmetics JWG members confirm that these microorganisms listed in Table 3 are in fact probiotics.

Types of Products and Associated Probiotics: Probiotic ingredients of known or unknown species were listed in different types of products, primarily in skin care leave-on products followed by oral care, skin care rinse-off products, and antiperspirants/deodorants (Table 4). According to product representations, the probiotics were viable, however, the actual viability is unknown in all cases as no additional verification was conducted. Furthermore, several products claimed to contain probiotics but as proprietary "microbiotic complexes".

TABLE 4. EXAMPLES OF PRODUCT TYPES VERSUS PROBIOTIC INGREDIENT TYPES.

PRODUCT TYPES	PROBIOTIC INGREDIENT TYPES
Skin Care- Moisturizers • Face & Body Cream • Face Serum • Face Mask • Body Lotion	**Known species:** *Lactobacillus (*e.g. *casei, paracasei), Bifidobacterium longum, Enterococcus faecium* **Known genus:** *Lactobacillus, Leuconostoc, Hansenula,* or *Kloeckera* **Undefined microorganisms:** Yogurt, yogurt powder, live kefir etc. **Note:** Viability determination was not performed during this study.
Oral Care • Toothpaste	
Skin Care- Cleansers • Hand/body wash • Intimate wash	
Hair Care • Shampoo	
Antiperspirant/Deodorant	

Note: Product types listed in the order of predominance.

Microorganisms, in general, require favorable conditions to survive, such as specific nutritional media, suitable temperature, pH, water activity, oxygen content, among others. While kefir, yogurt, and fermented milk are the well-known vehicles for probiotics, their survival in cosmetics may be technically challenging. In addition to the formulation, product manufacturing and storage conditions may also impact the stability and viability of the probiotics.

5.2.2. Non-Viable Ingredients - Prebiotics

The term "prebiotic" was first coined as non-digestible food ingredients for "beneficial" microbes (Gibson and Roberfroid, 1995). The notion of "beneficial" microbes was understood as encouraging certain microbes over others. Consistent with the original embodiment of prebiotics, but aware of the latest scientific and clinical developments, the International Scientific Association for Probiotics and

Prebiotics (ISAPP) expert panel recently updated the definition of a prebiotic as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (Gibson *et al.* 2017).

For survey purposes, the ICCR Microbiome Cosmetics JWG experts developed a different descriptor for prebiotics, to better reflect the cosmetics category. Again, it is important to highlight here that the description, developed by the JWG for "prebiotic" is by no means to be used or cited as a "definition." The prebiotic descriptor was developed to serve ONLY for ICCR 2019 survey purposes.

Description: Prebiotics are non-viable ingredients added to a cosmetic product with the intention of being actively used as nutrients by the microbiota of the application site in order to achieve a cosmetic benefit.

In essence, prebiotics, postbiotics, and probiotics may work together to help keep the microbiome healthy and balanced. With probiotic skin care products rising on the market, prebiotic products also seem to be emerging as a new trend. Our survey spreadsheet for the prebiotic products/ingredients was returned with a high number of product entries.

Types of Prebiotic Ingredients: The list of individual prebiotic ingredients gathered was vast; therefore, they were further grouped into several different types:

- **Carbohydrates:** Alpha-glucan oligosaccharide, Fructooligosaccharides, Fructose, Inulin, Fiber, Beta-glucans, Maltodextrin, Mannose, Inositol, Galactoarabinan
- **Plant- or Algae-derived ingredients:** Avena sativa (oat) kernel extract/flour/oil, Viola tricolor (pancy plant) extract, Cocos nucifera (coconut tree) extract, Salvia hispanica (chia) extract, Allantoin, Polymnia sonchifolia (yacón daisy) root juice, Cyathea Cumingii (fern) leaf extract, Morinda citrifolia callus (noni) culture lysate, Chlorella vulgaris extract, Parachlorella beijerinckii exopolysaccharides (alguronic acid), Kappaphycus Alvarezii Extract, etc.
- **Vitamins or pro-vitamins:** Tocopherol, Niacinamide, Panthenol
- **Postbiotic derivatives:** Teflose®, Ectoin, *Saccharomyces*/rice ferment filtrate, *Pseudoalteromonas* exopolysaccharides
- **Amino acids and peptide derivatives:** Hydrolyzed yeast protein, Glutamic acid
- **Organic acids:** Lactic acid, Citric acid
- **Minerals and metals:** Selenium, Oligo-elements, Strontium

Note: The above categories/groups within the "prebiotics" ingredients were created using cartesian or conceptual approach for the sake of comprehension.

While carbohydrates can also be derived from plants or algae, a few carbohydrates such as mannose or beta-glucan may be of microbial origin. In summary, survey results show that most prebiotic ingredients used in cosmetics are derived from plants, but some are synthesized by microorganisms.

Some prebiotic ingredients were also considered postbiotics based on their biological origin. For example, Teflose® is a byproduct of bacterial fermentation.

TABLE 5. EXAMPLES OF PRODUCT TYPES VERSUS PREBIOTIC INGREDIENT TYPES.

PRODUCT TYPES	PREBIOTIC INGREDIENT TYPES
Skin Care - Moisturizers • Face & Body Cream • Face Serum • Face Mask • Body Lotion	**All** categories of prebiotic ingredients
Skin Cleansers • Make-up Remover • Facial & Body Wash • Feminine Wash/Wipe	Mostly **Carbohydrates** and **Plant** or **Algae derived ingredients**
Hair Care • Shampoo • Hair Mask	Mostly **Carbohydrates**, **Vitamins** and some **Postbiotic derivatives**
Antiperspirant/Deodorant	**Carbohydrates**

Note: Product types listed in the order of predominance.

Types of Products and Associated Prebiotic Ingredients: Prebiotic ingredients were listed in different types of products, primarily in skin care leave-on products followed by rinse-off products (skin cleansers and hair care), and antiperspirant/deodorant (Table 5).

As shown in Table 5, carbohydrates seem to be the most abundant type of prebiotic ingredient across all types of cosmetic products.

5.2.3. Non-Viable Ingredients - Postbiotics

Postbiotic products/ingredients belong to the non-viable category. Based on their biological origin, postbiotic ingredients (ferments, extracts, lysates, filtrates) were merged with paraprobiotics (inactivated probiotics or ghost probiotics), under a revised, consolidated description. Therefore, for the purposes of the Task II survey, postbiotics ingredients were described as follows:

Description: Non-viable ingredients comprised of inactivated microorganisms and/or soluble factors (products or metabolic by-products) released by live or inactivated microorganisms, added to a cosmetic product in order to achieve a cosmetic benefit at the application site, either directly or via an effect on the existing microbiota.

It became apparent from the survey results that terms such as "postbiotic" or "paraprobiotic" are relatively new and not widely used in cosmetic product representation. Our ICCR product survey from the Japanese jurisdiction contained numerous cosmetic products that fit within this product category of postbiotic or paraprobiotic, namely sheet masks, creams, lotion and makeup base using "laflora EC-12" (*Enterococcus*) in their product descriptions.

In cosmetics, postbiotics may be an alternative to the use of whole microorganisms in probiotic form.

Types of Postbiotic Ingredients: The survey results for postbiotic products/ingredients came back with the highest number of product entries. In order to summarize the product entries, postbiotic ingredients were divided in three types:

- **Ferments, lysates, extracts, filtrates** or any combination of these ingredients that are not living but which have been obtained by means of probiotic bacteria (*Bacillus, Bifidobacterium, Lactobacillus, Lactococcus, Vitroscilla, Streptococcus thermophilus, Leuconostoc*) or fungi used primarily as fermentation facilitators (*Saccharomyces, Candida bombicola, Kloeckera, Hansenula-Pichia, Aspergillus*).
- **Non-viable microorganisms** (inactivated/heat-killed), mostly lactic-acid forming bacteria: *Enterococcus faecalis, Lactobacillus* (*paracasei, casei, acidophilus*), *Lactococcus,* or *Vitroscilla filiform.*
- **Metabolic products/by-products (isolated)** including bacteriocin extract, ectoin, succinic acid, lactic acid, hydrolyzed yogurt protein, sodium hyaluronate, and milk proteins.

As was mentioned earlier, in many cases postbiotic ingredients may have been presented on the product as "probiotics".

TABLE 6. EXAMPLES OF PRODUCT TYPES VERSUS POSTBIOTIC INGREDIENT TYPES.

PRODUCT TYPES	POSTBIOTIC INGREDIENT TYPES
Skin Care - Moisturizers • Face & Body Cream • Face Serum, Toner, Mist • Face Mask • Lip Treatment • Body Lotion	**All types** of postbiotic ingredients, but predominantly **ferments / lysates / extracts / filtrates** e.g., *Lactobacillus*/Salix Alba Bark Ferment Filtrate
Skin Care - Cleansers • Face & Body Wash • Scrub/Exfoliator • Feminine Wash	
Hair Care • Shampoo • Conditioner/serum • Scrub	**Ferments / lysates / extracts / filtrates** (e.g. *Lactococcus* Ferment Lysate) and **metabolic products / by-products** (e.g. Milk proteins)
Make-up • Primer • Foundation • Mascara	**All types** of postbiotic ingredients, but predominantly **ferments / lysates / extracts / filtrates** (e.g. *Saccharomyces*/Zinc Ferment)
Oral Care • Toothpaste	**Inactivated probiotics** (e.g. *Lactobacillus paracasei* – heat-inactivated) and **metabolic products / by-products** (Bacteriocin extract)
Antiperspirant/Deodorant	**Ferments / lysates / extracts / filtrates:** e.g., *Lactobacillus* Ferment

Note: Product types listed in the order of predominance. Ingredients in bold are also listed in order of predominance.

Likewise, paraprobiotics ingredients may have been captured as probiotics even if these products contained heat-inactivated probiotics. Likewise, freeze dried viable probiotics may have been presented as (non-viable) paraprobiotics. However, since viability was not confirmed as part of this report, no definitive statement can be made.

The "postbiotic" terminology was not used consistently or frequently in these products. Some products contained more than one category of ingredients and/or approaches e.g., combination of all three pro-/pre-/post-biotics ingredients – a novel approach some products market as "multibiotic".

Types of Products and Associated Postbiotic Ingredients:

Postbiotic ingredients were listed primarily in skin care leave-on products followed by rinse-off products (skin cleansers and hair care), make-up, oral care, and antiperspirant/deodorant (Table 6).

Based on the survey results, the most abundant types of postbiotic ingredients across all types of cosmetics were ferments, lysates, extracts, and filtrates except for oral care products. In oral care products, inactivated probiotics (paraprobiotics) and metabolic by-products were predominant.

5.2.4. Other Microbiome-Related Products/Ingredients

Description: Not captured by the prebiotic, postbiotic and probiotic sub-categories.

The ICCR jurisdictions were also instructed to capture "other" products that may have microbiome-related claims, but did not fit the probiotic, prebiotic, or postbiotic descriptions.

The survey results for "other" products/ingredients captured the least number of examples, which were loosely classified in three broad groups:

- **Containing microbiome regulating/balancing/restoring ingredients:** Sébocidine Complex™, Bioflorine®, XO-70®, Rosebay Extract, Bio9™, Zendium™ Lactoferrin, AGE Bright Complex™
- **Formulated without ingredients that may harm the microbiome (microbiome-friendly):** no preservatives, no sodium lauryl sulfate (SLS), no mint, no synthetic ingredients
- **Formula "gentle" to microbiome:** 100% natural ingredients, mild to skin pH, "bound" water

The "regulating", "balancing", "restoring" claims seen with some of these products are attributed to the use of specific ingredients, most of them are proprietary in nature, which allegedly exert a modulating effect on the existing microbiota.

Other types of products/approaches seen in this "catch-all" category suggest that a beneficial effect to the microbiome may not require a specific microbiome-targeting ingredient, but rather a formulation that excludes certain ingredients perceived as negatively interfering with the skin microbiome e.g. "preservatives" or "synthetic" ingredients.

Types of Product and Associated "Other" Ingredients:

Microbiome-associated "other" category of products entered in the survey were dominated by mostly rinse-off products (hair care and skin cleansers), followed by leave-on skin care products (moisturizers) and oral care products (toothpaste) (Table 7).

TABLE 7. EXAMPLES OF PRODUCT TYPES VERSUS "OTHER" INGREDIENTS TYPES.

PRODUCT TYPES	"OTHER" INGREDIENT TYPES
Hair Care • Shampoo • Treatment	Primarily **microbiome regulating / balancing / restoring ingredients** e.g. Rosebay extract, Bioflorine®
Skin Care – Cleansers • Body wash • Intimate Wash	**Formula "gentle" to the microbiome** (100% natural ingredients) and **free of ingredients that may harm the microbiome** (e.g. free of SLS)
Skin Care – Moisturizers • Cream • Serum • Mask • Peel	Primarily **microbiome regulating / balancing / restoring ingredients** (e.g. Sébocidine Complex™, AGE Bright Complex™)
Oral Care • Toothpaste	Primarily **microbiome regulating / balancing / restoring ingredients** (e.g. Zendium™, Bio9™)

Note: Product types listed in the order of predominance.

5.3. Regulatory Approach

The JWG reviewed TASK III (highlighted below) from the Terms of Reference (ToR).

> *Task III. Provide an overview of regulatory approaches in each jurisdiction governing cosmetic products that work with the skin's microbiome to achieve a cosmetic function.*

Further, the JWG agreed that it would be more useful to expand the question to include not only formal regulations but any other requirements that apply to cosmetic products marketed in different jurisdictions. To that end, the question was redrafted and circulated for response to the entire JWG. Furthermore, to facilitate consistent answers across jurisdictions, it was agreed that for Task III, regulator and industry representatives of the same jurisdiction would submit one consolidated response.

> TASK III Survey question: Are there any specific regulations or requirements within your jurisdiction that govern cosmetic products or ingredients intended to work specifically with the

skin's (or mucosal) commensal microbiome? Please describe the regulations or requirements including the basis for these requirements.

Ten responses were received covering all five Steering Committee member jurisdictions (Brazil, Canada, the European Union, Japan, and the United States) and from five observer jurisdictions (Israel, South Africa, South Korea, Taiwan, and Thailand) (details are available in ANNEX I).

In summary, the answers were uniform among the 10 jurisdictions. There were no unique regulations governing cosmetic products or ingredients intended to work specifically with the skin's (or mucosal) commensal microbiome. Rather, such products are subject to the applicable rules and regulations governing cosmetics in each respective jurisdiction, including those covering both safety and product representation (i.e. claims). Several jurisdictions pointed out that while no distinct regulations exist specific to these products there are general quality standard requirements such as microbiological limits which apply to all cosmetic products, including those containing live or viable microorganisms (ANNEX I).

5.4. Summary

- Based on the inputs from the five participating Steering Committee member jurisdictions (Brazil, Canada, the European Union, Japan, and the United States) and five observing jurisdictions (Israel, South Africa, South Korea, Taiwan, and Thailand) more than 300 microbiome-related products or ingredients were identified as representative examples for each proposed category.
- Products captured by the survey are intended to be used in Skin Care; Hair Care; Oral Care; Make-up; and Antiperspirant/Deodorants.
- Products or ingredients identified in the survey were assigned into one or several of the proposed categories: probiotics, prebiotics, postbiotics, and others.
- Probiotics in cosmetics are dominated by lactic acid bacteria (*Lactobacillus*). Viable or likely viable probiotic ingredients appeared to account for a small proportion of the products surveyed. However, an objective determination of viability was not possible based only on the labeling, thus the true prevalence of "live" or "viable" probiotic ingredients in cosmetic is not known at this time.
- The microbiome-related cosmetic products were found to primarily contain non-viable ingredients, namely prebiotics and postbiotics.
- The most common prebiotics are of plant origin, and most are carbohydrates.
- The majority of postbiotic ingredients are ferments, lysates, extracts, or filtrates of lactic acid forming probiotic genera *Lactobacillus* and *Lactococcus*. Postbiotic ingredients are sometimes mis-represented as "probiotics" in the product description.

- Some ingredients may fit into several categories. For example, postbiotics (e.g. ferment or lysate of a microorganism) could function as prebiotics in a product, by providing nutrients to the local microbiota.
- "Other" products/ingredients that did not fit the proposed categories were identified as claiming to have a microbiome regulating, balancing, or restoring function.
- The terms and descriptors used by the JWG are not intended to serve as formal terminology and definitions when discussing microbiome-related technologies and approaches but rather to facilitate the categorization of the available market survey data for purposes of a qualitative analysis.
- The participating jurisdictions in the JWG have no unique regulations governing cosmetic products intended to work on the skin (or mucosal) microbiome. As a common element across all participating jurisdictions, microbiome-related cosmetics products are subject to all the applicable regulations governing cosmetics as a whole.
- While no specific regulations exist that target this emerging class of cosmetic products, specific quality standard requirements and guidelines (e.g. microbiological limits) must be considered with respect to products containing live and viable microorganisms.

6. CONCLUSION

This report highlights that the topic of cosmetics working on the human skin (or mucosal) commensal microbiome to achieve a cosmetic function is evolving rapidly in the marketplace worldwide. As was observed, the cosmetic marketplace has an increasing number of products referring to the skin microbiome. Whilst only skin is referred to in this report, a large group of cosmetic products were identified and covered all relevant cosmetic product application sites.

The report further emphasizes that there is currently a lack of consistent terminology for cosmetic raw materials working with the microbiome. The work accomplished by the JWG has successfully identified and described the types of products, ingredients, and approaches that are most relevant to microbiome-related technologies in the cosmetic realm, thus setting the stage for further research in the areas of terminology and definition development, safety considerations, and potentially others.

A review of the regulatory approaches in the ICCR member and observer jurisdictions demonstrated that there are no unique regulations governing cosmetic products or ingredients intended to work specifically with the skin's (or mucosal) commensal microbiome. The same requirements as those governing other cosmetic products and ingredients apply.

The authors believe that the report prepared by the Microbiome and Cosmetics JWG, namely the survey of products, approaches and terminologies currently being used for cosmetic products that work with the skin's (or mucosal) microbiome will increase regulators awareness and may inform a path forward in this area.

6.1. Recommendations

The JWG recommends that a new ICCR-15 JWG be appointed to continue in Microbiome and Cosmetics.

1. Areas of further work include:
    a. Development of terminology along with working definitions for microbiome-related approaches in the context of cosmetics.
    b. Examination of microbial limits. Cosmetics have clear microbiological limits in terms of count and the presence of specified microorganisms. A JWG should examine if the current microbial limits are appropriate for products containing live or viable microorganisms that are intentionally introduced in cosmetic products and investigate whether additional safety considerations would be appropriate
2. The JWG also recommends considering when to reassess the "microbiome cosmetics" market-products periodically as the field advances.

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8. ANNEX I

Survey question for TASK III: Are there any specific regulations or requirements within your jurisdiction that govern cosmetic products or ingredients intended to work specifically with the skin's (or mucosal) commensal microbiome? Please describe the regulations or requirements including the basis for these requirements.

Responses:

8.1. BRAZIL

There are no specific regulation or requirement related to cosmetic products or ingredients intended to work specifically with the skin's (or mucosal) commensal microbiome.

However, according to Anvisa RDC Resolution N° 07/2015, applies to toiletries, cosmetics and perfumes:

- Toiletries, cosmetics and perfumes are preparations consisting of natural or synthetic substances for external use in human body: skin, hair, nails, lips, external genitals, teeth and mucous membranes of the oral cavity, for the sole or primary purpose of cleaning, perfuming, altering their appearance and/or correcting body odors and either protecting or maintaining them.
- The company responsible for cosmetic products must have data that attests to the quality, safety and efficacy of the products and proof of the respective labeling statements. The company must also ensure that the product does not constitute risk to health when used in accordance with the instructions for use and other measures contained in the product's sales packaging during the valid period of validity. This data must be presented to the Regulatory Authority, whenever requested or during inspections.

8.2. CANADA

There are no regulatory provisions pertaining directly to cosmetic products intended to work with the skin's microbiome, they are subject to the same requirements as other cosmetics. All cosmetics sold in Canada must be safe to use and must meet the requirements of the *Food and Drugs Act* (FDA) and its *Cosmetic Regulations*. Cosmetics are also subject to the requirements of the *Consumer Packaging and Labelling Act* (CPLA) and its Regulations, which include prohibitions on false or misleading representations.

Product Representation

As per section 2 of the FDA, a cosmetic is defined as "any substance or mixture of substances, manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth and includes deodorants and perfumes."

The use of the term ‘probiotic’ on a cosmetic must be consistent with representation as a cosmetic under the definition of the FDA. Any therapeutic claims, which would imply a product modifies body functions or prevents or treats disease, are not allowed on cosmetic products. Therapeutic claims are only allowed on drugs or natural health products, when supported by appropriate evidence.

Given the recent emergence of cosmetic products making references to or implying an influence on the skin microbiome, Health Canada has been evaluating whether products meet the cosmetic definition on a case by case basis. Products that meet the definition of a cosmetic are subject to requirements under the *Cosmetic Regulations*. Products that do not meet the definition of a cosmetic, may be subject to other requirements under the FDA.

Safety and Quality Requirements

It is the responsibility of the manufacturers and/or importers of cosmetic products to ensure that products that enter the Canadian marketplace are safe for the consumer, when used as intended. Specifically, the general prohibition under section 16 of the FDA states that “no person shall sell a cosmetic that has in it any substance that may injure the health of the user.”

In addition, section 18 of the FDA prohibits the acts of manufacturing, preparing, preserving, packaging and storing a cosmetic under unsanitary conditions with the intention of sale. Under the Act, "unsanitary" means: "such conditions or circumstances as might contaminate with dirt or filth, or render injurious to health, a food, drug or cosmetic."

In order to meet these safety and quality requirements, Health Canada encourages all cosmetic manufacturers to adhere to Good Manufacturing Practices (GMPs). More information on GMPs for cosmetics is available here: https://www.canada.ca/en/health-canada/services/consumer-product-safety/cosmetics/regulatory-information/good-manufacturing-practices.html

Furthermore, with regard to microbiological limits, Health Canada encourages all cosmetic manufacturers to meet the limits and use the methods outlined in the International Standards Organization (ISO) Standard on Cosmetics – Microbiology – Microbiological limits, ISO 17516:2014.

8.3. EUROPEAN UNION

There are no specific regulations or requirements in the European Union (EU) that govern cosmetic products or ingredients intended to work specifically with the skin's (or mucosal) commensal microbiome.

The requirements of the EU Cosmetics Regulation (Regulation (EC) No 1223/2009:

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R1223-20191127) apply also to these products and ingredients.

In the EU, REACH and CLP Regulations apply to all substances used as ingredients in these products.

For the case of probiotic ingredients, DIRECTIVE 2000/54/EC applies with regard to the protection of workers from risks related to exposure to biological agents at work.

8.4. JAPAN

There is no specific regulation for microbiome cosmetics in Japan. General cosmetics are controlled under the regulatory schemes including Standards for Cosmetics. Microbiome cosmetics must meet the requirements defined in the Standards for Cosmetics such as "Ingredients of cosmetics, including any impurities contained therein, shall not contain anything that may cause infection or that otherwise makes the use of the cosmetics a potential health hazard."

8.5. USA

There is no specific regulation in place in the U.S. for microbiome cosmetics. However, a microbiome-targeting product that is intended for therapeutic use or claims to affect the structure and function of the body, such as: affect the biodiversity of the skin ecosystem and Cure, mitigate, treat, or prevent diseases, would, by definition be a drug product.

U.S. Food and Drug Administration (FDA) has no official policy on probiotics in cosmetics. Although, cosmetic products are not required to be sterile in the U.S., the FDA's position has been that any topical product that contains live or dormant microorganisms beyond the acceptable limits in the Bacteriological Analytical Manual (BAM) Chapter 23 (https://www.fda.gov/food/laboratory-methods-food/bam-methods-cosmetics) is adulterated. .How the BAM should be applied to cosmetics intended to affect the microbiome is undergoing further discussion. Of note, the Center for Biologics Evaluation and Research (CBER) is currently evaluating products altering the microbiome and making specific

disease and/or structure/function claims as new drugs (https://www.fda.gov/about-fda/center-biologics-evaluation-and-research-cber/cber-product-jurisdiction).

8.6. ISRAEL

The Cosmetic Regulation in Israel is based on pre-marketing registration. Each cosmetic product is checked and licensed before going to the market, as part of the licensing process, we also approve the labels. Due to the complexity and uncertainty that exists in the microbiome in the context of cosmetic products, at this time we do not confirm these claims.

Naturally, when products bearing such marketing claims began to arrive, we began to look into this issue, and even consulted with a number of researchers in this field in Israel. To our understanding, the issue is very problematic to prove, and there is no "gold standard" of "healthy- microbiome" that can be compared and no protocols for this kind of testing exist.

We also expressed concern about whether there is any reason for such claims in cosmetics - for the fear that these are claims that border on a gray area since it may affect the physiological state of the person. Therefore, at this stage, it was decided not to approve such claims in the product label in Israel.

8.7. SOUTH AFRICA

In South Africa the cosmetic industry is currently self-regulated and CTFA assists with providing guidelines based on the EU Cosmetics Regulation (Regulation (EU) No 1223/2009). The Department of Health (DOH) has published Draft Regulations relating to labelling, advertising and composition of cosmetics, R 1469, 22 December 2017 – which requires all cosmetics to comply with the requirements stipulated on GMP; Product composition (ingredients); Labelling; Product safety; Product claims and Post-marketing surveillance.

The draft regulations do not specifically refer to specific product types based on their function, but rather the categories (clause 2.(1))that are identified as cosmetic products in the market that must comply with the definition of a cosmetic (Foodstuffs, Cosmetics and Disinfectants Act, 1972 (Act no. 54 of 1972). Thus, cosmetic products or ingredients intended to work with the skin's (or mucosal) commensal microbiome, will be "regulated" by the draft regulations and CTFA will advise based on the clauses of this draft document. In other words, all aspects of safety, ingredients, labelling and claims etc. must comply with the requirements of current best practice and guidelines that are available for the industry. This is applicable to both locally manufactured products as well as imported products.

The link to the draft regulation referred can be found at:

https://www.gov.za/sites/default/files/gcis_document/201712/41351rg10790gon1469s.pdf

It is important to note that DOH is the custodian of the Medicines Act 101 and therefore controls all types of medicinal products.

The current status for microbiome uses in medicines: Depending on the indication; the concentration level/s and the dosage of microbiomes, a medicine can either be classed as a Category A (Allopathic) medicine or a Category D (Complementary) medicine.

Terminology i.e. probiotic cannot be used on a product unless it is a medicine.

8.8. SOUTH KOREA

There are no specific regulations established or enforced on cosmetic products or their ingredients intended to work with skin. However, there are safety standards regarding microbial limit for cosmetic products on the market according to the Regulations on Cosmetics Safety, and etc. (MFDS Notification). On the other hand, oral care products are managed within a different product category (as quasi drug products), not as cosmetic products microbiome.

Unfortunately, using live micro-organisms in cosmetics is not actually possible in Korea now because there is a regulation on permissible limits of total aerobic microbes in cosmetics. At the current stage, we are investigating Korea's development status of products intended to work with skin microbiome and discussing the need to review the appropriateness of our regulatory frameworks (safety standards, product claim advertisements, etc.).

8.9. TAIWAN

TFDA regulations on cosmetic products that work with the skin's microbiome to achieve a cosmetic function:

1. Regarding cosmetics, must meet the requirements of the "List of Micro-organisms Limits in Cosmetic Products", and *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* cannot be detected.

   The allowable amount of bacterial count is as follows:

   a. Cosmetic Products for infants, around the eyes, and for contact with mucous membranes:

less than 100 CFU/g or CFU/mL

b. Other cosmetic Products: 1000 CFU/g or below CFU/mL

2. The usage of probiotics, prebiotics and postbiotics must comply with the prohibited and restricted in cosmetic products requirements. There should be scientific evidence to determine the safety of the product, may have to refer to relevant international standards and safety assessment of materials approved for use in cosmetics. The contents of the labeling, promotion, and advertisement of cosmetics shall not be deceptive, exaggerated or have medical efficacy.

8.10. THAILAND

There are not specific regulation or requirements. This group of the ingredients can be used as cosmetic ingredients according to general requirements of cosmetic control as stated below.

- They are included in recognized references mainly from Cosing and PCPC.
- The products containing such ingredients are not allowed to explain any claims which are over scope of cosmetic or it can change function of human body.

However, with regards to safety requirements, Thailand has a limit of microbial contamination for cosmetic products according to the regulations.