REPORT FOR THE INTERNATIONAL COOPERATION ON COSMETICS REGULATION

Allergens in Cosmetics and Personal Care Products: Comparison of Jurisdictional Regulatory Approaches

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1. PURPOSE

This report is intended to provide direct comparison of the existing regulatory approaches and can serve as the groundwork for the development of further guidance in this area.

Cosmetic and personal care products placed on the market in the ICCR jurisdictional regions have high standards of safety and quality. Undesirable effects as a result of normal or reasonably foreseeable use of cosmetic products are uncommonly reported, and typically involve mild and reversible skin reactions, such as irritation, redness, itching that are successfully self-managed by the consumer and do not require medical intervention. However, on occasion, allergic reactions can be induced and elicited by ingredients in cosmetic products in a subset of consumers.

A very wide range of chemicals have inherent sensitization potential or are known sensitizers and allergens. Exposure to allergens can occur from many sources in daily life. It is not feasible to totally avoid all potential allergens in cosmetic formulations. As a consequence, the allergy risk of cosmetics and personal care products remains an integral consideration towards the overall safety assessment and management of these products.

At the 6th meeting of ICCR (2012, Rockville, Maryland, USA), it was agreed that a joint working group be established to develop a white paper to assess the current relevant regulatory policies with regard to allergens in cosmetics in the ICCR member jurisdictions.

At the 7th meeting of the ICCR, this commitment was reaffirmed. The Terms of Reference (ToR) of the Working Group specify the task of:

Compiling the present jurisdictional regulatory approaches to manage allergenic ingredients in cosmetic and personal care products (including labeling).

It was understood that each jurisdiction may have different approaches or authorities in managing allergy risks for cosmetic and personal care products. It was also understood that different potential allergens in cosmetic products may present different levels of safety concerns. The deliverable from this effort will be a high-level report, based on the review of jurisdictional risk management approaches for allergenic ingredients in cosmetic and personal care products that could then serve as the groundwork for further guidance in this area.

2. SCOPE

This report describes risk management and regulatory approaches to allergens in cosmetics and personal care products that are in the scope of ICCR and its member jurisdictions, with an emphasis on skin allergens.

It does not attempt to provide an overview of the basic science and epidemiology of allergenicity, since this information has been published abundantly elsewhere in scientific literature (see Supplemental References in section 8.2 - for examples).

It also does not attempt to provide any comprehensive lists of allergens or potential allergens. Any described allergens are provided solely as examples for general comparison of regulatory approaches.

3. DEFINITIONS

Allergen	A substance that is capable of priming the immune system to respond, upon re-exposure, with a systemic or local immune mediated inflammatory reaction that may be mediated by histamines and IgE. Some of these may be known, but new sensitizing ingredients may emerge with broader population exposure.
Allergic Reaction	Allergic reactions are systemic or local systemic immune mediated inflammatory reactions to a substance (allergen), e.g. a particular food or cosmetic ingredient, to which a person or animal has become hypersensitive.
Elicitation	This phase is the later phase of an allergic reaction, in which the response is triggered. It is the result of a re-exposure to the allergens in sensitized individuals. Sensitized individuals are individuals with a prior exposure to the allergenic substance who react with contact or exposure to that substance.
Induction	This is the first phase of an allergic reaction, which primes the immune system for an allergic response to a specific ingredient.
Label	A display of written, printed or graphic matter upon the immediate container.
Labeling	All labels and other written, printed or graphic matter on or accompanying such article. Including labels, inserts, risers, display packs, leaflets, promotional literature or any other written or printed information distributed with a product or in certain jurisdictions as provided on a company's website that correlates with the specific marketed product.
Primary prevention	Risk management measures aiming at preventing the induction of allergy in non-allergic consumers
Secondary prevention	Risk management measures aiming at prevention of eliciting of an allergic reaction in sensitized consumers

4. SELECTED ACRONYMS

ABIHPEC	Brazilian Association of Personal Cosmetics, Toiletry and Fragrance (Associação Brasileira da Indústria de Higiene Pessoal, Perfumaria e Cosméticos)
ANVISA	Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária)
CCTFA	Canadian Cosmetic, Toiletry and Fragrance Association
CFSAN	Center for Food Safety and Nutrition (FDA)
EU	European Union
FDA	Food and Drug Administration (United States)
HC	Health Canada
HWG	hydrolyzed wheat gluten
HWP	hydrolyzed wheat protein
ICCR	International Cooperation on Cosmetics Regulation
IFRA	International Fragrance Association
INCI	International Nomenclature Cosmetic Ingredient (INCI)
JCIA	Japan Cosmetic Industry Association
MHLW/PMDA	Ministry of Health, Labour, and Welfare/Pharmaceuticals and Medical Devices Agency (Japan)
PCPC	Personal Care Products Council
QRA	Quantitative Risk Assessment
WG	Working Group, specifically the ICCR Allergens Working Group

5. RESPONSIBILITIES

This report was drafted by the ICCR Working Group on Allergens, including the following representatives of regulators and industry from the US, Japan, Europe and Canada.

List of organizations and the representatives who are affiliated with that organization:

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6. DISCUSSION

In order to facilitate a side by side comparison of regulation of allergens, the WG agreed to address five specific topics:

a) **Definition of "allergen" applicable for purposes of cosmetics regulation**
b) **Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools**
c) **Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)**
d) **Regulatory provisions and industry self-regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)**
e) **Post market surveillance measures and tools that cover allergic reactions**

An overview of the present jurisdictional regulatory approaches to manage allergenic ingredients and their risks in cosmetic and personal care products in ICCR Regions is presented.

6.1 Brazil

The Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária - Anvisa) is the government body responsible for surveillance of the marketing of cosmetics, toiletry and perfumes in Brazil. Inside the Anvisa structure, General Office of Cosmetics (Gerência-Geral de Cosméticos - GGCOS) deals with issues related to cosmetics and their ingredients.

To guarantee the quality of Cosmetic products, Anvisa works at registration, notification, market inspection and post marketing surveillance. The Agency also creates norms and rules applicable to production processes, techniques, methods and use of those products by consumers.

The ANVISA's Affairs Law for cosmetics place responsibility on the manufacturer and/or importers of cosmetic products to ensure that products that enter the Brazilian marketplace are safe for the consumer, when used as intended (RDC 04/2014).

Cosmetic products must comply with:

- list of preservative which cosmetics products may contain (Resolution - RDC nº 29/2012);
- list of substance that cosmetics products must not contain (Resolution - RDC nº 48/ 2006);
- list of allowed colorants (Resolution - RDC nº 44/ 2012);
- list of substances that cosmetics products must not contain except subject to restrictions and conditions (Resolution - RDC nº 03/2012);
- list of permitted UV filters for cosmetics products (Resolution - RDC nº 47/2006).

These requirements undertake a systematic review of ingredients and a battery of data of international benchmarks, such as European Union Directive, United States of America laws, and technical criteria recognized by the scientific community of Mercosur States Parties (Resolution GMC N° 51/08 e Resolution GMC N.º133/96)

a) Definition of "allergen" applicable for purposes of cosmetics regulation

There is no formal definition of allergen in Brazilian Cosmetic Legislation. The concept of allergens, allergenicity and consequent reactions is inherent to the regulation that states that a cosmetic product should be safe in normal and foreseeable circumstances of use and recognizes that there are some substances known to cause sensitization.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

Cosmetics must be safe for consumers in normal or foreseeable conditions of use. In order to achieve this safety, Brazilian Resolution RDC 03/2012 recognizes that some substances in fragrances and aromas are important allergens. Thus the presence of these substances in the formulation should be indicated in the description of the ingredients in the product labeling (in the list of ingredients or composition) in order to facilitate the identification of these substances by consumers who do not tolerate them. Therefore, these substances must be labeled on the product by the INCI nomenclature when its concentration exceeds: 0.001% in rinse products and 0.01% in rinse-off products. Nowadays, there are 26 substances in this list.

Safety assessments of cosmetic ingredients recommended by the ANVISA guidelines also include OECD criteria for skin sensitization.

These guidelines describe sensitization risk and primary and secondary reactions that may occur. The guidelines also include the conditions for clinical testing for sensitization, which can be performed for cosmetic products.

c) Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)

The industry is responsible for the products on the market. In order to assure safety of ingredients and cosmetics products, the industry carefully selects the ingredients, packaging and conditions of manufacturing practices (GMP).

The ingredients and their concentration are chosen according to their intrinsic features taking into consideration their provenience, MSDS, IFRA recommendations, history of safe use, among other characteristics.

The Safety Evaluation Guidelines published by ANVISA (2nd edition published in 2013) recommends a wide variety of tests in the cosmetic ingredients and also in the final product. All the safety evaluation and tests are performed before the cosmetic is placed on the market.

d) Regulatory provisions and industry self-regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)

Cosmetic labelling should include instructions for safe use of the product by the consumer. When a consumer has already undergone a sensitization process with a specific substance, the consumer should avoid the elicitation process which would create a stronger allergic reaction. The mandatory inclusion in the labelling of the 26 known fragrance allergens is useful to let the

consumer distinguish, before purchasing the cosmetic product, if the substance that the consumer is allergic to is present in the composition.

e) Post market surveillance measures and tools that cover allergic reactions

According to Resolution RDC 332/2005, cosmetic companies in Brazil must implement a Cosmetovigilance system in order to assure that consumers and health professionals are able to report health incidents to these companies. This system should be easy for the consumer to contact.

Industry must keep a database of all the incidents that may be related with the use of cosmetics products, including adverse effects. There is an obligation to investigate the occurrences, including allergic reactions, which might be reported in order to establish causality. Whenever these adverse effects put in risk the consumer health, the companies must notify the authorities.

Brazilian authorities (ANVISA) can restrict the concentration of any ingredient, allergenic or not, and can withdraw the ingredients and cosmetics products that contain them from the market if duly justified.

6.2 Canada

In Canada, cosmetics are regulated under the *Food and Drugs Act* (FDA), its associated *Cosmetic Regulations* and other applicable regulations, as well as the *Consumer Packaging and Labelling Act* and *Competition Act*, and corresponding regulations. The Canadian regulatory framework for cosmetics outlines legislative requirements that place responsibility on the manufacturers and/or importers of cosmetic products to ensure that products that enter the Canadian marketplace are safe for the consumer, when utilized as intended.

a) Definition of "allergen" applicable for purposes of cosmetics regulation

There is no definition of an "allergen" in the *Food and Drugs Act*, nor in the *Cosmetic Regulations* or any other applicable legislation, related to cosmetics.

Although, there is no statutory definition of an "allergen" in this context, section 24 of the *Cosmetic Regulations* requires that the label of a cosmetic product presenting an avoidable hazard includes appropriate direction(s) for safe use. Such cautionary statements could extend to specific direction(s) intended to address potential allergens in cosmetics products.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

The general prohibition (section 16 of the *Food and Drugs Act*) requires that cosmetics be safe and manufactured, prepared, preserved, packaged and stored under sanitary conditions in order to be sold in Canada.

To this end, the *Cosmetic Regulations* outline the requirements for composition, labelling, evidence of safety and product notification. These regulations feature a post-market system whereby cosmetic products are notified to Health Canada within 10 days of their first sale in Canada. These completed Cosmetic Notifications (CN) provide Health Canada with key

information about the product placed on the Canadian marketplace, such as product composition and formulation.

The regulatory framework in Canada reflects a risk-based-approach towards cosmetic ingredient safety and product assessment. Under this framework, manufacturers/importers of cosmetic products are responsible for ensuring that products entering the Canadian marketplace are safe for the consumer, when utilized as intended.

Health Canada maintains the Cosmetic Ingredient Hotlist, which is an administrative tool used to communicate to manufacturers and other stakeholders that certain substances, when present in a cosmetic, may contravene (a) the general prohibition outlined under Section 16 of the *Food and Drugs Act* (as outlined above), or (b) a provision of the *Cosmetic Regulations*. Specifically, this administrative instrument outlines ingredients that are prohibited or restricted in cosmetics, stipulating conditions under which an ingredient may be used.

The Cosmetic Ingredient Hotlist is used to highlight and manage ingredients in cosmetic products that under certain conditions may present a potential risk, including potential allergens. On this basis, ingredients in cosmetic products are evaluated using scientific evidence, to determine if a prohibition or restriction, such as appropriate directions(s) for use, concentration limits, or avoidable hazard labelling, is necessary.

Furthermore, the *Canadian Environmental Protection Act* (CEPA) extends to substances in Canadian commerce, including those that may be found in cosmetics. This legislation outlines specific testing provisions with regards to skin sensitization among many other toxicological endpoints for consideration. It should be noted that the testing provisions as outlined are intended to provide data to support hazard identification (under a risk assessment framework) and therefore make no conclusion as to whether or not a substance presents an allergenicity risk.

c) Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)

Currently, any risks associated with potential allergens in cosmetics are managed through the general prohibition (Section 16) under the Food and Drugs Act, and the regulatory requirement for ingredient labelling in the *Cosmetic Regulations*. As outlined previously, the general prohibition places the onus on the manufacturer/importer to sell cosmetic products that are safe when used as intended. This safety consideration extends to potential allergens in cosmetic products.

The Cosmetic Ingredient Hotlist contains over 500 substances that cannot be used, or whose use is restricted, in cosmetics. It is updated regularly and includes references to ingredients that that present an allergenic risk such as sensitization.

Health Canada regularly monitors the scientific and regulatory literature for any new information on ingredient safety (including sensitization and allergenicity considerations) to make sure that the Hotlist reflects the most up-to-date safety considerations regarding specific ingredients. If the scientific evidence suggests that a cosmetic ingredient presents a risk to

consumers, Health Canada will take measures to mitigate the risk, including appropriate compliance action where appropriate and necessary.

d) Regulatory provisions and industry self-regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)

The *Cosmetic Regulations* require that all intentionally added ingredients be disclosed upon notification of a cosmetic, as well as disclosure on product labels using the INCI naming convention. These mandatory disclosure provisions helps consumers identify and avoid cosmetics containing ingredients to which they may be sensitive.

Under the INCI naming convention, components of a fragrance can be listed as individual ingredients or can be listed under the term "parfum" or "fragrance". Manufacturers and importers are permitted under section 21.4 of the *Cosmetic Regulations* to use the term "parfum" in place of fragrance ingredients that have been added to produce or to mask a particular odor. There are currently more than 3000 fragrance ingredients used to create various fragrance compounds; of these thousands, hundreds could appear in trace amounts in a finished cosmetic product. For this reason, inclusion of all fragrance ingredients in a cosmetic could result in a product label that would be impractically long and illegible.

In addition, section 24 of the *Cosmetic Regulations* requires that an avoidable hazard be labelled to include directions of safe use. An avoidable hazard means a threat of injury to the health of the user of a cosmetic that can be:

(a) Predicted form the cosmetic composition, the toxicology of the ingredients and the site of application
(b) Reasonable anticipated during normal use and
(c) Eliminated by specified limitations on the usage of the cosmetic

Although this regulatory provision has yet to be used to highlight specific hazards regarding the presence of a potential allergen in a cosmetic product; it is a risk management measure that may indeed be used to address any such risk.

e) Post market surveillance measures and tools that cover allergic reactions

Consumers that experience an adverse event following the use of a cosmetic are encouraged to report the incident to Health Canada. These reporting measures include experiences that relate to allergic-type responses. Under the current regulatory framework, such adverse event reporting for cosmetic products is not mandatory.

6.3 European Union

In the European Union, the cosmetic products are regulated by Regulation (EC) No 1223/2009 (hereunder "Cosmetics Regulation").

The purpose of the Cosmetics Regulation is two-fold: providing a high level of protection of human health and ensuring the functioning of the Union's internal market.

Cosmetics products placed on the EU market must be safe, and the manufacturers, importers or, under certain circumstances, the distributors, are responsible for compliance with the Cosmetics Regulation.

a) Definition of "allergen" applicable for purposes of cosmetics regulation

There is no definition of "allergen" for purposes of the Cosmetic.

Classification criteria for skin sensitization exist in the EU Chemical legislation (Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures, based on the WHO GHS criteria). This classification is hazard-based and does not predict whether or not a substance will actually create a consumer risk when used in a specific cosmetic formulation at a specific concentration. However, classification as a sensitizer under chemical legislation does indicate a potential for consumer risk and needs to be taken into account in the mandatory product safety assessment required under the EU Cosmetics legislation.

Allergens become subject to risk management measures in cosmetics (industry driven or regulatory) mainly as a result of pre-market safety assessments, post market surveillance or dermatologicepidemiological studies.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

Cosmetic products have to be safe for the consumer. Skin sensitization is one of the safety endpoints that companies are required to assess in the preparation of the mandatory Cosmetic Product Safety Report. Annex I of the Cosmetics Regulation states:

"… Without prejudice to Article 18, the toxicological profile of substance contained in the cosmetic product for all relevant toxicological endpoints. A particular focus on local toxicity evaluation (skin and eye irritation), skin sensitisation, and in the case of UV absorption photo-induced toxicity shall be made. All significant toxicological routes of absorption shall be considered as well as the systemic effects and margin of safety (MoS) based on a no observed adverse effects level (NOAEL) shall be calculated. The absence of these considerations shall be duly justified." …

Guidelines by the Scientific Committee on Consumers Safety (SCCS) exist on how to assess the safety of cosmetic ingredients with regard to all relevant toxicological endpoints, including skin allergy (SCCS Notes of Guidance[1]). Industry has developed methodologies for quantitative risk assessment (QRA) of skin allergy which are used for instance for fragrance ingredient assessment process by IFRA. As of the date of this report, the QRA method is not formally accepted by SCCS. Industry is in the process of improving it.

Member States competent authorities have the obligation under the Cosmetics Regulation to carry out in-market controls, which include random inspection of companies' safety assessments and cosmetic product safety reports. If unsafe/non-compliant products are

[1] SCCS/1501/12, http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_s_006.pdf.

detected (including, but not limited to skin allergy), the authorities have the power to impose penalties and require corrective actions.

Furthermore, a process exists through which Member States' competent authorities can raise safety concerns (including, but not limited to skin allergy) to the European Commission over specific substances used in cosmetics. These concerns are evaluated by the SCCS who, on the basis of a submission from industry or information gathered through a public call for data, will issue an opinion (risk assessment). If deemed necessary by the European Commission, risk management measures are proposed and — included in the EU Cosmetics regulation.

The legal basis for taking measures in relation to any substance, including allergens, is Article 31 (1) and (2) of the Cosmetics Regulation, which allows the Commission to amend the Annexes II to VI of the Cosmetics Regulation.

Finally, certain substances (colorants, preservatives and UV-filters) must be explicitly authorized and need an SCCS positive assessment before being added to one of the positive lists. Skin sensitization would be one of the endpoints to be taken into account in this assessment.

There are different tools provided in the regulatory framework to manage allergen risks.

The use of substances can be restricted and/or certain conditions can be imposed on their use. These measures would be envisaged for substances which are likely to cause allergy to a significant part of the population.

In order to ensure that consumers are adequately informed, the labelling of the ingredients' list is required. In addition, the presence of 26 fragrance allergens must be indicated in addition to the expression "parfum" or "aroma". This information may improve the diagnosis of contact allergies among consumers and should enable them to avoid the use of cosmetic products which they do not tolerate.

Taken together these risk management measures address both the prevention of the induction of allergy in non-allergic consumers (i.e., Primary prevention) and preventing the eliciting of an allergic reaction in sensitized consumers (i.e., Secondary prevention).

Recital (49) of the Cosmetics Regulation summarizes the approach with regard to allergens:

'A number of substances have been identified by the SCCS as likely to cause allergic reactions and it will be necessary to restrict their use and/or impose certain conditions concerning them. In order to ensure that consumers are adequately informed, the presence of these substances should be mentioned in the list of ingredients and consumers' attention should be drawn to the presence of these ingredients. This information should improve the diagnosis of contact allergies among consumers and should enable them to avoid the use of cosmetic products which they do not tolerate. For substances which are likely to cause allergy to a significant part of the population, other restrictive measures such as a ban or a restriction of concentration should be considered.'

c) Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)

Primary prevention: The way to protect individuals from developing allergies related to allergens contained in cosmetics is the avoidance of induction of sensitization by limiting exposure to stay below induction thresholds. This is done by providing formulators with suitable use concentrations through SCCS opinions and/or regulatory limits in the EU Regulation. Consumers can also benefit from improved information on the correct use of products to avoid behavior that would increase the risk of inducing an allergy. These include legally prescribed use instructions and warnings, as well as awareness campaigns by medical associations, industry associations or regulatory bodies.

Restrictions or bans via the Cosmetics Regulation Annexes:
For example:

- MDBGN banned due to risk of allergy (Annex II)
- Restrictions of fragrance allergens (Annex III)

General warning statements and use instructions to ensure correct use and minimise unnecessary exposure:
For example:

- General allergy warning and use instructions on hair dyes required to be provided with the product when it contains specific substances, such as *'Can cause an allergic reaction'*.

Industry initiatives aiming at prevention of induction of allergies:
For example:

- IFRA Code of Practice on the (non) use of fragrance ingredients
- Voluntary labelling of hair dyes
- Cosmetics Europe recommendation to phase out MIT from leave-on products
- Individual companies may have internal standards for managing allergenic substances.

Compliance with legal requirements is monitored by EU Member States' competent authorities who issue regular market surveillance reports. Compliance with the IFRA Code of Practice is monitored by IFRA through regular random product analysis.

d) Regulatory provisions and industry self-regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)

Secondary prevention: Individuals who are sensitized to a substance (from whatever source) may react to very low concentrations that can be below the safe induction thresholds in cosmetics. Consequently, the way to help allergic consumers is to make available the most effective information on the presence of ingredients in a product so that they can choose to avoid exposure, while the products remain available for the safe enjoyment of the vast majority of the population. This is achieved through mandatory ingredient labeling on cosmetic products In the EU, product labelling must include according to Article 19 (1) (g) of the Cosmetics Regulation a list of ingredients inclusive to a relevant level. This will generally allow consumers to identify specific allergens in a product.

For perfume and aromatic compositions it is sufficient to refer to 'parfum' or 'aroma', thus it is not necessary to label all components. Special provisions are, however, in place, which require the labelling of 26 established fragrance allergens and further labelling requirements in relation to fragrance allergens are under consideration.

e) Post market surveillance measures and tools that cover allergic reactions

Generally, compliance of cosmetic products with the Cosmetics regulation is monitored via market surveillance by the Member State authorities. This is not allergen-specific ingredient monitoring.

Cosmetic companies are obliged to receive, assess and keep records of all undesirable effects causally linked to the use of a cosmetic product. Summaries of these records are accessible to the EU competent authorities via the Product Information File. However, undesirable reactions cannot always be clearly assessed as allergy and/or be linked to a specific ingredient.

Furthermore, Article 23 of the Cosmetics Regulation establishes a system under which any responsible person or distributor is obliged to report serious undesirable effects to the competent authorities, which will disseminate the information to all EU competent authorities. In addition competent authorities also receive reports directly from end users or health professionals, which will equally be transmitted to all EU competent authorities.

Dermatologist associations carry out multi-center epidemiology studies which can identify substances with a high rate of patch-test positive patients. However, most substances have multiple sources of exposure and such studies cannot easily link the rate of positive patch-test reactions to a real-life safety issue (induction or elicitation) related to cosmetics.

All findings from post market surveillance can be used to feed back into the regulatory processes described above.

6.4 Japan

Japan's Pharmaceutical Affairs Law requires the marketing license holder of cosmetics to make sure cosmetics shipped to the market are safe under normal conditions of use. The marketing license holder, who must have authorization from the prefectural government, needs to inform the prefectural government of the product name prior to marketing. The safety of ingredients is to be guaranteed by the marketing license holder beforehand. Products containing prohibited ingredients and restricted ingredients with usage beyond the limit are not allowed to be introduced into the market.

a) Definition of "allergen" applicable for purposes of cosmetics regulation

There is no definition of "allergen" in Pharmaceutical Affairs Law. See Appendix I with regard to definitions of allergen in other regulatory contexts in Japan.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

In the past, the Japanese Pharmaceutical Affairs Law required industry to submit a product by product (including iterations of product color, style, etc.) application to get permission for marketing. The examination system was transformed into notification system for cosmetics in 2006 in which marketing license holder is required to make a notification only to prefectural government.

Prior to this change, an "all ingredients labelling system" was introduced in 2001, allowing consumers to select a cosmetic product after checking the ingredients used. Also in 2001, the Standard for Cosmetics was implemented showing the list of prohibited ingredients, restricted ingredients as well as "positive lists" of preservatives and UV filters (Ministry of Health and Welfare Notification No.331 of 2000). There are 30 prohibited ingredients which are not always allergenic but considered to be unsafe when formulated in cosmetics. Colorants are regulated by Ministerial Ordinance No.30 (1966). To include a new ingredient to the positive list of Standard for Cosmetics, or to increase the percentage of an ingredient in a formula, one can submit a request for examination to MHLW attaching safety data for the ingredient.

In case of Quasi-drugs, the product should be approved by government prior to marketing under Pharmaceutical Affairs Law requirements. The marketing license holder submits safety data on the product according to the level of newness.

c) Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)

Pharmaceutical Affairs Law require the marketing license holder of cosmetics to make sure cosmetics to be shipped to market are safe under normal conditions of use. The Standard for Cosmetics includes a list of prohibited ingredients and restricted ingredients in the use of cosmetics.

In the past, designated ingredients only were to be labeled on products. As far as cosmetics are concerned, "all ingredient labeling" is mandatory to allow consumers an opportunity to avoid the use of potentially problematic cosmetics and to limit the exposure to allergens. Other ingredients are evaluated by the responsible company or companies. However, MHLW is empowered to prohibit any ingredient in question when serious allergic reactions are considered to be caused by the ingredient, and may publish the ingredient in question in the list of the Standard for Cosmetics.

Necessary precautions and other warnings should be indicated in the packaging or insert according to the law. The proposed text for precautions is provided by Japan Cosmetic Industry Association (herein after JCIA) for an example such as: "In case you find any reaction with the use of cosmetics, please stop the use of the product. If you feel any intolerance considered to be caused by the use of products, please consult a dermatologist."

In case of Quasi-drugs, 141 ingredients are designated to label on products (Ministry of Health and Welfare Notification No.332 of 2000). All ingredients labelling is done on a voluntary basis.

Necessary precautions and other should also be indicated in the packaging or insert according to the law.

d) Regulatory provisions and industry self-regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)

In the cases of reported anaphylaxis that occurred in Japan, considered to be caused by the use of cosmetic (soaps) formulated with hydrolyzed wheat protein, MHLW published a notification instructing that caution was to be taken with those products. These cautions were placed on the product container describing the ingredient in question. The cosmetic ingredient "hydrolyzed wheat protein" was not prohibited. JCIA shared the information and informed its' members not to use the said ingredient with specified chemical characterization. Another case with the use of cochineal dye in cosmetics was handled in the same way.

e) Post market surveillance measures and tools that cover allergic reactions

Pharmaceutical Affairs Law is characterized by licensing of the marketing license holder. The license is given by prefectural government where the head office of marketing license holder is located and is valid for 5 years. The prefectural government makes inspection at licensee site(s) regularly, and surveys cosmetics in the market.

The other regulatory measure is Ministerial Ordinance No.135 (2004) that stipulates Good Vigilance practices asking marketing license holder to pursue safety evaluations of cosmetics shipped to the market. Specifically, the ordinance requires the nomination of a qualified Safety Assessor to set safety management procedures resulting from information collected with the marketed products.

Marketing License holders of cosmetics are requested by law to collect information on marketed products and ingredients formulated in these products. Should there be any reports of potential harm from ingredients used in its products, the company/license holder are required to report these to the Pharmaceutical and Medical Device Agency (PMDA).

Thus, in both sides: regulatory authority and industry, a monitoring system is provided under Pharmaceutical Affairs Law.

6.5 United States of America

Cosmetics are regulated in the United States by the Food and Drug Administration and much of the laws governing cosmetic marketing in this regulatory jurisdiction derive from the 1938 Federal Food, Drug, and Cosmetic Act (FD&C Act), the 1960 Color Additive Amendments to the Act, the 1966 Federal Fair Packaging and Labeling Act (FPLA), and regulations published under the authority of these statutes.

a) Definition of "allergen" applicable for purposes of cosmetics regulation

Neither the FD&C Act nor the FPLA provide a definition of allergen targeted specifically to cosmetic products or cosmetic ingredients. Major food allergens are, however, defined in the

context of the Food Allergen Labeling and Consumer Protection Act (FALCPA) of 2004, 21 USC 301. See Appendix I below.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

The FD&C Act (the Act) granted the Food and Drug Administration (FDA) the authority to regulate cosmetic products and their ingredients. The statutory provisions of the Act that address cosmetics include adulteration (Sec. 601) and misbranding (Sec. 602) provisions. The cosmetics provisions were amended by the 1960 Color Additive Amendments to the Act. With the exception of color additives that are not coal-tar hair dyes, cosmetic ingredients are not subject to FDA premarket approval authority. However, regulations prohibit the use of some substances and restrict the use of others because of safety concerns or environmental factors. (21 CFR, Parts 250.250 and 700.11 through 700.35)

"Adulterated" cosmetics are those which (1) contain poisonous or deleterious substances rendering the cosmetics harmful or injurious (2) contain filthy, putrid, or decomposed substances, (3) have been prepared, packaged, or held under unsanitary conditions, or (4) have containers composed of poisonous or deleterious substances. Except for special "safe harbor" exceptions for "coal-tar hair dyes", a cosmetic product will also be deemed adulterated if it contains an "unsafe" color additive. "*Misbranded"* cosmetics generally are those which (1) have false or misleading labeling, (2) have labels without all required information displayed prominently and conspicuously, (3) have containers made, formed, or filled as to be misleading, or (4) which lack "adequate safety substantiation" and fail to warn consumers of this "material " fact (21 CFR 740.10).

FDA may also propose regulations to restrict or prohibit the use of any specific ingredient according to the procedures and requirements of notice and comment rule-making (see http://www.fda.gov/RegulatoryInformation/RulesRegulations/).

FDA has previously effectively prohibited use of specific allergens in cosmetics. Under 21 CFR 700.11 and 700.15, FDA has formally designated two allergens (bithionol and halogenated salicylanilides) as deleterious substances which render any cosmetic product that contains these ingredients adulterated under section 601(a) of the FD&C Act.

The statuary authority under the FD&C Act grants FDA the *implicit* authority to regulate the management of allergens in cosmetic products. Section 201(n) defines misbranding in any particular to include the failure to reveal "material" facts with respect to a product and consequences which might result from its use. FDA has statutory authority to require the declaration of cosmetic ingredient within the meaning of section 21 CFR 701.3, or, when necessary, a cautionary statement where there is potential health hazard that may be prevented or alleviated by a warning as required by sections 21 CFR 740.1 and 21 CFR 740.2.

In those cases where FDA determines that a cosmetic product bears or contains an ingredient shown to be a poisonous or deleterious substance which may render it harmful or injurious to consumers under the intended conditions of use specified in product package labeling, the Agency may conclude that the cosmetic product is, therefore, adulterated. FDA may then consider removal of the product and/or the ingredient from the marketplace, either through

voluntary recall actions, regulatory enforcement activities or by requests through the courts (see http://www.fda.gov/aboutfda/transparency/basics/ucm262353.htm).

FDA may also propose the promulgation of guidance or regulations to restrict or prohibit, respectively, the use of that ingredient according to the procedures and requirements that apply to notice and comment rule-making
(see http://www.fda.gov/RegulatoryInformation/RulesRegulations/)

c) Regulatory provisions and industry self- regulatory measures used to manage induction risks related to allergens in cosmetics (including region specific examples)

As previously discussed above in Section (b), FDA has effectively prohibited use of specific allergens in cosmetics. Under 21 CFR 700.11 and 700.15, FDA has formally designated two allergens (bithionol and halogenated salicylanilides) as deleterious substances which render any cosmetic product that contains these ingredients as adulterated under section 601(a) of the FD&C Act.

Aside from color additives employed in food and/or drug products (i.e. tartrazine and carmine/cochineal extract), FDA does not have any explicit regulations related to induction risk for allergens in cosmetics.

FDA regulations require that the presence of fragrance or flavors in a cosmetic be declared on the labeling (21 CFR 701.3(a)), but do not require the identification of individual fragrance or flavor ingredients because of the large number of such ingredients that may be present in any one product. While FDA does not require the explicit label declaration of fragrance allergens, FDA regulations do not preclude listing fragrance or flavor allergens in the labeling.

The Cosmetic Ingredient Review (CIR), an industry sponsored Panel of academic experts, including dermatologists, toxicologists, pharmacologists, and chemists, undertakes a systematic review of ingredients and evaluates a battery of data comprising human experience and general toxicology endpoints, including dermal sensitization and irritation potential of these ingredients. Based on these data the panel issues its conclusion that may include qualifications on end use application or concentration of use. This information is published and made available to the public. While the opinions of CIR are not binding on either FDA or the regulated industry, the conclusions may be used for guidance when considering ingredient use in the formulation of finished products.

Examples of issues identified by FDA concerning specific allergens of concern are ingredients contained in tattoo and henna cosmetic products. FDA issued risk communication measures to address products that were being marketed that posed risk of sensitization and allergenicity. Please refer to the following http://www.fda.gov/Cosmetics/default.htm for more information about these examples. Similarly the issue of allergic reactions to hydrolyzed wheat protein (HWP) and hydrolyzed wheat gluten (HWG) has recently been discussed at the 130th meeting of the Cosmetic Ingredient Review (CIR) Expert Panel (see http://www.cir-safety.org) with the Panel setting limitations on protein size establishing an expected non-sensitizing threshold.

d) Regulatory provisions and industry self- regulatory measures used to manage elicitation risks related to allergens in cosmetics, including labelling (including region specific examples)

FDA regulation of cosmetics is through codified regulations and guidance published under the authority of the 1938 FD&C Act, the 1960 Color Additive Amendments to the Act, and the 1966 Federal Fair Packaging & Labeling Act (FPLA); the 1973 cosmetic labeling regulations (see, 21 CFR 701), including the requirement for mandatory ingredient declaration, (see, 21 CFR 701.3).

There is no specific U.S. statutory authority or codified FDA regulation that addresses the labeling of allergens in cosmetics. Regulatory requirements for the mandatory labeling of a few allergens in color additives, such as tartrazine (21 CFR 74.2705) in FD&C Yellow No. 5 and Carmine/Cochineal [21 CFR 73.2087(c)] have been published. The regulation for tartrazine applies to drugs and/or foods but not cosmetics (21 CFR 201.20}

One of the benefits of ingredient labeling in 21 CFR 701.3 is that it enables persons with known allergies to specific ingredients to avoid purchase of cosmetic products containing them. As mentioned above, FDA regulations require that the presence of fragrance or flavors in a cosmetic be declared on the labeling (21 CFR 701.3(a)), but do not require the identification of individual fragrance or flavor ingredients because of the large number of such ingredients that may be present in any one product. While FDA does not require the explicit label declaration of fragrance allergens, FDA regulations do not preclude listing fragrance or flavor allergens in the labeling. FDA also does not currently require ingredients to be mentioned in the label if they constitute less than 1% of the total ingredients by mass.

Hair dye products containing coal-tar colors are not deemed by FDA to be "adulterated" if they bear the "exclusivity language" cautionary statement provided in section 601(a) of the FD&C Act and if they offer adequate directions for preliminary patch testing by consumers for skin sensitivity. The caution statement reads as follows:

"*Caution - This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should first be made. This product must not be used for dyeing the eyelashes or eyebrows; to do may cause blindness If the label of a coal-tar color-containing hair dye product does not bear the caution statement of section 601(a) and the patch testing directions, it may be subject to regulatory action if it is determined to be harmful under customary conditions of use."*

http://www.fda.gov/Cosmetics/CosmeticLabelingLabelClaims/CosmeticLabelingManual/ucm126438.htm

e) Post market surveillance measures and tools that cover allergic reactions

FDA uses a variety of post-market resources to assist with monitoring ingredient safety. These include FDA's database of adverse event reporting (CFSAN's Adverse Event Reporting System or CAERS). http://www.fda.gov/Safety/MedWatch/default.htm; FDA's historical recall data and inspectional findings; and data from FDA's Voluntary Cosmetic Registration Program (VCRP - see, http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/VoluntaryCosmeticsRegistrationProgramVCRP/default.htm); FDA's intramural research projects; information from published peer-review scientific literature; data provided directly to FDA by other governmental agencies (i.e. National Toxicology Program); data and information submitted to FDA, either upon the agency's request, or otherwise, on a voluntary basis by the

cosmetic industry or other stakeholders/parties; and conclusions of the Cosmetic Ingredient Review (CIR) Expert Panel (see, http://www.cir-safety.org) and other authoritative bodies (such as The National Academy of Science, Institute of Medicine).

At the present time, FDA has no specific monitoring program for allergens in cosmetic products; however, the Agency does take into account whether a product or ingredient has skin sensitization potential or has caused an allergic response. In those cases where FDA determines that a cosmetic product bears or contains an ingredient shown to be a poisonous or deleterious substance which may render it harmful or injurious to consumers under the intended conditions of use specified in product package labeling, the Agency may conclude that the cosmetic product is, therefore, adulterated. FDA may then consider removal of the product and/or the ingredient from the marketplace, either through voluntary recall actions, regulatory enforcement activities or by requests through the courts (see http://www.fda.gov/aboutfda/transparency/basics/ucm262353.htm).

FDA may also propose the promulgation of guidance or regulations to restrict or prohibit, respectively, the use of that ingredient according to the procedures and requirements that apply to notice and comment rule-making (see http://www.fda.gov/RegulatoryInformation/RulesRegulations/)

6.6 Working Group Analysis of Jurisdictional Discussions

A very wide range of chemicals have an inherent sensitization potential and exposure to allergens can occur from many sources in daily life and. it is not feasible to totally avoid all potential allergens, including those in cosmetic formulations. All five jurisdictions consider allergy as an important toxicological endpoint that needs to be properly managed to ensure a high level of confidence in the safety of cosmetic products for consumers.

In all five jurisdictions, risk management of allergy to cosmetics happens at two levels:

- Minimizing the risk of creating allergies in on-allergic consumers (induction)
- Enabling allergic consumers to avoid contact with their specific allergens (elicitation)

For both aspects, a mix of regulatory and voluntary (by industry) measures exists in the five jurisdiction who participated in the drafting of this report.

a) Definition of “allergen” applicable for purposes of cosmetics regulation

Although explicit and implicit risk management measures of skin allergens in cosmetics are implemented in all five jurisdictions who participated in the drafting of this report, none of them has a specific definition of allergen in the context of their respective cosmetics statutory authorities (i.e. legislative provisions).

Some of the jurisdictions have definitions of allergens in the context of regulation of other products (examples of food regulation are given in Appendix I). The direct relevance of such definitions into cosmetics use is limited due to different scope and objective of these regulations. However, classification of a substance as an allergen for another use is important information for the safety assessment of an eventual cosmetic use of the substance.

b) Basic regulatory framework that covers – explicitly or implicitly – allergens in cosmetics, including applicable guidelines and risk assessment tools.

The cosmetics legislation in all five jurisdictions is based on the principle that products sold to the consumer must be safe for the consumer under normal or reasonably foreseeable use. All five legislations have regulatory tools to specifically regulate or restrict individual ingredients for their use in cosmetics based on risk assessment, including potential allergens. Furthermore cosmetics legislation in of all five jurisdictions also requires comprehensive ingredient labeling of cosmetics. Cosmetic product safety is established through a robust safety assessment under the responsibility of the company marketing the product. Such safety assessment is explicitly required under the laws of the EU, Canada, Brazil, Japan and the US. Allergy is but one important aspect taken into account within this assessment. The lists of ingredients mentioned by each jurisdiction that use lists to monitor or guide cosmetic manufacture may have some overlap with ingredients that have allergenic potential, but evaluating the extent of this was thought to be beyond the task or ability of this working group.

Verification of compliance of products with the legislation is the responsibility of the authorities in the five jurisdictions. If unsafe/non-compliant products are identified in the marketplace (including but not limited to skin allergy), the authorities have the power to impose penalties and/or require corrective actions. All jurisdictions have voluntary or mandatory procedures for notifying to the authorities products that are placed on the market. Notification facilitates the identification of products on the market and the responsible marketer and is vital for the appropriate function of regulatory surveillance and follow-up, as appropriate.

Post-market controls are further facilitated by the notification of adverse effects to the authorities after marketing. In Japan, EU, and Brazil such adverse event notification is mandatory while in the US and Canada it is voluntary. Memorandums of understanding exist between most jurisdictions to allow for communication of such notifications; however, this may or may not be exercised in the context of cosmetic post-marketing surveillance. See also Section (e) below for further information on post-marketing controls.

c) Regulatory provisions and industry self-regulatory measures used to manage induction risks related to allergens in cosmetics

Primary prevention, when proactively implemented, aims to protect individuals from developing allergies by limiting exposure to stay below induction thresholds. This is done by identifying appropriate safe use concentrations through, either the responsibility of the companies using the substance or by setting regulatory limits and use conditions.

Consumers can also benefit from improved information on the correct use of products to avoid behavior that would increase the risk of inducing an allergy. These include legally prescribed use instructions and warnings as well as awareness campaigns by medical associations, industry associations or regulatory bodies.

Guidelines from both industry and certification groups, as well as some with input from regulatory bodies (e.g. through standards working groups), exist in all five jurisdictions to help

cosmetic companies in the establishment of high quality safety assessment. With regard to specific risk assessment methodologies for allergy, industry has developed methodologies for quantitative risk assessment of skin allergy. This methodology is today widely used for in house safety assessments and is the basis for the fragrance ingredient assessment process by IFRA (Refer to Appendix II).

Substances used in cosmetics and personal care products may be assessed for their allergenic potential as part of an specific manufacturer's pre-market safety assessment and a decision may be made to include or not include that substance.

All jurisdictions have examples, where the allergic properties of a substance have triggered specific regulatory restrictions. However, the lists are not aligned across the five jurisdictions. These lists of ingredients which are prohibited, restricted or allowed under certain conditions may be administrative or formally part of the legislation. Authorities update regularly these lists. In the US, the FDA published list of specifically regulated ingredients is shorter than in the other jurisdictions. However, an industry sponsored review program of ingredients exists (CIR) to which FDA participates (as a non-voting liaison) and may inform product safety for cosmetic manufacturers and consumers.

Industry wide voluntary measures on allergens exist for fragrance allergens by the International Fragrance Association (IFRA) which bans and restricts certain fragrance ingredients, which are found to be unsafe or cause skin sensitization.

Additional industry initiatives exist in the various jurisdictions, such as labelling / use instructions for hair dyes, or recommendations on the safe use / non use of specific allergens. These initiatives are, however, not aligned between the jurisdictions.

d) Regulatory provisions and industry voluntary measures used to manage elicitation risks related to allergens in cosmetics, including labelling

Secondary prevention aims to avoid the elicitation of allergic skin reactions in individuals who are sensitized to a substance (from whatever source). It is not feasible in practice to manage elicitation risk from allergens in cosmetics by lowering use levels below the elicitation thresholds. Since sensitized individuals can react to very low concentrations, such an approach may effectively restrict most allergens below a technically useful concentration (i.e. may not serve a useful purpose). The most efficient risk management approach is by informing allergic consumers on the presence of ingredients in a product so that they can choose to avoid exposure, while the products remain available for the safe enjoyment of the vast majority of the population.

All jurisdictions follow this risk management approach through mandatory full ingredient labeling on cosmetic products.

For perfume and aromatic compositions it may be sufficient to refer to 'parfum' / 'fragrance'or 'aroma', thus it may not always be necessary to label all individual constituents. There are currently more than 3000 fragrance ingredients used to create various fragrance compounds; of these thousands, hundreds could appear in trace amounts in a finished cosmetic product. As such it is not practical for all fragrance ingredients to be included on a product container label,

while keeping information legible. Special provisions are however in place in Brazil and the EU that require labelling 26 established fragrance allergens, even if they are part of a fragrance or flavour composition. Consideration may be given to on product links to website content to bypass space considerations.

e) Post market surveillance measures and tools that cover allergic reactions

Generally, the safety performance of cosmetic products on the market is monitored in parallel by the competent regulatory authorities and the companies. These surveillance measures are not specific to allergens, but certainly, allergic reactions are an important part of these monitoring programs.

Although not legally mandated in all jurisdictions, cosmetic companies typically have processes to receive, assess and keep records of undesirable effects causally linked to the use of a cosmetic product. This information allows the detection of "in market trends" and signals that measure the safety performance of any given product.

In all jurisdictions, authorities encourage consumers that experience an adverse event (or medical professionals consulted by them) to report adverse incidences, including allergic-type responses.

In addition, dermatology and professional contact dermatitis associations carry out multi-center epidemiology studies which can identify substances with a high rate of patch-test positive patients. This information provides useful information and can alert regulators and industry to emerging allergy issues. However, most substances have multiple sources of exposure and such studies cannot easily link the rate of positive patch-test reactions to a real-life safety issue (induction or elicitation) related specifically to cosmetics.

7. CONCLUSIONS AND RECOMMENDATIONS

This survey of regulatory approaches regarding surveillance and management of potential allergens in cosmetics as practiced within the ICCR jurisdictional regions confirms that all ICCR jurisdictions consider allergy to be a key consideration and an important toxicological endpoint that needs to be addressed and properly managed to ensure a high level of safety of cosmetic products. It is acknowledged that a wide range of chemicals may present an inherent sensitization potential and that it is not feasible to totally prevent exposure to allergens as a result of the use of products (including, but not limited to cosmetics) that may contain ingredient(s) to which someone may be particularly sensitized to.

Allergy is a toxicological endpoint that is not specific to cosmetics, and as such none of the ICCR jurisdictions provide for an *a priori* definition of allergen for the sole purposes of cosmetics legislation. The relevance of definitions in other product sectors is limited due to different scope and objective of these regulations. Cosmetic ingredients become recognized or acknowledged as contact allergens mainly as a result of post-market surveillance or published dermatological studies that may trigger regulatory follow-up and/or industry reaction.

Cosmetics legislations in all ICCR jurisdictions are based on the common principle that products sold must be safe for the consumer under normal or reasonably foreseeable use. Guidelines exist in all ICCR jurisdictions (including a Safety Assessment Principles document, as published under the ICCR) to help ensure a comprehensive and robust approach towards the safety assessments of cosmetic products, including the management of potential allergens in cosmetics.

In conclusion, although the specific laws and regulations governing cosmetics differ in the ICCR jurisdictions, the principal tools for risk management of allergens in cosmetics are somewhat comparable across these jurisdictions and reflect the following two complementary targeted approaches:

- A goal of minimizing the risk of creating allergies in non-allergic consumers (induction) by restricting exposure to safe levels; and

- A hope of enabling sensitized consumers to avoid contact with specific allergens to prevent allergic reactions (elicitation) by informing consumers of their presence in a cosmetic product. In this context it is recognized that it is generally not feasible to lower the use levels of allergens below the levels where they elicit skin reactions in already sensitized consumers.

Although all jurisdictions have examples, where the allergic properties of a substance have triggered specific regulatory restrictions, the specific substances are not the same across the ICCR jurisdictions. The effectiveness of each of the jurisdictional approaches have not been assessed or compared by this Working Group, or to our knowledge, by any other entity. While labelling is mentioned, jurisdictional approaches to labeling have also not been evaluated on a granular level.

Notification of adverse effects to the authorities after marketing exists in all ICCR jurisdictions and is mandatory in some. Memorandums of understanding exist between most jurisdictions to allow for communication of such notifications; however, this may or may not be exercised in the context of cosmetic post-marketing surveillance.

This initial iteration of ICCR's Working Group (as envisioned in ICCR 6 and under the ToR from ICCR 7, 2013) for allergens in cosmetics and personal care products recommends to ICCR that consideration be given to establishment of a second iteration of the Allergen Working Group (i.e., ICCR Allergens Working Group 2.0) with the appropriate expertise necessary to extend the current evaluation as deemed appropriate.

8. REFERENCES

8.1 Guidance Documents and Regulations

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2. Regulation (EC) on cosmetic products - http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:342:0059:0209:EN:PDF
3. FDA Cosmetics Labeling Requirements http://www.fda.gov/Cosmetics/Labeling/Regulations/ucm126438.htm
4. Label Claims and Expiration Dating Hypoallergenic Cosmetics - http://www.fda.gov/Cosmetics/Labeling/Claims/ucm2005203.htm
5. US Fair Packaging and Labeling Act http://www.fda.gov/RegulatoryInformation/Legislation/ucm148722.htm
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APPENDICES

APPENDIX I

Definitions of Allergens in other Regulatory Contexts

As noted in the above descriptions, there is no definition of "allergen" with regard to its context in cosmetics and personal care product regulation in each of the regulatory jurisdictions participating in the working group.

In Canada, under the *Food and Drugs Regulations*, a "food allergen" is described as "any protein from any of the following foods, or any modified protein, including any protein fraction, that is derived from any of the following foods: almonds, Brazil nuts, almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios or walnuts, peanuts, sesame seeds, wheat or triticale, eggs, milk, soybeans, crustaceans, shellfish, fish or mustard seeds. This definition does not apply to cosmetics. If present in a pre-packaged food, the food allergen must be clearly labelled in the list of ingredients or in a statement that begins with "contains…".

In Japan, for food allergens, the Japanese Ministry of Health Labour and Welfare has mandated allergen labeling for food containing allergenic ingredients since 2001 in order to try to prevent the occurrence of health hazards. Egg, milk, wheat, buckwheat and peanut, and more recently shrimp and crab have been required to have mandatory labeling. In the answer to A-1 of FAQs on Labeling System for Foods Containing Allergens, food allergen was defined (http://www.caa.go.jp/foods/pdf/syokuhin13.pdf). The definition is the same as the one for medical definition.

In the United States, major food allergens are defined in the context of the *Food Allergen Labeling and Consumer Protection Act* of 2004, 21 USC 301, as follows:

> The term 'major food allergen' means any of the following:
> Milk, egg, fish (e.g., bass, flounder, or cod), Crustacean shellfish (e.g., crab, lobster, or shrimp), tree nuts (e.g., almonds, pecans, or walnuts), wheat, peanuts, and soybeans. Also proteins from these sources are considered major food allergens.

While food allergens may not always be applicable to cosmetic products, their inclusion (intentional or accidental) in personal care products or cosmetics that may result in oral exposure can result in a similar allergenic reaction as would be possible due to nutritional or dietary exposure.

APPENDIX II

IFRA and Allergens

This section was provided by IFRA for the Working Group's inclusion in this report.

IFRA briefed the working group in March, 2014 regarding their role in evaluating ingredients used as fragrances in cosmetics and personal care products. IFRA was asked to prepare a short description of the IFRA program for inclusion as an appendix in this Report. This is included below:

The International Fragrance Association (IFRA, www.ifraorg.org) since 1973 maintains a harmonised global system of voluntary Standards for the fragrance industry. These Standards set restrictions (use limitations or purity requirements, or a combination) or prohibits the use of ingredients for the compounding of fragrance raw materials. They are publicly available, binding for the IFRA membership but beyond this, achieve broad global recognition. Although mostly not referenced in the body text, consumer product regulation for example in Argentina, Brazil, the ASEAN region or China e.g. via guidance documents make a certification of compliance with the IFRA Standards a requirement for introducing fragranced consumer products in the market. In other countries/regions, IFRA restrictions or prohibitions were introduced in the Annexes of regulations, such as the European Cosmetics Regulation.

IFRA Standards are the outcome of a transparent process, where exposure information collected within the industry in combination with a robust collection of safety data (via the Research Institute for Fragrance Materials) is reviewed by an independent expert panel.

Currently there are 186 IFRA Standards (47th Amendment to the IFRA CoP, notified June 10, 2013). 77 Standards prohibit the use of certain fragrance ingredients, 100 Standards restrict the use by setting limits in the finished product and 9 raw materials have purity criteria (e.g. limitation of sensitizing hydroperoxides). Some Standards cover more than one ingredient (the Rose Ketone Standard for example covers 14 structurally similar ingredients).

The Standards are driven by the toxicity endpoint of (highest) concern for a certain material. Many IFRA Standards address potential sensitizing properties of certain fragrance ingredients. Since 2006 all new IFRA Standards for the endpoint of sensitization are based on the dermal sensitization Quantitative Risk Assessment (QRA). Existing Standards have also since then progressively updated incorporating the QRA approach.

The QRA takes advantage of the fact that dermal sensitization is a threshold phenomenon. Thresholds for induction can be determined with a high level of reliability. Well described models are available to assist in determining a human relevant No Expected Sensitization Induction Level (NESIL) by a weight of evidence approach using all existing human and animal data plus knowledge resulting from read across etc. The NESIL is the level of a sensitizer that is demonstrated not to activate the immune system in a manner that will lead to later allergic responses. Unlike for other endpoints, these levels are confirmed in humans utilizing a Repeated Insult Patch Test (HRIPT).

The output of the QRA for dermal sensitizers is a level at which the sensitizer can be used in consumer products that for the vast majority of the population will not cause induction of skin sensitization.

For pragmatic reasons (allowing effective application by the users) the QRA outcome is translated into 11 categories, reflected in the IFRA Standards, in which products are grouped together based on the same safety assessment factor and comparable exposure, using the highest exposure to define the category.

IFRA and the industry it represents is committed to enhance the safety of fragrance ingredients and arrive at a better understanding of allergic responses to fragrance ingredients by initiating a broad engagement of the scientific and medical community through a multi-stakeholder initiative. More information on this initiative and its outcomes as well as the EU Commissions involvement is available on www.ideaproject.info/.