ASSESSING THE SAFETY OF PERSONAL CARE PRODUCTS:

COMPARATIVE ANALYSIS OF HEALTH RISK ASSESSMENT FRAMEWORKS AND RECOMMENDATIONS FOR BEST PRACTICES

Comparative Analysis of Health Risk Assessment Frameworks and Recommendations for Best Practices

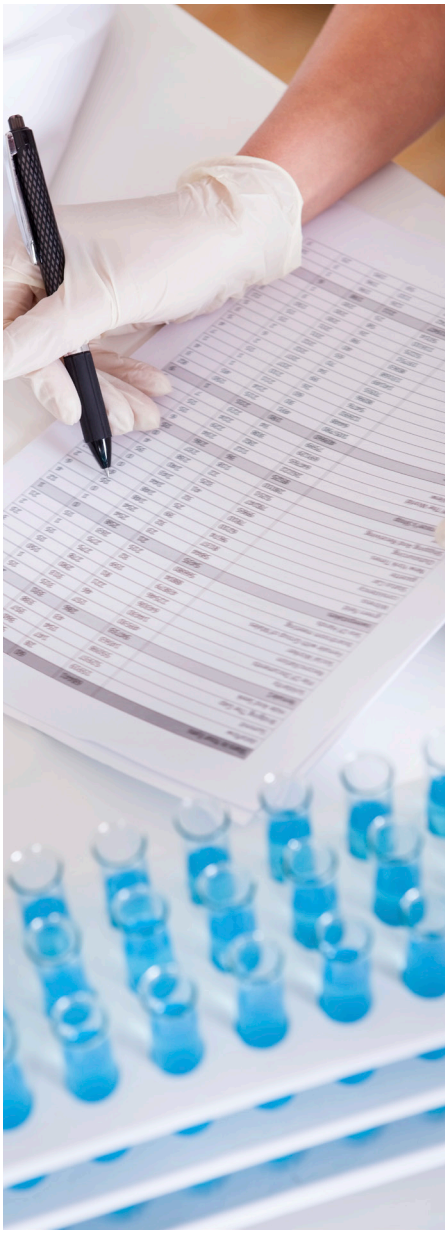
Executive Summary

UL conducted this research to identify best practices for health-risk-based product safety assessment and to facilitate a path forward for personal care product development. This research includes an assessment of views expressed by non-governmental organizations (NGOs) and activists, as well as views from safety, stewardship, and sustainability experts from the retail, brand, and chemical supplier communities. It explores various elements of a full safety assessment, including hazard characterization, exposure assessment, dose response, and risk characterization.

The personal care products landscape discussed in this paper includes five areas: ingredients disclosure, priority ingredients and alternatives, aggregate exposure, regulatory science, and availability of data. This report will touch on elements of each area, particularly as related to human safety assessment best practices. Best practices were identified through a detailed expert review of the five primary product safety risk assessment frameworks available for consumer products: Cosmetic Ingredient Review (CIR), Scientific Committee on Consumer Safety (SCCS), International Fragrance Association (IFRA), Research Institute for Fragrance Materials (RIFM), and Flavor and Extract Manufacturers Association (FEMA), as well as other safety frameworks outside of personal care (International Council of Chemical Associations (ICCA).

These frameworks were assessed against the following criteria:

- Assessment of individual ingredients vs. finished formulations;
- Considerations for ingredients with specific properties or function;
- Data quality and requirements;
- Toxicity evaluation (hazard and risk);
- Exposure assessment;
- Quantitative safety assessment; and
- Alternatives assessment guidance.



The criteria were selected based on UL's expert knowledge of what constitutes a robust risk-based approach and the elements most central to addressing the identified stakeholder issues. Based on these criteria, UL found many commonalities between frameworks, including the health endpoints evaluated and the data types used to form conclusions. However, the frameworks varied considerably in terms of the assessment and determination of the endpoints to undergo quantitative risk assessment.

Of the 26 individual safety elements assessments assessed, SCCS was identified as the leading or co-leading practice in 15 elements, CIR in 13 elements, ICCA in nine elements, RIFM in six elements, and FEMA in three elements.

Despite all the regulations and safety systems in place for cosmetics today, questions remain about the safety of cosmetic ingredients and the standards associated with them. The key message coming from consumers is confusion around ingredient safety. While some of these questions and issues are addressed in this paper in the context of their relevance to best practices, this paper is not intended to provide a detailed analysis of stakeholder issues or their positions.

As a means of moving the debate forward, UL proposes a consensus-based set of voluntary risk-based standards designed to go beyond what is required by the existing regulations. The best practices identified in this paper would form the basis of such risk-based standards.

Introduction

The market for personal care products is expanding rapidly. According to market researcher Lucintel, the global personal care products industry is poised to reach $630 (€487) billion by 2017, with a CAGR of 3.4 per cent over the next five years[1] .

With the rapid increase in global access to information, more consumers are actively seeking information on the health impacts of the products they consume. This is especially true for the personal care sector, where consumers are becoming increasingly interested in the products they and their families use every day.

Non-governmental organizations (NGOs) are active in this area and have developed several online resources to fill the information demands of consumers. EWG's "Skin Deep" database has been searched over 232 million times since 2004. GoodGuide launched in 2007, and now offers science-backed sustainability ratings on the health, environmental and social impacts of nearly 240,000 everyday consumer products. Over 500,000 consumers visit GoodGuide.com each month, looking for data.

In light of this growing market and the corresponding demand for safety information by consumers, there is a need to understand and develop a "best practice" for evaluating personal care product safety.

In this study, UL Environment reviewed current perceptions of product safety assessment amongst non-governmental organizations (NGOs) and advocates through a review of secondary sources, interviews with individuals from key stakeholder groups (retailers, brands, NGOs, and industry associations), and a comparative review of some of the primary product safety risk assessment frameworks available, with the intent of identifying best practices of those frameworks as a means of moving both the debate and industry practice forward.

A total of five primary frameworks were selected for review. These include:

- Cosmetic Ingredient Review (CIR);
- Scientific Committee on Consumer Safety (SCCS);
- International Council of Chemistry Associations (ICCA);
- International Fragrance Association (IFRA) RIFM Process; and
- Flavor and Extract Manufacturers Association (FEMA).

Four of these frameworks were selected because they are relied upon by a wide variety of stakeholders, including those in regulatory and industrial sectors. While UL's primary focus was on these frameworks, in some cases, we also evaluated risk assessment frameworks that are not specific to the personal care products industry such as ICCA. Consideration of supplementary materials most commonly occurred when one of the primary frameworks referred readers to additional guidance documents.

We established a set of fundamental review criteria so that a systematic comparison could be performed across all of the frameworks. Several key categories were evaluated, with regard to the following:

- Assessment of individual ingredients vs. finished formulations;
- Considerations for ingredients with specific properties or function;
- Data quality and requirements;
- Toxicity evaluation (hazard and risk);
- Exposure assessment; and
- Quantitative safety assessment

The study also examined approaches to alternatives assessment. Although alternatives assessment is not solely linked to risk assessment, many stakeholders identified it as an emerging area in need of attention.

After an initial review of the key frameworks, it became apparent that comprehensive evaluation of CIR, SCCS, and ICCA (with selected supplemental materials) provided the most robust basis to assess best practices, and it would not be necessary to include the IFRA and FEMA frameworks in a comprehensive criterion-by-criterion evaluation.

The study also examined approaches to alternatives assessment. Although alternatives assessment is not solely linked to risk assessment, many stakeholders identified it as an emerging area in need of attention.

The review indicated that while there were many commonalities, such as the health endpoints evaluated and the data types used to form conclusions, other aspects of the frameworks were variable, particularly with respect to the endpoints that undergo quantitative risk assessment. Several deficiencies among the frameworks were also noted, including:

- Lack of hazard determinations or classifications that are clearly delineated from the risk assessment process;
- Lack of considerations of additivity in mixtures for special cases; and
- Lack of guidance on filling data gaps.

Based on a review of the ingredient assessment approaches described in the five primary frameworks, UL has developed a series of best practice recommendations for assessing ingredient safety in personal care products. While the SCCS framework serves as the basis for many of the best practices recommendations, attributes of the CIR, RIFM, and ICCA assessment approaches are also included, as are more general risk assessment practices identified in supplemental materials (*i.e.*, United States Environmental Protection Agency [U.S. EPA], Organization for Economic Co-operation and Development [OECD] guidance).

It is important to note that although UL has identified a framework of best practices in this paper, several significant challenges remain, including best practices for alternatives assessment and managing hazard data gaps. Finally, UL acknowledges that further work needs to be done to more clearly articulate public concerns as well as the communications necessary to alleviate those concerns. Some of these public and stakeholder concerns are outlined in the next section.

Stakeholder Perceptions of Product Safety

UL reviewed on-line sources of information related to stakeholder perceptions of product safety and conducted six telephone interviews. This section summarizes some of the major issues identified by stakeholders but is not intended to be a comprehensive analysis of stakeholder views on the issue of product safety in personal care products.

Some stakeholders are critical of the proliferation of chemicals-of-concern lists generated by legislators, regulators, brands, and NGOs. Their criticisms are aimed at lists based primarily on hazard-based assessments rather than at those that also include risk-based assessments which take exposure into account. A list-based approach to product formulation could, they argue, result in unintended consequences of selecting an untested but "preferred" alternative to chemicals known and tested as safe when used in a particular context, and lead to the de-selection of chemicals which pose little or no risk to consumers in final products.

In contrast, other stakeholders express skepticism that safety information is not easily accessible or fully disclosed. As result, they are demanding more information and are creating various "red lists" of chemicals-of-concern.

It is important that stakeholders along the value chain understand market perceptions and drivers of market demand when developing "best practice" approaches to product safety and when communicating about those approaches.

In this section, UL summarizes the secondary and primary research it completed on stakeholder perceptions of product safety and personal care products. Section 2.1 summarizes the key issues of concern cited in the public discourse, and specifically by NGOs that actively track health concerns related to personal care products. Section 2.2 covers information collected through interviews with stakeholder representatives from industry associations, retailers, and specific NGOs working on these issues.

2.1 Background Research

UL reviewed positions on product safety available on the Internet. A number of NGOs are actively campaigning on health issues connected with personal care products and as a result, there has been regular media attention on the questions being raised by these organizations. The most frequent topics being raised include:

- Ingredient disclosure and product labelling
- Use of chemicals of concern and / or red-listed ingredients
- Aggregate chemical exposure[2]
- Belief that regulations are inadequate or inadequately enforced, or that manufacturers are not conducting adequate safety assessments

2.1.1 Ingredient Disclosure and Product Labelling

As part of the Fair Packaging and Labeling Act (FPLA), U.S. federal law requires that all ingredients contained in personal care products appear on the label. However, U.S. regulations also permit fragrance and flavor ingredients to be listed simply as "Fragrance" or "Flavor." The FPLA cannot be used to force a company to disclose "trade secrets." Fragrance and flavor formulas are complex mixtures of many different natural and synthetic chemical ingredients, and they are the kinds of cosmetic components most likely to be considered "trade secrets."

This lack of disclosure of the details of fragrance and flavor product ingredients, coupled with incomplete public information or understanding of the existing safety assessment of these products, has resulted in increasing distrust of both the use of fragrances and of the companies that manufacture them.

For example, the Environmental Working Group (EWG) and the Campaign for Safe Cosmetics (CSC) cite studies that found products containing "fragrance" in the ingredient list had an average of 14 hidden compounds per formulation, including ingredients linked to hormone disruption[3]. Furthermore, the CSC website states that "if personal care products contain harmful chemicals, consumers have a right to know what ingredients in fragrance may pose a risk to their health." While IFRA does publish fragrance ingredients and makes safety information available to the public, NGOs clearly do not see this as adequate in terms of disclosure since it is not associated with specific products.

A study by Globescan found that 82% of consumers feel that ingredient transparency is a "very important" or "important" factor in purchase decisions relating to beauty and personal care products[4]. It also found that while there is increased use of databases like Skin Deep®, only 57% of consumers regularly check the list of ingredients in a product before purchasing. What is unknown is how many of the consumers who do check the ingredients list know how to interpret the information presented. This suggests that what consumers really want is the assurance that the product is safe, not necessarily an ingredient list.

In terms of general product claims, a recent UL research report examining the impact of green claims on purchase intent and brand perception shows that in the category of personal care products, claims that positively impacted purchase intent were primarily those that explicitly related to natural/organic/bio-based content. In the study, claims in this category were chosen by 44% of respondents. Claims relating to chemicals and toxins were also highly ranked and were chosen by 42% of respondents. Interestingly, a significant subset of respondents also reported confusion around natural and organic designations. This could indicate that the market is in a transitional state as consumers are becoming more educated and therefore more skeptical[5].

This demand is translating to a shift in spending as consumers demonstrate their concern about the ingredients in their personal care products by purchasing more products they feel are inherently safer. In the U.S., sales of natural and organic personal care products reached $12.6 billion in 2013, an increase of 11.2% over 2012, and representing 17.9% of the entire personal care industry[6].

Despite these increases, in the US there is a growing consumer distrust of natural and organic personal care products because the U.S. Federal Drug Administration (FDA) currently does not have specific requirements for products bearing the label "hypoallergenic" or "natural".

2.1.2 Chemicals of Concern and Alternatives

"Red Lists" of chemicals to be avoided as ingredients are integral to the regulations supporting cosmetic products. Red lists are becoming a common tool employed by the value chain, including retailers, chemical manufacturers, and brands. NGOs are also increasingly using red lists to identify priority ingredients. For example, the Environmental Defense Fund produced a pocket product guide list of *"10 ingredients to avoid"*; the Campaign for Safe Cosmetics profiles nearly 20 'chemicals of concern'; Women's Voices for the Earth lists 20 chemicals of concern found in feminine care products; the Frank Lipman website lists just over a dozen chemicals to avoid; the Environmental Law Centre in the UK lists nine chemicals to avoid in its *"Toxic Tour of Toiletries"*; and the David Suzuki Foundation in Canada developed a cosmetics shoppers' guide titled the *Dirty Dozen*[7].

Based on a review of these lists, the most commonly noted priority ingredients or impurities include:

- 1,4 dioxane
- Coal Tar
- BHA/BHT
- Formaldehyde and Formaldehyde-Releasing Preservatives
- Ethanolamine Compounds (*e.g.*, MEA, DEA, TEA)
- Hydroquinone
- Lead and heavy metals
- Microbeads
- Nanoparticles
- Nitrosamines
- Parabens
- Petrolatum
- Phthalates
- Silicones
- Triclosan

Many of these ingredients, including parabens, phthalates, and triclosan, are now being voluntarily phased out by major manufacturers.

The State of California also adopted a red-list type approach, with the passage of the California Safe Cosmetics Act (the Act) in 2005. This Act requires manufacturers of cosmetics to report any products that contain ingredients known or suspected to cause cancer, birth defects, or other reproductive harm. The California Safe Cosmetics Program (CSCP) collects this data and makes it available to the public via an online database which currently contains nearly 900 chemicals[8].

The key challenge with the list based approaches is that some are only working lists which have not been fully assessed, while others take into account mitigating factors such as chemical potency or dose as well as hazard information. However, in general, these lists do not reflect our understanding of "risk". In some cases, chemical hazards do not present significant risks when they are used in products with low exposure potential.

Over-reliance on red list approaches may lead manufacturers to substitute alternatives that have not yet made it onto red lists or have data gaps. In short, the unintended consequence of a red list approach is that it may encourage use of chemicals for which potential health and safety impacts are poorly understood. The emerging science of alternative assessments may offer a solution to help limit unintended consequences.

2.1.3 Aggregate and Cumulative Exposure to Chemicals

Risks associated with specific ingredients may be increased due to a typical person's use of multiple products daily and over a lifetime (cumulative exposure), or through exposure to similar chemicals in a number of different products (aggregate). For example, a study by the Campaign for Safe Cosmetics indicates that women use an average of nine personal care products each day, exposing themselves to a mixture of over 100 individual chemicals. It is also not clear whether other sources of exposure to the same chemicals (*e.g.* in food) has been considered by these groups in terms of overall risk. However, it should be noted ingredients are generally specific to product types and that consumers rarely use the same products over their lifetime.

Samuel Epstein, M.D., from the University of Illinois School of Public Health, suggests that the hazardous ingredients present in cosmetics pose high risks of cancer, genetic damage, and reproductive toxicity. Epstein states that this is due to: "the virtual lifelong use of many cosmetic products, such as shampoos and lotions; their routine daily application to large areas of skin; the ready skin absorption of some ingredients, facilitated by detergents in most products; the inhalation absorption of volatile ingredients or their contaminants; and the additive or synergistic interactions between multiple carcinogenic or otherwise toxic ingredients"[9]. Other authors making similar points include Drs. Anne Steinemann and Lance Wallace[10].

These claims are being investigated through research at academic institutions. For example, a study conducted in Reading, UK concluded that exposure to low doses of many different chemicals resulting from application of cosmetics and other environmental exposures combine to create the conditions to produce cancer. In particular, the study indicated a higher incidence of cancer in areas of the breast where multiple products are typically applied[11].

Aggregate exposure is explored further in UL's analysis of the product safety assessment frameworks.

2.1.4 Inadequate or Poorly Enforced Regulations

NGOs and the public have indicated low levels of trust in regulatory oversight of the personal care products industry, due in part to a perception that current regulations of personal care products are weak or that they are poorly enforced.

NGOs have shared concerns that manufacturers or marketers of cosmetics are not required to share their safety information with the FDA, nor are they required to register their establishments or file product formulations with the FDA; and importers of cosmetics are not required to obtain a registration number[1].

In a similar vein, the Cancer Prevention Coalition (CPC) highlights what, in its opinion, is a lack of oversight and states that "cosmetics are the least regulated products under the Federal Food, Drug, and Cosmetic Act (FFDCA)." CPC notes that the National Institute of Occupational Safety and Health found that 884 of the chemicals available for use in cosmetics have been reported to the government as toxic substances[12].

U.S. federal law states that cosmetics do not need to be approved by the FDA. However, the law specifies that manufacturers "have a legal responsibility to ensure the safety of their products" before being placed on the market, and that safety can be substantiated through trained toxicologists. Further, the FDA authorizes the cosmetics industry to provide a second safety opinion through the Cosmetics Ingredient Review panel. The FDA does have a seat on the CIR panel and therefore is privy to all information submitted. EWG notes on its website that in 36 years, this industry panel has only rejected 11 ingredients as unsafe for use in cosmetics. The European Union on the other hand banned more than a thousand ingredients from use in cosmetics in 2003[13]. It should be noted that virtually all of the banned EU ingredients have never been used in cosmetics.

Cosmetics and personal care products in the United States are affected by number of different regulations- see text box for overview.

Cosmetics Regulation

The FDA regulates cosmetics under the authority of two laws: the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Fair Packaging and Labeling Act (FPLA). According to these laws, cosmetic products and ingredients (with the exception of color additives) do not need FDA premarket approval. The law does state that manufacturers or marketers of cosmetics have a legal responsibility to ensure the safety of their products.

Over the past few years a number of legislative proposals have been put forward to increase the FDA's authority over regulating cosmetics. The latest proposal is the Safe Cosmetics and Personal Care Products Act which was introduced in March 2013 and would amend the FD&C Act. This Act would require[1]:

- *Cosmetics brand owners that market in the US to register annually and submit safety data for the ingredients in their products.*
- *The Secretary of Health and Human Services (HHS) to establish labeling requirements, establish a safety standard, issue guidance for good manufacturing practices, and issue recalls on products in violation of the FFDCA.*
- *The Secretary of HHS to evaluate the safety of cosmetics and ingredients to create three lists for ingredients: (1) a prohibited and restricted list, (2) a safe without limits list, and (3) a priority assessment list.*

This Act was referred to the Subcommittee on Workforce Protections in August 2013 and no further action has been noted.

Washington State and the State of California have enacted their own legislation focused on personal care products. Washington State's Children's Safe Products Act, adopted in 2008, includes a ban of phthalates from personal care products marketed to or used by children[7]. The California Safe Cosmetics Act was passed in 2005, which requires manufacturers of cosmetics to report any products that contain ingredients known or suspected to cause cancer, birth defects, or other reproductive harm. The California Safe Cosmetics Program (CSCP) collects this data and makes it available to the public via an online database which currently lists nearly 900 chemicals.

2.2 Stakeholder Interviews

To supplement the research, UL conducted a small number of structured telephone interviews with individual stakeholders from four distinct groups: brands, industry associations, retailers, and NGOs. These interviews were not intended to be fully representative or quantitative, but rather were designed to expand on our research findings. Key findings are outlined below.

2.2.1 Research into Viable Alternatives

All stakeholders agreed that alternatives assessment is an emerging area which requires more attention. The retailer representative felt that the safety standards actually do a good job in addressing risk but that hazards have been insufficiently addressed. In particular, in terms of (ingredient) transparency and development of "safer formulations", this individual felt that many "unwanted" chemicals remain on the market. At the same time, this retailer questioned whether "natural" products are actually performing better than other products.

Similarly, the NGO representative felt that product development should start with identifying the least hazardous possible alternative ingredients, followed by risk assessment. This interviewee also felt that there is inadequate consideration of product "end of life", or of the impacts of complex mixtures[14]. Industry association members felt that while hazard is important, consideration of exposure

and resultant risk is critical to the safety assessment by authorities and agreed that more work needs to be done on ingredient alternatives assessment. Both risk- and hazard-based approaches will be supported by an agreed upon alternatives assessment process.

2.2.2 Inadequate Consumer Information

Both the retailer and NGO interviewees felt that consumers were demanding ingredient disclosure and, that in the absence of disclosure, they do not have adequate information to make informed purchasing decisions. Although neither interviewee specified fragrances in their comments, at present these are the only ingredients which are not disclosed. The retailer representative said that the products they buy and sell are safe and that regulations are being sufficiently followed and enforced–but that consumers have changing expectations about safety and that industry safety authorities need to do more to meet these expectations.

2.2.3 Data Availability

Data availability regarding key ingredients and alternatives and the integration of such data into safety authority assessments was cited as a key concern by both industry association and NGO representatives.

2.2.4 Patchwork of Regulations

All stakeholders commented on the fragmented regulatory and quasi-regulatory landscape facing personal care product manufacturers. The industry association representative commented that the regulatory framework (*i.e.* the Federal Food, Drug, and Cosmetic Act) needs to be modernized and that a "stronger federal statute would be better than patchworks from different state-level regulations"[15]. The retailer representative also commented on the patchwork of regulations.

The next sections provide a brief overview of the regulatory framework currently in place, followed by a detailed review those frameworks in section 4, leading to identification of best practices in section 5. The conclusion identifies the best practices recommendations and how they address the concerns identified.

Assessment of Product Safety Risk Assessment Frameworks

As noted in the introduction, a total of five primary frameworks were selected for review:

- Cosmetic Ingredient Review (CIR);
- Scientific Committee on Consumer Safety (SCCS);
- International Council of Chemical Associations (ICCA);
- International Fragrance Association (IFRA) RIFM; and
- Flavor and Extract Manufacturers Association (FEMA).

A more detailed description of each of these frameworks is provided below.

3.1 Frameworks Evaluated

3.1.1 Cosmetic Ingredient Review

CIR, established by the Personal Care Product Council (PCPC), is an Expert Panel comprising industry representatives, and expert toxicologists, chemists, and dermatologists[16]. The charge of the CIR Expert Panel is to review published (and unpublished/industry-provided) literature and data for all cosmetic ingredients or group of chemically similar ingredients (as determined by internal chemists early in the process) to determine whether the ingredients are safe under their current use.

Following its review, the CIR Expert Panel votes on a final safety evaluation and summarizes its findings in a final safety evaluation report, which is published in a peer-reviewed journal (the *International Journal of Toxicology*). Toxicity evaluation and guidance documents are then developed for the personal care products industry. CIR meetings are open to the public and that public comment is accommodated for each of the substance/product review. The U.S. FDA, which serves as a non-voting member of the CIR Expert Panel, often relies on or considers CIR assessments when a safety determination is needed, but it is not bound by CIR safety conclusions[17].

It should be noted that UL was not able to identify an assessment guideline document from CIR. In the absence of such a document, UL's research team relied on individual ingredient assessments (and personal communication in some cases) to inform the evaluation of this framework.

3.1.2 Scientific Committee on Consumer Safety

Europe's SCCS is a group of independent scientists that provides opinions to the European Commission (or EC, the executive body of the European Union [EU]). SCCS provides guidance for testing and evaluating the safety of cosmetic based upon a risk assessment process defined by the World Health Organization (WHO)[18]. The charge of SCCS is to evaluate select cosmetics ingredients on the positive list or by mandate from EU commission. SCCS often works in partnership and harmonizes assessment approaches with other European Union (EU) agencies, such as the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks.

3.1.3 International Council of Chemical Associations

The ICCA is comprised of numerous trade associations representing companies involved in all aspects of the chemical industry – for example, the American Chemistry Council (ACC). ICCA was created in 1989 to coordinate the work of chemical companies and associations on issues and programs of international interest. ICCA operates by coordinating the work of member associations and their member companies through the exchange of information and the development of common positions on policy issues of international significance.

Three main areas on which ICCA focuses include Chemicals Policy & Health, Climate Change & Energy, and Responsible Care®. ICCA often partners with the United Nations Environment Programme (UNEP), United Nations Institute for Training and Research (UNITAR), and the Organization for Economic Co-operation and Development (OECD).

ICCA published a detailed guidance document titled, *"International Council of Chemical Associations (ICCA) Guidance on Chemical Risk Assessment"*[19], which provides a comprehensive approach to assessing risks in chemicals on an ingredient basis. The guidance was produced for developing regions and small- and medium-sized companies, and is part of a series of guidance documents to help ICCA member companies fulfill their commitment to perform risk assessment under global product strategy, define safe use conditions, and if necessary, implement risk management measures so that safe use conditions are met. Although, the ICCA framework is not followed within the personal care industry, it is widely recognized as a best risk assessment practice.

3.1.4 International Fragrance Association

IFRA was founded in 1973 to develop and publish standards for the safe use of fragrance ingredients and materials in a wide variety of consumer products[20]. Together with its scientific arm, the Research Institute for Fragrance Materials (RIFM), IFRA develops standards for individual fragrance ingredients based on a risk assessment approach that incorporates current use levels, product type, and the potential for exposure when products are used as intended[21,22]. RIFM's analyses and conclusions are vetted by an independent Expert Advisory Panel of dermatologists, pathologists, toxicologists, and environmental scientists with no ties to the fragrance industry. The scientific analyses produced by RIFM are published in peer-reviewed journals and IFRA's standards for fragrance ingredients are posted to its website. IFRA represents an $8 billion global industry and its members supply 90% of the global market for fragrance materials.

3.1.5 Flavor and Extract Manufacturers Association

FEMA, in conjunction with its Expert Panel of scientists, has developed and published safety data to support the self-affirmed Generally Recognized as Safe (GRAS) status of over 2,700 individual flavoring ingredients since 1970[23]. The FEMA Expert Panel relies on groups of structurally related chemicals as a key component of its risk assessment approach for food flavoring ingredients. This is much like the safety evaluation approaches used for these ingredients by the WHO's Joint Expert Committee on Food Additives (JECFA) and the European Food Safety Authority[24, 25, 26]. The primary stakeholders include flavoring and food manufacturers who rely on the self-affirmed GRAS status of individual flavoring ingredients, the U.S. FDA, and the general public, who can review the FEMA Expert Panel's GRAS lists and the scientific analysis supporting ingredients' GRAS status. The Expert Panel is recognized by the U.S. FDA and by the domestic and international food industry.

3.2 Key Attributes Reviewed

Although the information reviewed during this analysis is "qualitative", it was critical to establish a set of fundamental review criteria so that a systematic comparison could be performed across all of the frameworks. Several key categories were evaluated and are presented in Table 3.1.

Table 3.1 Key Framework Evaluation Criteria

Category	Criteria/Questions Addressed
Individual Ingredients *vs.* Finished Formulations	How are ingredients identified? Is formulation-level analysis preferred and, if so, for what endpoints? Is a method provided for "roll-up" of individual ingredient assessments into a product assessment? Does the framework address chemical loading, additivity, or synergistic reactions within a formulation?
Considerations for Ingredients with Specific Properties or Functions	Does the framework distinguish between intentionally added ingredients and impurities? If so, does the evaluation methodology for intentionally added ingredients and impurities differ? Do compounds with certain hazardous properties undergo a distinct assessment process (*i.e.*, are suspected carcinogenic, mutagens, and reproductive toxins treated differently than irritants)? Does the framework have any chemical-specific recommendations (*i.e.*, are certain chemicals prohibited outright or required to undergo a more rigorous assessment process)? Do the frameworks have special considerations for flavorings, fragrances, and nanomaterials?
Data Quality/ Requirement	Does the framework specify minimum health data requirements for evaluating product safety? Does the framework specifically address data quality? What studies should and should not be used and is there a specific scoring system (*e.g.*, the Klimisch system) utilized to evaluate product safety? Are there recommended data sources? If no ingredient-specific data are available, what are the recommendations for filling data gaps?
Toxicity Evaluation	What toxicity endpoints are evaluated? Does the framework have separate evaluation of hazard *versus* risk? Does the framework recommend the use of regulatory lists to establish hazard? What endpoints are subject to quantitative risk assessment?
Toxicity Assessment by Endpoint	
Repeated Dose Toxicology	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint? Is there a discussion of what constitutes an adverse *vs.* adaptive effect (chronic toxicity)? Are there specific endpoints the LOAEL* should not be based on (*e.g.*, changes in body weight, chronic toxicity)? Is/how is the issue of human relevance addressed?
Mutagenicity	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint? How is positive/negative *in vitro* mutagenicity data interpreted?
Carcinogenicity	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint? How is carcinogenic MOA* considered in the analysis by the frameworks, and how do the framework approaches compare? How does the framework handle linear vs. nonlinear extrapolation conceptually and what specific extrapolation methods are used?

Category	Criteria/Questions Addressed
Skin and Eye Irritation	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint?
Developmental and Reproductive Toxicity	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint? How is the issue of maternal toxicity addressed?
Sensitization	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint?
Neurotoxicity	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint?
Phototoxicity	Is this endpoint required/assessed? What are the data recommendations/requirements for the framework? What is the general methodology for the evaluation of this endpoint?
Endocrine Activity	Is this activity required/assessed? What is the general methodology for the evaluation of this activity?
Exposure Assessment	Does the framework address assessment of aggregate exposures (*i.e.*, exposure to same ingredient across multiple products/exposures)? What are the sources of exposure equations and exposure assumptions?
Safety Determination Comparisons – Uncertainty Assessment	How is overall safety determined for each endpoint? Does the framework address approaches for characterizing uncertainty in evaluation? How do the different SFs* compare across assessments? How does each endpoint assessment factor into overall safety assessment?
Alternatives Assessment	Does the framework provide any approaches for evaluating alternatives?

*Notes: LOAEL = Lowest Observed No Affect Level; MOA = Mode of Action; SF = Safety Factor.

Summary of Framework Comparison

Based on the criteria detailed in table 3.1, UL found many commonalities among frameworks, such as the health endpoints evaluated and the data types used to form conclusions. However, the frameworks varied considerably both in terms of the assessment to be conducted and in the determination of the endpoints to undergo quantitative risk assessment.

UL's analysis also identified the following potential development areas:

- Lack of consistent hazard classifications and processes that are clearly delineated from the risk assessment process
- Lack of generally agreed upon or consistent approaches to alternative assessment
- Lack of consistency in terms of consideration of additivity in mixtures
- Lack of a clear process in event of data deficiency

This analysis derived several leading practices from across the frameworks to inform development of an overarching "best practice" framework for evaluating personal care product safety in a way that is transparent and can be consistently applied.

A detailed summary of the framework comparison results is presented in Appendix A.

Best Practices Recommendations

The Table below summarizes best practices for all of the criteria reviewed.

Table 5.1 Best Practices

Category	Question	Best Practice
Ingredient vs. Full Formulation	Ingredient Identification	All Ingredients should be identified using the INCI system, and CAS numbers where available.
	Product Level Testing	Evaluation of the toxicity of whole-product formulation. Recognizing that it is not feasible to test animals and/or conduct long-term toxicity testing in humans, whole-product testing for skin irritation, eye irritation, and sensitization in humans is recommended. If a company opts out of product-level testing (*e.g.*, because a new formulation is very similar to a product that has already been tested), a scientific justification should be presented.
	Product Level Risk Assessment	Specific consideration should always be given to possible chemical interactions that could increase the toxicity of the individual ingredients. Recognizing that information on specific chemical interactions is sparse, best practices for the safety evaluation of personal care products should consider dose additivity for ingredients that have a similar mode of action or affect chronic toxicity to the same target organ via a common mechanism.
Considerations for Ingredients with Specific Properties or Function	Impurities/ Byproducts	Best practices require reliably identifying and quantifying ingredient impurities and by-products. Priority impurities should be evaluated as intentionally added ingredients.
	CMR and Other High Hazard Ingredients as Determined by Authoritative Agencies	Excluding hazardous CMRs without a risk assessment, based on other agency/industry determinations (*e.g.*, Proposition 65) reflects a conservative best practice. From a purely scientific perspective excluding chemicals below a risk threshold derived used best risk assessment practices, will not improve product safety.
	Fragrances	Reliance on IFRA and bans and restrictions established by SCCS over levels established by IFRA for overlapping ingredients. If a compound with a sensitizing hazard is present in a final product at a level greater than 100 ppm, the manufacturer should perform an independent assessment of the sensitization potential to determine if a "safe level" can be derived based on the data, as well as investigate any clinical/epidemiological evidence. With respect to respiratory sensitization, the only best practice is to prohibit the use of ingredients that are classified as respiratory sensitizers.
	Flavorings	Reliance on FEMA assessments. However, if a flavoring has been evaluated by EFSA or JECFA and a lower acceptable limit has been derived, that level should be used preferentially.
	Nanomaterials	Best practices for safety evaluation of nanomaterials should consider both U.S. FDA's recommended approach and SCCS's mandatory requirements; risk assessment needs to be carried out on a case by case basis.
	Use of CIR and SCCS Assessments	Ingredient safety assessments are conducted by authoritative agencies (*e.g.*, CIR, SCCS, and U.S. FDA). Where safety determinations vary, the most restrictive levels should be used preferentially. The manufacturer should perform an independent MOS assessment.

Category	Question	Best Practice
Data Quality/ Requirement Comparisons	Data Requirements	Toxicological characterization for each ingredient for the following health endpoints, at a minimum: Skin Irritation, Eye Irritation, Sensitization, Mutagenicity, Repeat-dose Toxicity, Carcinogenicity (for mutagenic ingredients), and Phototoxicity. There should also be information on dermal penetration[27]. If information exists for other endpoints, such as neurotoxicity or immunotoxicity, this should also be reviewed.
	Data Quality	If a guideline (*e.g.* OECD, GLP) study is not available or additional studies are used in a hazard determination, the study quality should be assessed for reliability, evaluated according to a recognized framework (*e.g.*, Klimisch rating). It is best practices to establish the criteria related to study reliability for hazard determination (*i.e.*, there should be a priori criteria regarding when a study can be used in hazard assessment or is considered too unreliable for use in a hazard determination).
	Data Sources	Articulation of a comprehensive and repeatable data identification strategy. The general types of data sources that should be considered when conducting a safety assessment include animal, in silico and *in vitro* ingredient information from ALL key available sources, including: peer-reviewed literature, publicly available industry studies, supplier toxicology tests, and assessments conducted by regulatory/authoritative agencies.
	Filling Data Gaps — Read-Across/Chemical Groupings	Using read-across data is an accepted best practice; however, manufacturers should rely on established guidance (*e.g.*, OECD or CIR [in draft] and recent RIFM guidance) when evaluating the reliability of read-across ingredients for assessing safety.
	Filling Data Gaps —QSAR	QSAR and other computational-based tools are rapidly being developed, and while their acceptance in safety determination will likely substantially increase over the next 5-10 years, current best practices do not accept the use of QSAR and other computational, high-throughput data for use in a safety determinations (*i.e.*, to rule in or rule-out hazards). These methods, however, are useful for prioritizing ingredients for further assessment.
	Filling Data Gaps —Toxicological Threshold of Concern	Best practices for the assessment of personal care products can involve the use of a TTC to fill data gaps. However, some important caveats are noted: (1) consistent with the SCCS (2012a)[28] recommendations, non-cancer ingredients should be allotted into two groups instead of three; (2) the threshold-acceptable intake levels should be adjusted to reflect infant weights for personal care products targeted to infants; and (3) there should be a specific assessment to ensure that ingredients similar to the ingredient of interest are well represented in the TTC dataset. Also, if there is reason to suspect that oral bioavailability is lower than skin bioavailability, or that the ingredient is expected to undergo first-pass metabolism, further adjustments should be made.
Hazard and Risk		Conducts a distinct toxicological profile using GHS criteria. The endpoints requiring evaluation include acute toxicity, skin and eye Irritation, sensitization, mutagenicity, carcinogenicity, reproductive toxicity (includes developmental toxicity), and repeated dose toxicity. Other related endpoints that require evaluation that do not have associated GHS criteria include dermal/percutaneous absorption; toxicokinetics, and phototoxicity where relevant. A complete hazard characterization should be followed by a quantitative risk assessment for relevant endpoints (carcinogenicity, chronic toxicity, reproductive/ developmental toxicity, and sensitization). A risk assessment needs to include a comprehensive evaluation of exposure potential. Although the prioritization of ingredient assessments should focus on specific hazard categories (*i.e.*, suspected carcinogens, mutagens, reproductive toxins, sensitizers), once an ingredient is assessed, it should undergo a hazard evaluation for all relevant endpoints.

Category	Question	Best Practice
Toxicity Assessment by Endpoint	Repeated Dose Toxicity	All ingredients should be evaluated in a quantitative risk assessment for non-cancer chronic toxicity, regardless of the degree of hazard. The identification of an appropriate NOAEL or LOAEL should be conducted in accordance with GHS guidance, although a more conservative approach that identifies effects that fall outside GHS criteria (*e.g.*, changes in body weight) can be adopted. If it is expected that a product will be used for more than 7 years, an adjustment to reflect chronic exposures (as specified by U.S. EPA or ECHA) should be considered[29, 30, 31].
	Mutagenicity	Tests for gene mutation (*e.g.*, OECD 471 or OECD 476) and clastogenicity/anugencicity (OECD 487 or OECD 473) should be conducted. As a conservative guiding principle, ingredients that meet GHS classification (GHS Cat. 1A, 1B or 2 for mutagenicity) should not be intentionally added as an ingredient (including any compounds in fragrances or flavorings).
	Carcinogenicity	As a conservative guiding principle, ingredients that meet GHS classification (GHS Cat. 1A, 1B or 2 for carcinogenicity), should not be intentionally added as an ingredient to personal care products (including any compounds in fragrances or flavorings). For ingredients not already evaluated by a safety authority, cancer risk should be evaluated using the guidelines established by SCCS, whereby ingredients with a non-genotoxic mode of action can be assessed via the methodology used for non-cancer assessment, and carcinogens with a genotoxic mode of action should be evaluated using linear extrapolation.
	Skin Irritation	Skin irritation should be investigated and characterized where information exists (animal tests, human experience) and classified in accordance with the GHS. It is considered best practices to test all formulated products in human clinical studies using standardized testing approaches.
	Eye Irritation	Eye irritation hazards should be investigated and characterized where information exists (animal tests, human experience) and classified in accordance with the GHS. In addition, clinical studies should be considered where possible.
	Reproductive Toxicity	As a conservative guiding principle, ingredients that meet GHS classification (GHS Cat. 1A, 1B or 2 for reproductive toxicity) should not be intentionally added as an ingredient to personal care products (including any compounds in fragrances or flavorings). If an alternative assessment has been performed and there is no suitable alternative, the ingredient should be evaluated in a quantitative risk assessment using the methodology used for non-cancer repeated dose exposures.
	Skin Sensitization	Best practices should utilize multiple lines of evidence to establish safety. As a first step, skin sensitization hazard should be evaluated in accordance with GHS criteria. If the potential for skin sensitization exists, a quantitative risk assessment should be performed.
	Endocrine Activity	No current best practice. Positive results in endocrine screening models can only be used qualitatively to inform assessments related to carcinogenicity, reproductive toxicity, and repeated dose toxicity.
	Phototoxicity	Phototoxicity should be assessed when the substance present in a cosmetic product is expected or intended to be used on sunlight-exposed skin. Substances should first be evaluated to determine if there is significant absorbance in the range of 290- 760 nm[32]. For substances with significant absorption, it is considered best practices to test the formulated products on human volunteers.
Exposure Assessment	Exposure and Use Assumptions	Best practices involve relying on use estimates (the more conservative of CIR, IFRA, and SCCS)

Category	Question	Best Practice
	Aggregate Exposures	Under best practices, aggregate exposures should be considered to the extent possible. For products that have the potential to involve exposure via multiple routes (*e.g.*, spray sunscreen, baby powder), aggregate exposure across routes should be assessed.
	Dermal and Oral Absorption Assumptions	Whenever possible existing ingredient-specific information on oral bioavailability should be made available. If ingredient-specific information is not available, conservative default values should be used.
Alternative Assessment		Formal consideration of alternatives that minimize ingredient hazard and optimize functionality.

Conclusion

Research shows that three out of four consumers in North America believe that personal care products can impact their health, and 80% of consumers report they are interested in purchasing more sustainable personal care products[33]. However, a key message coming from consumers is confusion around ingredient safety.

As a means of moving the debate forward, UL proposes a consensus based set of voluntary standards designed to go beyond what is required by the existing regulations for assessing personal care product safety. The best practices identified in this paper reflect current guidelines that could be used for this purpose. Overall, the best practices recommendations are largely consistent with the guidance provided by SCCS, followed by CIR, ICCA, RIFM, and FEMA.

While a credible, transparent best practice as suggested here should address many stakeholder concerns from a technical perspective, public acceptance may remain a challenge. UL believes there is a role for third parties to bridge the confidence gap and provide an effective means to validate and communicate the safety and safety practices for personal care products. UL consumer research shows that consumers are receptive to third-party certification as a means of recognizing safety standards of the products they use[34].

Appendix A: Summary of Results

The tables below summarize a detailed analysis of a very complex set of processes that have multiple ways of reaching a pass/fail determination or setting a limiting concentration. The exact evaluation is often dependent on the data available, the endpoint and the hazard level for the endpoint. The summary, in tabular form, should be used as a starting place for further in depth research into the systems reviewed.

x Not covered by protocol

✓ Explicitly covered by protocol

= Partially covered by protocol or covered but no details on specific methods

Table A.1 - Summary of Toxicity Endpoints Evaluated by Each Framework (CIR, ICCA and SCCS)[35]

Framework	Hazard Endpoints	Quantitative Risk Assessment (Criteria)
CIR	• Acute Toxicity • Skin/Eye Irritation & Corrosivity • Sensitization • Mutagenicity/Genotoxicity • Repeated Dose Toxicity • Reproductive & Developmental Toxicity and Carcinogenicity • Phototoxicity	• Repeat-dose Toxicity (selective assessment, criteria unclear) • Skin Sensitization (if hazard exists) • Reproductive & Developmental Toxicity (selective assessment, criteria unclear)
ICCA	• Acute Toxicity • Skin/Eye Irritation & Corrosivity • Sensitization • Mutagenicity/Genotoxicity • Repeated Dose Toxicity • Reproductive & Developmental Toxicity and Carcinogenicity • Ecotoxicity • Some physical hazards also addressed	• Acute Toxicity (all compounds, if data are available) • Repeat-dose Toxicity (all compounds) • Skin Sensitization (all compounds, if data are available) • Skin/Eye Irritation & Corrosivity (all compounds if data are available) • Reproductive & Developmental Toxicity (all compounds, if data are available) • Carcinogenicity (all compounds, if data are available)
SCCS	• Acute Toxicity • Skin/Eye Irritation & Corrosivity • Sensitization • Mutagenicity/Genotoxicity • Repeated Dose Toxicity • Reproductive & Developmental Toxicity and Carcinogenicity • Phototoxicity	• Repeat-dose Toxicity (all compounds) • Reproductive & Developmental Toxicity (if hazard exists) • Carcinogenicity (if hazard exists)

Table A.1 - Summary of Toxicity Endpoints Evaluated by Each Framework (CIR, ICCA and SCCS)

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Individual Ingredients vs. Finished Formulations	How are ingredients identified?	INCI/CAS	CAS	INCI/CAS	CAS	INCI/CAS
	Is formulation-level analysis preferred and, if so, for what endpoints?	Ingredient	Ingredient	Ingredient	Recommended for Chronic endpoints	Recommended also final product testing
	Is a method provided for "roll-up" of individual ingredient assessments into a product assessment?	X	X	X	✓	✓
	Does the framework address synergistic reactions within a formulation?	X	X	X	X	=
Considerations for Ingredients with Specific Properties or Functions	Does the framework distinguish between intentionally added ingredients and impurities? If so, does the evaluation methodology for intentionally added ingredients and impurities differ?	X	X	Separate limits of impurity of concern for acceptance of mixture as ingredient	Yes, all above 1%, hazard above 0.1%	No distinction but specific to supply source
	Do compounds with certain hazardous properties undergo a distinct assessment process (*i.e.*, are suspected carcinogenic, mutagens, and reproductive toxins treated differently than irritants)?		Repeat dose, oral and dermal, carcinogenicity, genotoxicity, development and repro, immune toxicity and neuro toxicity	Sensitization, phototoxicity, or systemic effects		
	Does the framework have any chemical-specific recommendations (*i.e.*, are certain chemicals prohibited outright or required to go through a more rigorous assessment process)?		Database of NOAEL values used for screening			
	Do the frameworks have special considerations for flavorings, fragrances, and nanomaterials?	Nanomaterials covered in current system	Flavorings focused	Fragrances focused		Fragrances Nanomaterials

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Data Quality/ Requirement	Does the framework specify minimum health data requirements for evaluating product safety?					
	Does the framework specifically address data quality? What studies should and should not be used and is there a specific scoring system (*e.g.*, the Klimisch system) utilized to evaluate product safety?	OED/EPA or Case by Case	OED/EPA	OED/EPA	OED/EPA or Klimisch	OED/EPA or Scientifically Justified
	Are there recommended data sources?	All Available Government databases, peer-reviewed literature, and proprietary industry studies	All Available	All Available	All Available Guidelines include suggestions without priority	All Available
	If no ingredient-specific data are available, what are the recommendations for filling data gaps?					
Toxicity Evaluation	What toxicity endpoints are evaluated?	See Table A.1	See Table A.1	See Table A.1	See Table A.1	See Table A.1
	Does the framework have separate evaluation of hazard versus risk?				✓	Some Endpoints
	Does the framework recommend the use of regulatory lists to establish hazard?				GHS	GHS
	What endpoints are subject to quantitative risk assessment?	See Table A.1			See Table A.1	See Table A.1
Exposure Assessment	Does the framework address assessment of aggregate exposures (*i.e.*, exposure to same ingredient across multiple products/ exposures)?	=	✓		X	✓
	What are the sources of exposure equations and exposure assumptions?	US Voluntary Cosmetic Registration Program (VCRP)		Habits and Practice Data U.S. EPA Netherlands National Institute for Public Health and the Environment		European Study and probabilistic analysis 90th percentile
	Are exposure assumptions for infants specifically articulated?	Developing system				

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Safety Determination Comparisons – Uncertainty Assessment	How is overall safety determined for each endpoint?					
	Does the framework address approaches for characterizing uncertainty in evaluation?	Quantitative risk for repeated exposure, reproductive/ developmental toxicity, carcinogenicity, and sensitization See Table A.1			Quantitative risk for repeated exposure, reproductive/ developmental toxicity, carcinogenicity, and sensitization See Table A.1	Quantitative risk for repeated exposure, reproductive/ developmental toxicity, carcinogenicity, and sensitization See Table A.1
	How do the different SFs compare across assessments?	X			100-1000 dependent on route T25 be divided by 25,000 and a BMDL10 divided by 10,000 for genotoxic carcinogens	100-600 dependent on route T25 be divided by 25,000 and a BMDL10 divided by 10,000 for genotoxic carcinogens
	How does each endpoint assessment factor into overall safety assessment?					
Alternatives Assessment	Does the framework provide any approaches for evaluating alternatives?	X	X	X	X	=

Table A2- Toxicity Assessment by End Point

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Repeated Dose Toxicology	Is this endpoint required/assessed?	✓			✓	✓
	What are the data recommendations/ requirements for the framework?				Human preferred then 28 or 90 day rat	Human preferred then 28 or 90 day rat
	What is the general methodology for the evaluation of this endpoint?	Qualitative			Quantitative Risk	Quantitative Risk
	Is there a discussion of what constitutes an adverse vs. adaptive effect (chronic toxicity)?				X	✓
	Are there specific endpoints the LOAEL should not be based on (*e.g.*, changes in body weight, chronic toxicity)?				Include morphology, physiology, growth, clinical chemistry, and behavior	
	Is/how is the issue of human relevance addressed?				Reflective of potential human exposure	Reflective of potential human exposure
Mutagenicity	Is this endpoint required/assessed?	✓	✓	✓	✓	✓
	What are the data recommendations/ requirements for the framework?	*In vivo* genotoxicity tests *in vitro* bacterial and mammalian cell			Human epidemiological data or *in vivo* bacterial or mammalian cell lines QSAR	Human epidemiological data or *in vivo* bacterial or mammalian cell lines QSAR
	What is the general methodology for the evaluation of this endpoint?	Expert judgment				(1) Mutagenicity at a gene level; (2) Chromosome breakage and/or rearrangements (clastogenicity); and (3) Numerical chromosome aberrations (aneugenicity)
	How is positive/negative *in vitro* mutagenicity data interpreted?					Negative data in tests excludes endpoint Positive is considered mutagen Follows GHS

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Carcinogenicity	Is this endpoint required/assessed?	=			✓	✓
	What are the data recommendations/ requirements for the framework?	Human epidemiological data and *in vivo* carcinogenicity assays			GHS data and QSAR	*In vivo* preferred but no longer available
	What is the general methodology for the evaluation of this endpoint?				GHS	GHS
	How is carcinogenic MOA considered in the analysis by the frameworks, and how do the framework approaches compare?				Non-genotoxic use MOS and calculate NOAEL Genotoxic assume no safe exposure	Non-genotoxic use MOS and calculate NOAEL Genotoxic assume no safe exposure
	How does the framework handle linear vs. nonlinear extrapolation conceptually and what specific extrapolation methods are used?				Non-genotoxic establish NOAEL Genotoxic use T25 or BMDL10 and Lifetime Cancer Risk using linear extrapolation	Non-genotoxic establish NOAEL Genotoxic use T25 or BMDL10 and Lifetime Cancer Risk using linear extrapolation
Skin and Eye Irritation	Is this endpoint required/assessed?	✓			✓	✓
	What are the data recommendations/ requirements for the framework?	Animal for skin and eye irritation			Rabbit *in vivo* Also recognizes some QSARs	Skin corrosion-Five validated *in vitro* substitutes are recognized Skin irritation – three recognized Physicochemical properties Chemical reactivity Eye - Draize *in vivo* only Human compatibility testing after safety review
	What is the general methodology for the evaluation of this endpoint?				Quantitative risk using NOAEL or LOAELs applied as repeated dose toxicity	

Category	Criteria/Questions Addressed	CIR	FEMA	IFRA	ICCA	SCCS
Developmental and Reproductive Toxicity	Is this endpoint required/assessed?	✓			✓	✓
	What are the data recommendations/ requirements for the framework?	Unspecified reproductive toxicity studies				Epidemiological studies OECD or U.S. EPA OPPTS animal studies QSAR
	What is the general methodology for the evaluation of this endpoint?	NOAEL and MOS			NOAEL and LOAEL GHS framework	NOAEL and LOAEL GHS framework
	How is the issue of maternal toxicity addressed?				Included in testing protocols	Included in testing protocols
Sensitization	Is this endpoint required/assessed?	✓		✓	✓	✓
	What are the data recommendations/ requirements for the framework?	Human or animal sensitization data			Human or animal sensitization data QSAR	Human(preferred) HRIPT or animal sensitization data Select in vivo tests Also human compatibility testing
	What is the general methodology for the evaluation of this endpoint?	Quantitative Risk assessment (IFRA method) Weight of Evidence determined NESIL		Quantitative Risk assessment	Quantitative Risk assessment (IFRA method) Weight of Evidence determined NESIL	Clinical data and/or elicitation low-effect levels to for known sensitizing substances
Neurotoxicity	Is this endpoint required/assessed?	X	X	X	X	X
	What are the data recommendations/ requirements for the framework?					
	What is the general methodology for the evaluation of this endpoint?					
Phototoxicity	Is this endpoint required/assessed?	✓	X	X	X	✓
	What are the data recommendations/ requirements for the framework?					3T3 Neutral Red Uptake Phototoxicity Test (with reserve) Select photomutagenicity tests
	What is the general methodology for the evaluation of this endpoint?					
Endocrine Activity	Is this activity required/assessed?	X	X	X	X	X
	What is the general methodology for the evaluation of this activity?					

1 Yeomans, M., 2012 “Global beauty market to reach $265 bn in 2017 due to an increase in GDP”, CosmeticDesign.com, http://www.cosmeticsdesign.com/Market-Trends/Global-beauty-market-to-reach-265-billion-in-2017-due-to-an-increase-in-GDP (accessed on 2 April 2015).

2 Aggregate chemical exposure is also referred to as “loading” or “additivity”

3 EWG & CSC, http://www.safecosmetics.org/article.php?id=644

4 Globescan, http://tinyurl.com/jvtaqh2

5 *Under the Lens: Claiming Green* (UL LLC, 2014) http://environment.ul.com/claiminggreen

6 The entire personal care products industry is growing by about 3% per year (communication with brand representative)

7 Environmental Defence Fund, http://tinyurl.com/6m7q04n, Campaign for Safe Cosmetics, http://www.safecosmetics.org/section.php?id=46, Women’s Voices for the Earth. http://tinyurl.com/k6hvbnq, Frank Lipman, http://tinyurl.com/26s3ttp, Environmental Law Centre, http://www.elc.org.uk/pages/envirotoxictour.htm . David Suzuki Foundation, http://tinyurl.com/y2kq033

8 California Department of Public Health, https://safecosmetics.cdph.ca.gov/search/

9 Epstein, S. 2013. Avoidable Causes of Childhood Cancer. XLibris, US.

10 http://www.drsteinemann.com/publications.html
http://www.cdc.gov/biomonitoring/environmental_chemicals.html
K. Sexton and D. Hattis, Assessing Cumulative Health Risks from Exposure to Environmental Mixtures—Three Fundamental Questions, Environmental Health Perspectives 115(5): 825–832 (2007)

11 Darbre, P., http://ar.iiarjournals.org/content/30/3/815.short

12 Cancer Prevention Coalition, http://tinyurl.com/olltz4h

13 It is not clear if many of these 1000 chemicals were previously used in cosmetics

14 This research covers the use phase of personal care products.

15 TSCA does not apply to personal care products per se, but fragrances and preservative ingredients are covered because fragrances can also be used in cleaning products and preservatives are covered by FIFRA

16 Cosmetic Ingredient Review (CIR). 2010. "Cosmetic Ingredient Review Procedures." 27p. October.

17 US Food and Drug Administration (US FDA). 2014a. "Product Testing." Accessed at http://www.fda.gov/Cosmetics/ScienceResearch/ProductTesting/default.htm.

18 WHO/UNEP/ILO Approaches to Integrated Risk Assessment, Doc. WHO/IPCS/IRA/01/12 of December 2001; European Commission, DG Health and Consumer Protection. First Report on the Harmonisation of Risk Assessment Procedures, Part 1. The Report of the Scientific Steering Committee's Working Group on Harmonisation of Risk Assessment Procedures in the Scientific Committees advising the European Commission in the area of human and environmental health (2000), published on the Internet 20.12.2000.

19 International Council of Chemical Associations (ICCA). 2011. "Global Product Strategy: ICCA Guidance on Chemical Risk Assessment (2nd Edition)." 192p.

20 International Fragrance Research Association (IFRA). 2014. "About IFRA." Accessed at http://www.ifraorg.org/en-us/about-ifra-text#.VJsCB5BoMA.

21 International Fragrance Research Association (IFRA). 2011. "IFRA RIFM QRA Information Booklet (Version 6.0)." 37p., July.

22 International Fragrance Research Association (IFRA). 2013. "IFRA Standards (47th Amendment)." 350p.

23 Munro, IC; Kennepohl, E; Kroes, R. 1999. "A procedure for the safety evaluation of flavouring substances." *Food Chem. Toxicol*. 37:207-232.

24 JECFA is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of flavorings, contaminants, naturally occurring toxicants, and residues of veterinary drugs in food (FAO and WHO, 2006).

25 World Health Organization (WHO). 2014. "Joint FAO/WHO Expert Committee on Food Additives (JECFA)." Accessed at http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/.

26 European Food Safety Authority (EFSA). 2014. "About EFSA." 2p. Accessed at http://www.efsa.europa.eu/en/aboutefsa.htm.

27 Note that additional data on dermal absorption may not be required if an assumed 100% penetration yields a satisfactory MOS

28 European Commission, Health & Consumer Protection Directorate-General, Scientific Committee on Consumer Safety (SCCS). 2012a. "The SCCS'S Notes of Guidance for the Testing of Cosmetic Substances and Their Safety Evaluation (8th Revision)." SCCS/1501/12. 133p., December 11.

29 U.S. EPA. 1989. "Risk Assessment Guidance for Superfund (RAGS). Volume I: Human Health Evaluation Manual (Part A) (Interim final)." Office of Emergency and Remedial Response. NTIS PB90-155581; EPA-540/1-89-002. 287p., December.

30 U.S. EPA. 2002. "A Review of the Reference Dose and Reference Concentration Processes (Final)." Risk Assessment Forum, Reference Dose/Reference Concentration (RfD/RfC) Technical Panel. EPA/630-P-02/002F. 192p., December. Accessed at http://www.epa.gov/raf/publications/pdfs/rfd-final.pdf.

31 International Council of Chemical Associations (ICCA). 2011. "Global Product Strategy: ICCA Guidance on Chemical Risk Assessment (2nd Edition)." 192p.

32 Significant absorption is defined as exceeding 1000L x mol^{-1} x cm^{-1}. European Medicines Agency. 2010. “Note for Guidance on PhotoSafety Testing”.

33 NMI: U.S. Consumer Perspectives and Trends in Sustainability 2013

34 *Under the Lens: Claiming Green* (UL LLC, 2014) http://environment.ul.com/claiminggreen

35 FEMA and IFRA were not reviewed on an endpoint by endpoint basis but were included in the best practices review and recommendations