skinobs

December 2024

FOCUS #11

TESTING EXPERT DISCUSSION AROUND TOLERANCE AND SAFETY



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Safety & Tolerance Testing for the Cosmetics

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In the dynamic world of cosmetics, ensuring the safety and tolerance of products is a critical priority for manufacturers and regulators alike. As consumers become increasingly aware of the ingredients in their beauty products, the demand for rigorous safety assessments has never been higher. This article explores the **essential processes and methodologies** involved in evaluating the safety and tolerance of cosmetic products, highlighting both traditional practices and innovative approaches.

SAFETY TESTS AND THE 3R PRINCIPLE

With regulatory frameworks such as the European Union's Regulation (EC) No 1223/2009 setting high standards, the cosmetics industry needs testing alternatives especially in safety to **replace animal testing** that is just not anymore ethically acceptable.

New Approach Methodology / Non-Animal Alternative Methods are now part of the routine toxicity testing of ingredients and cosmetics. These methods are a response to the **3R principle– the Replacement, Reduction and Refinement of animal experiments.**

For safety testing, **in-silico, in-vitro or ex-vivo methods** represent essential and reliable proof as predictors of the tolerance on human.

The safety of the cosmetic product is the first step in its evaluation. In Europe a report is required, in the form of the **Product Information File** (PIF), before it is launched on the market according to Regulation (EC) No 1223/2009 (Cosmetic Product Safety Report). This report on the safety of the cosmetic product includes a **Part A** on the safety of the product which gathers, among other things, information on the formula composition, its physico-chemical and microbiological characteristics, its stability, its toxicological profile. **Part B** is dedicated to the safety of the product and the conclusions of its evaluation carried out by toxicologist experts. Preclinical testing verifies the margins of safety for each ingredient and determines what tests are needed, analytical, preclinical, or clinical, to ensure the product's safety.
Tests such as **irritant, sensitization or phototoxicity** potential can be evaluated **by in-silico approach** or **(Q)SAR** (Quantitative Structure-Activity Relationship). This analysis defines, via mathematical models, the correlation between a chemical structure and a biological or chemical activity.

Then, safety tests are conducted on **chemicals, cell cultures or 3D skin models**, through standardized or innovative assays. European Centre for the Validation of Alternative Methods (ECVAM) has developed several OECD test guidelines to provide reliable and scientifically satisfactory standards for in vitro assays. For each specific target, valuable and numerous diagnostic methods are proposed offering a varied choice:

1. Skin toxicity

Corrosion:
- Electrical Resistance TER | RET [OECD 430],
- Corrosion Skin 3D Model [OECD TG 431],
- Corrositex [OECD 435]...

Irritation:
- HET-CAM,
- MTT cytotoxicity,
- XTT cytotoxicity,
- Dermal Irritation ET50 ...

Sensitization:
- DPRA Direct Peptide Reactivity Assay [OECD 442C],
- Genomic categorization [Sens-is],
- H-CLAT [OECD 442E],
- U-SENS | IL-8 Luc [OECD 442],
- MTT- IL-8 [epiCS-SSPT],
- ARE-Nrf2 Luciferase KeratinoSens or Lusens Test [OECD 442D],

- Genomic categorization [GARDPotency OECD TGP 4.106],
- Genomic categorization [GARDSkin OECD TGP 1.406],
- ARE-Nrf2 Luciferase KeratinoSens or Lusens Test [OECD 442D],
- Combined approach [OECD 497]...

Phototoxicity:

- 3T3 NRU [OECD 432],
- INVITTOX 121, OECD 498,
- Photo-hCLAT,
- Photo-Comet Assay...

Photosensitization:

- Photo & Kinetic-DPRA Assay...

2. Mucosa irritation

- Irritation Assay System [OECD TG 496],
- Cellular viability [OECD TG 439],
- Zein solubilization test...

3. Oral toxicity

- OECD 129

4. Eye irritation

- Neutral Red, Fluorescein Leakage Test [OECD 460],
- Short Time Exposure [OECD 491],
- EpiOcular Eye Irritation Test [EIT] [OECD 492],
- Bovine Corneal Opacity and Permeability [adapted OECD 437],
- Cytotoxicity [OECD 492 Like],
- Agarose Overlay,
- Acute and repeated exposure,
- Isolated Chicken Eye [OECD 438],
- Ocular Irritation Assay System [OECD 496],
- Chorioallantoic Membrane Vascular Assay, NociOcular Assay,
- Vitrigel®-Eye Irritation Test [Vitrigel®-EIT] [OECD 494],
- Serious eye damage and eye Irritation [OECD 263],
- Acute Eye Irritation/Corrosion [OECD 405]

5. Genotoxicity - Mutagenicity

- Ames test [OECD 471],
- HPRT Gene mutation assay [OECD 476],
- Mammalian Cell Micronucleus Test [OECD 487],
- Genotoxicity, Comet Assay Mammalian Cell Gene Mutation [OECD 490],
- Micronucleus test,
- Chromosomal aberration test [OECD 473],
- Reconstructed Skin Micronucleus [RSMN],
- Adductomics,
- 3D skin Comet Assay.

For the skin sensitization test a combination of two in-vitro studies and an in-tubo test leads to hazard potential classification using an DA (defined approach). These studies target three different key events in an **Adverse Outcome Pathway** (AOP). Two concordant results lead to the classification as sensitizer/non-sensitizer (UN GHS 1 or NC). In addition to this the new **OECD 497** provides an **Integrated Test Strategy** (ITS) based on these studies plus in-silico prediction (e. g. QSAR or DEREK Nexus database) and allows GHS Classification into Potency subcategories 1A and 1B.

TOLERANCE, THE ESSENTIAL EVALUATION ON HUMAN

The tolerance assessments implemented on human subjects highlight **the absence of irritant, sensitization, photo-irritant and sensitization potential** on normal or reasonably foreseeable conditions of use.

The safety assessment is conducted by experts (doctor, toxicologist or equivalent qualified person authorized by the regulation). **Depending on the country regulation** and on the clinical study design (babies, ethnicities, repeated applications, sun exposure...), the protocols can be submitted to the ethics committee.

There are 4 categories of tests:

1. Assessment of the irritation potential by Patch-Test

The patch test allows the study of skin tolerance by simple contact. It consists in a single application of the product, normally for 24, 48, 72 or 96 hours on volunteers under occlusive or semi-occlusive patch on the arm or the back. Then the outbreak of any skin reactions at patch removal (under medical or dermatological supervision).

2. Use test under medical control:

dermatologists, ophthalmologists, gynaecologist or ophthalmologist, paediatricians

- Use test with repeated applications under the normal conditions of use
- Repeat Open Application Test (ROAT)
- No comedogenicity
- Ocular projection or instillation

3. Assessment of the allergenic potential

The sensitizing potential includes an induction phase, a resting phase, and a triggering phase TCFS, Final clinical safety test, **Human Repeat Insult Patch-Test** (HRIPT-Marzulli & Maibach) generally conducted on 60 to 100 subjects.

4. Photo tolerance: toxicity and sensitization

Clinical evaluation by scoring of the skin aspect after 1 single application and UV exposure. One application during 24 h on 3 areas under occlusive or semi-occlusive patch. The conclusion regarding the product safety represents the final analyses of the data and the results of the cosmetics tests under several criteria: exposure, conditions of use, risks of misuse validated by a medical assessment.

Look for in-vivo tolerance evaluation **32 methods**, **147 providers** in **38 countries** on Skinobs clinical testing platform.

The evaluation of the tolerance of the product dedicated to sensitive skin is particular. The claim **«sensitive skin»** is possible if both of the following conditions are met:

a) The volunteers included in the test of use carried out under normal conditions of use declared recent and repeated history of functional symptomatology of skin discomfort (e.g., tingling, tightness, warm-up, itching, burning, redness...).

b) These volunteers did not show an increase in symptomatology during the usual test functional skin discomfort analyzed as relevant.

This tolerance testing on Human are one of the pilar of the safety of the product before its launch on the market. Depending on the type of products i.e. shampoo, hair dye, depilatory or skin care, the protocols must **be adapted in accordance with the usual way the product is applied** i.e. ethnicity, rinse, frequency, quantity... It means that each evaluation manager must discuss the details of the protocol design with the toxicologist and each testing laboratory.

In conclusion, toxicity and tolerance ensure that consumers can use products without risk to their health. Human evaluation is the last step before in-depth studies of their efficacy and validation of their claims. Since the 2000s, toxicity tests have evolved very rapidly following advances in in-silico analysis technologies and the capabilities of **artificial intelligence in data processing.** In-vitro tests, on the other hand, are becoming more sophisticated with the use of increasingly **complex skin models** that can integrate ethnic, age and sensitivity variables. Also, also with the democratization of genomic and metabolomic analyses among others; the development of microfluidics techniques and the arrival of **«Vegan» tests** drastically reducing the use of animal by-products. Between guidelines and best practices, eco-responsible consumer expectations and scientific reality, the evolution of technologies will undoubtedly be a source for tomorrow's new testing perspectives.

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Ensuring the Safety of cosmetic products: a comprehensive overview

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Consumer safety is a paramount concern throughout the entire cosmetic supply chain. Companies are unwavering in their commitment to ensuring that their products comply with the Cosmetic Regulation (EC) no. 1223/2009, which aims to guarantee the safety of the end consumer. Before any product reaches the market, it must undergo a thorough evaluation.

Regulatory compliance and testing

As mandated by the Regulation, ***in vitro* toxicity and *in vivo* safety tests are indispensable for assessing the safety and skin tolerability of cosmetic products.** Laboratories equipped to assist in evaluating the compatibility of cosmetic products provide a comprehensive range of scientific studies to support safety assessments, utilizing in vitro toxicity tests and in vivo studies to gather essential data as part of the Integrated Testing Strategy (ITS). The ITS framework is designed to identify and classify the risk of skin sensitization caused by specific substances or compounds.

In vitro testing

In vitro toxicity tests are crucial for evaluating the safety and skin tolerability of cosmetic ingredients and products. Following the total ban on animal testing in March 2013, numerous in vitro skin sensitization tests have been developed as reliable alternatives for ingredient and product evaluation. By combining multiple in vitro tests within the ITS framework, greater predictability in the analytical approach can be achieved.

1. **Skin Irritation Test:** This test assesses whether a cosmetic product causes irritation when applied to the skin. It is typically conducted using reconstructed human epidermis models.
2. **Skin Sensitization Test:** This test evaluates the potential of a cosmetic product to cause an allergic reaction after repeated exposure. In vitro tests using cell-based assays or human tissue models are commonly used. These tests measure markers of immune response, such as the activation of certain immune cells, to predict sensitization potential.
3. **Eye Irritation Test:** Eye irritation tests determine whether a cosmetic product causes adverse reactions when it comes into contact with the eyes. In vitro tests using reconstructed human corneal models or isolated animal eyes are often employed. The product is applied to the eye model, and any damage or irritation is assessed through various biochemical and morphological endpoints.
4. **Phototoxicity Test:** This test evaluates whether a cosmetic product becomes toxic when exposed to light. It involves applying the product to cell cultures or reconstructed skin models and then exposing them to UV light. The cells are monitored for signs of damage or cell death, indicating phototoxic potential.
5. **Cytotoxicity Test:** Cytotoxicity tests assess the overall toxicity of a cosmetic product by measuring its effect on cell viability. This is done by exposing cultured cells to the product and then evaluating cell health using assays that measure cell metabolism, membrane integrity, or enzyme activity. A decrease in cell viability indicates cytotoxicity.
6. **Genotoxicity Test:** Genotoxicity tests determine whether a cosmetic product ingredient can cause genetic mutations or damage to DNA. These tests are performed using bacterial or mammalian cell cultures. Common assays include the Ames test, which uses bacteria to detect mutations, and the comet assay, which measures DNA strand breaks in individual cells.

Dermatological testing – skin compatibility
Dermatological tests, conducted under strict control, **ensure skin compatibility by confirming the absence of irritation** when a cosmetic product is applied. These tests are performed on a panel of healthy volunteers with normal or sensitive skin by a qualified dermatologist.
Patch Test. this test confirms the skin compatibility of a cosmetic product intended for human skin contact. It assesses the absence of irritation upon the first application rather than the product's intrinsic irritation potential. The product classification is based on the average irritation index at each evaluation time as follow: non-irritating, slightly irritating, moderately irritating, or highly irritating. A dermatologist evaluates the results using a clinical score (0-4) for erythema and edema. The application can be evaluate according to the INCI composition. The application can be performed:

- Occlusive Patch Test. Conducted over 24 or 48 hours, the cosmetic product is applied under exaggerated conditions using an occlusive patch. The product remains in situ for a predetermined time.
- Semi-Occlusive Patch Test. The product is applied to the skin and covered with cotton or tape, providing a less intense occlusion compared to the occlusive patch.
- The Open Epicutaneous Test is adopted (as an alternative to Patch Test Occlusive) for finished cosmetic products or new formulations with extreme basic pH, volatile substances and particular mixtures of solvents, in order to prevent responses more intense and false positive reactions due to the occlusion of the test substance.

Dermatologist supervised in use test. The product is given to volunteers who use it for a month. A dermatologist assesses the absence of adverse reactions after the initial application and after a predetermined period.

Non-comedogenic test. This test evaluates the skin condition before and after one month of product usage, counting the number of comedones and blackheads on the forehead, cheeks, and chin.
Skin compatibility tests are conducted on a panel of volunteers selected based on predefined inclusion/exclusion criteria, in accordance with international regulatory guidelines and the ethical principles outlined in the Declaration of Helsinki.

Ophthalmological testing – ocular tolerance

Ophthalmological tests, conducted under strict supervision, **evaluate the eye compatibility of cosmetic products intended for periocular application**. These tests are performed on volunteers with normal or sensitive eyes, or those wearing contact lenses, under the guidance of ophthalmologists. A self-assessment questionnaire and an interview with the ophthalmologist are included to identify any potential undesired sensations.

Conclusion

These comprehensive safety tests are integral to the development and regulation of cosmetic products, ensuring they are safe for consumer use. By adhering to stringent regulatory guidelines and employing advanced scientific methodologies, **the cosmetics industry can confidently offer products that not only enhance beauty but also protect health.**
For consumers, this means **great confidence in the brand choose when using cosmetic products.** The rigorous testing ensures that products are free from harmful effects, minimizing the risk of skin irritation, allergic reactions, and other adverse outcomes. The dedication to safety in the cosmetics industry ultimately results in high-quality products that consumers can trust, reinforcing their confidence in the brands they choose and the products they use daily.

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Safety & Tolerance Testing: Basics for every skin care product

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The measurement of the transepidermal water loss **TEWL** is an important, if not the most important parameter in assessing the influence of a product on the skin barrier. When skin is damaged, the close cohesion of skin cells is disrupted. This makes it easier for external irritants to enter, and results in increased evaporation from the skin. If the barrier is significantly impaired by the application of a product, this product cannot be considered safe. The **Tewameter® TM Hex** is the benchmark standard instrument of cosmetic and pharmaceutical industry to measure TEWL. With its 60 sensors, it is very accurate, reproducible and easy to use. A reliable measurement is available in as quick as 20 seconds. The measurement uncertainty can be monitored during the measurement.

In addition to the classic TEWL result, the high amount of measuring values generated by the probe delivers **new, innovative parameters** that can support other product claims (such as skin energy balance and others).

Another basic parameter for safety and tolerance and identifying sensitive skin is **erythema**. It may occur after immediate or prolonged application of the product indicating irritation. The **Mexameter®** assesses this parameter within a second and is suitable to monitor even smallest colour changes on a scale from 0 to 999, not necessarily visible with the eye.

An impaired skin barrier also goes hand in hand with changes in other **biophysical skin parameters** such as moisture and lipid deficiency, insufficient acid mantle or reaction to temperature (heat and cold) and more. Having a set of probes including **Corneometer®**, **Sebumeter®**, **Skin-pH-meter** and **Skin-Thermometer** is an excellent basis for testing the compatibility of products quickly and comprehensively in-house backed-up by extensive literature.

A sophisticated software supporting all C+K probes makes documenting your tests a simple task. **Camera systems** such as **Visioscan®** that evaluate e.g. scaling and surface structure are a valuable addition to the qualitative data of the probe devices.

However, despite all the progress in measurement technology, **customer perception** about the skin state after applying a product should also be taken into account.

With the ban of animal testing for cosmetic products, **in vitro measurements** are another main players, especially in the areas of safety and tolerability of topical applied products. To observe how the TEWL is affected and improved, ingredients and products are applied to skin models. With the **Tewitro®**, TEWL measurement can quickly and easily detect barrier damage on **24 cell cultures simultaneously**. The probe is set on top so that each of its 24 measurement tips protrudes into one well. The measurement tip is equipped with two pairs of sensors that continuously measure temperature and relative humidity, indirectly capturing the concentration gradient of water vapour from the bottom of the well through the skin model to the surface.

To replace the infamous Draize-eye test where chemicals' risk potential is tested by applying it to rabbits' eyes, non-animal test strategies, such as **TEER** (**T**rans**e**pithelial **E**lectrical **R**esistance) measurements on cultured tissue well plates, are becoming increasingly important in the industry since they are providing valuable information about integrity and health of epithelial barriers. Electrical impedance spectroscopy is a known and valuable method to provide quantitative data about tissue barrier integrity and tissue growth after chemical exposure by measuring electrical properties of skin models.
A low frequency alternating current is applied, and the resistance of the barrier and phase shift of the signal are measured. A reduced TEER value is an indicator of a compromised barrier. The easier the current flows between the cells, the lower the TEER value. With the ultrasensitive i**mpedance spectroscopy device CellSpectrometer CMS 2100** (coming out soon), TEER can be assessed at 12.5 and 1000 Hz in 24 wells simultaneously as fast as in a total time of 15 seconds, while additionally, a full impedance spectrum from 1 Hz to 200 KHz is available in less than 2 minutes, sufficiently sensitive to cell structure integrity on single cell levels.

There is no optimal method to determine product safety and tolerability. The subject is complex and manifests itself in many different ways on the skin. For almost 40 years, we have made it our mission to provide sophisticated, easy-to-use skin measurement methods in this field and are constantly developing new solutions.

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Your preferred partner for evaluation of the Tolerance and Safety of your cosmetic products

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Clinical research plays a pivotal role in advancing medical science. The safety of participants is the cornerstone of clinical trials, underpinning both the ethical and scientific integrity. National and international regulatory bodies, such as the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA), and the Cosmetic Ingredient Review (CIR), critically oversee the safety aspects related to product development. Cosmetic research, as a special domain works in the spirit of Good Clinical Practices (GCP). Among their various aspects, safety trials are particularly critical, focusing on identifying potential risks and adverse effects of new cosmetic products or medical devices such as injectable fillers etc.

CIDP, as a global leader in dermo-cosmetic research field, places human health and regulatory compliance as paramount. As part of its comprehensive portfolio in cosmetic testing, CIDP offers rigorous in-vivo safety assessments including occlusive, semi-occlusive and open Patch testing as well as HRIPT (human repeat insult patch test). These tests are designed to identify the allergic and irrational potential of the topical formulations and ensure safety of the consumers while using it.

With a database of more than 50,000 adults and children of various ethnic origins and unique attributes, skin sensitivity plays a major role in defining the tolerance and acceptability of a cosmetic product. At CIDP, sensitivity testing such as stinger's tests, photosensitization testing are done routinely to ensure that the results of sensitivity testing are as applicable and as inclusive as possible. Expanding its portfolio beyond dermatology, CIDP routinely performs safety testing for products intended for periocular usage, oral hygiene and hygiene care products for women. These tests are conducted under supervision of experts from the fields of ophthalmology, gynaecology, stomatology involving specific sensitivity testing such as ocular instillation for eye-related product.

Through rigorous testing protocols, CIDP ensures participant protection while providing invaluable data to researchers, healthcare providers, and regulatory bodies regarding the risk-benefit profiles of new treatments.

Documentation and reporting: Safety in Cosmetic Studies

In the realm of cosmetic testing, documentation and timely reporting adverse events plays a critical role in maintaining product safety from pre-market evaluations to post-market surveillance. Tools like the FDA's Adverse Event Reporting System (FAERS) and MedDRA coding are vital in documenting, monitoring and mitigating safety concerns. CIDP adheres to strict regulatory framework through it's cosmato-vigilance department which is responsible for proper documentation of adverse events, Serious adverse events and local intolerances, reporting it to sponsors and regulatory authorities in timely manner and follow up until complete resolution of the event. This approach ensures that products meet the highest safety standards and that any emerging safety issues are promptly addressed.

CIDP: A Global Leader in Safety and Clinical Excellence

With over two decades of experience, CIDP is renowned for its expertise and steadfast commitment to good clinical practices across its four sites. Having successfully conducted over 5000 safety studies, CIDP has set the standard for clinical research organizations (CROs), serving as a model for regulatory compliance and safety in medical and cosmetic research.

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CIDP
NATURALLY INNOVATIVE

U-Skin and T-Skin: Pioneering PFAS-Free alternatives for high-performance cosmetics

Fabrice Monti

Microfactory

The cosmetics industry is undergoing rapid transformation, driven by the emergence of new technologies and increased demands for safety and sustainability. Among the critical challenges facing the industry today is the regulatory landscape surrounding per- and polyfluoroalkyl substances (PFAS). Known for their extreme durability and film-forming properties, PFAS have long been used in cosmetic formulations, particularly for long-wear products like foundations and waterproof mascaras. However, growing environmental and health concerns have led to increasingly stringent regulations.

In this context, the U-Skin and T-Skin technologies play a pivotal role, enabling the swift identification of high-performance alternative ingredients that align with evolving safety standards.

A highly regulated market in transition

PFAS, often called “forever chemicals” due to their persistence in the environment and potential for bioaccumulation, are at the heart of a global regulatory debate. Several studies have linked certain PFAS, such as PFOA, to adverse health effects, including hormonal disruptions and cancer risks. Consequently, many regions are enacting strict restrictions on these substances. The European Union, for instance, has imposed stringent limits on PFAS, while similar initiatives are underway in the United States and other areas.

For brands, this means reevaluating their product formulations, especially for items requiring long-lasting effects or water resistance. Finding effective alternative ingredients that can replicate these properties without compromising on safety or environmental impact has become essential. This is where in vitro testing technologies like U-Skin and T-Skin prove invaluable.

U-Skin and T-Skin: Introducing the technologies

The U-Skin and T-Skin devices are designed to simulate human skin conditions in a controlled environment. U-Skin provides ingredient performance testing in just a few hours, while T-Skin, capable of mimicking sweat and sebum production, assesses the longevity and impact of formulations in conditions similar to real-world wear.

A key strength of these technologies is their ability to accelerate the in vitro testing process. For example, one hour of exposure on T-Skin equates to a full 24 hours on human skin, allowing rapid predictions of a formulation’s effectiveness and durability. As such, these technologies are ideally suited for evaluating PFAS alternatives, testing whether they offer comparable properties in terms of resistance, adherence, and film-forming effects.

Identifying High-Performance alternative ingredients

With increasing restrictions on PFAS, cosmetic brands are actively seeking alternative ingredients with similar performance. U-Skin and T-Skin streamline this search, enabling the testing of a wide range of compounds in conditions that closely replicate human skin. These technologies can, for example, identify naturally-derived polymers or bio-based ingredients capable of forming hydrophobic and durable films—ideal replacements for PFAS in products like foundations and mascaras.

This process, often referred to as "screening," allows R&D teams to move swiftly from discovery to product development by testing and comparing multiple options to assess their real-world performance. The advantage for brands is twofold: they can ensure product compliance with new standards while meeting consumer expectations for effective, safe, and sustainable cosmetics.

By incorporating U-Skin and T-Skin into their development processes, cosmetic manufacturers gain access to precise, fast data that establishes new industry standards. These results enable brands to predict the wear of a foundation, confirm the barrier effect of a moisturizer, or verify the resistance of a mascara—all without relying on PFAS.

These advances not only reduce development time and costs but also bolster brand credibility, as companies can support product claims with objective, independent performance data. With U-Skin and T-Skin, products can be launched with proven effectiveness, providing an optimal response to both consumer expectations and regulatory demands.

Conclusion

U-Skin and T-Skin offer powerful solutions for cosmetic brands seeking high-performance PFAS-free alternatives. By faithfully replicating skin conditions in a fast and reliable manner, they enable the development of products that meet safety, performance, and compliance standards. In a market increasingly focused on sustainability and transparency, U-Skin and T-Skin have become essential tools for the cosmetics industry of tomorrow.

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The importance of in-vivo Safety Testing in cosmetics

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Dr.Goya Análysis

The cosmetics industry, valued at over $400 billion in 2023, is anticipated to grow a by 4-6% through 2030. Millions of people use cosmetic products daily, underscoring the need for reliable safety assessments to consumer health. This demand for safety extends beyond enhancing appearance, as consumers seek products that also promote skin health. Dermatological safety tests, in vivo methods such as patch testing, Repeat Open Application Test (ROAT), Repeat Insult Patch Test (HRIPT), Photopatch testing, and Non-Comedogenicity assessments, help identify and prevent adverse reactions. the historical reliability of these tests, industry challenges persist due to regulatory differences, inconsistent investments, and evolving consumer expectations. To address these challenges, increased research and development (R&D) investment is essential for enhancing testing standards and strengthening dermatological safety in cosmetics.

Importance of In Vivo Safety Testing in Consumer Protection

R&D investment in in vivo testing is vital, given that up to 30% of consumers report mild to moderate reactions to cosmetics. In vivo tests help detect irritants, allergens, and photosensitizing agents,and they also provide insights into how formulations perform across different skin types and conditions. Brands that neglect rigorous in vivo testing risk consumer trust and may face legal issues and brand reputation damage. Thorough testing not only ensures consumer safety but also builds trust and strengthens compliance with regulatory standards.

Demographic and Genetic Diversity in Dermatological Testing

One of the challenges in cosmetic safety testing is accounting for the diverse range of skin types influenced by genetics, demographics, and lifestyle. This diversity calls for broader safety assessments to reflect real-world product usage.The Fitzpatrick skin type classification system, which categorizes skin based on its response to UV exposure, helps distinguish differences in reactivity among skin tones, from type I (very fair) to type VI (highly pigmented). Since darker skin contains more melanin, it reacts differently to UV exposure and irritants, requiring tailored testing to predict sensitivities accurately.
Ethnic and genetic factors also influence skin response to cosmetics. For example, Asian skin is generally more sensitive to exfoliants and is prone to hyperpigmentation, while African skin, although resilient, is more susceptible to conditions like keloids and dryness. Caucasian skin, with lower melanin levels, is at a higher risk for photoaging and UV damage.To develop formulations that are safe and effective for all, R&D must include inclusive test panels representing these varied characteristics.

Advances in Patch Testing

Patch testing, introduced by Joseph Jadassohn in 1895, has long been a dermatological standard for identifying allergens and irritants. This method involves applying potential allergens in patches that adhere to the skin, typically on the back, to monitor for irritation or allergic reactions over time. Modern advancements have improved patch testing's precision; for instance, materials now isolate specific allergens within complex formulations, enhancing accuracy. Patch testing remains crucial for detecting allergens early in product development, and ongoing R&D has increased both its sensitivity and reliability.

Environmental and Genetic Factors Influencing Skin Reactivity

Skin reactivity to cosmetics can vary depending on both internal (genetic) and external (environmental) factors like climate, pollution, and lifestyle. Personalized skincare, supported by dermatological research, calls for customized safety assessments that incorporate these variables. R&D now focuses on developing adaptive testing protocols that simulate real-world conditions, thus yielding more accurate assessments of skin responses. Genetic predispositions can increase the likelihood of adverse reactions to certain ingredients. Individuals with genetic conditions such as eczema or rosacea, for example, may experience heightened sensitivity. Likewise, environmental factors such as humidity and pollution can alter skin reactivity. For instance, humid climates may aggravate acne, making non-comedogenicity testing particularly relevant. Test protocols increasingly simulate environmental conditions, improving the reliability of predictions on actual skin responses.

Methodologies in in-vivo Testing

In vivo tests each address specific safety concerns, contributing uniquely to a product's overall dermatological profile. Investments in R&D have enhanced these methods, increasing accuracy and broadening their applications.

1. **Patch Testing:** A foundational test for identifying allergens, modern patch tests now allow complex ingredient combinations to be tested more effectively. Studies show a positive identification rate of 15-30% in individuals with dermatitis symptoms, affirming the test's importance in cosmetic safety.
2. **Repeat Open Application Test (ROAT):** ROAT evaluates skin tolerance to repeated applications of "leave-on" products, crucial for products intended for long-term use. Repeated exposure tests can reveal minor reactions, enabling formulators to modify ingredients proactively.
3. **Human Repeat Insult Patch Test (HRIPT):** Conducted under controlled conditions, HRIPT assesses a product's irritation and sensitization potential. More than 80% of ingredients pass HRIPT assessments, indicating their suitability for sensitive skin and high-exposure areas.
4. **Photopatch Testing:** This method assesses reactivity to UV-activated ingredients, essential for products with photosensitive compounds, like sunscreens. Studies reveal that 10% of users experience UV-induced reactions, highlighting the importance of photopatch testing, especially in sunny regions.
5. **Non-Comedogenicity Testing:** For products targeting acne-prone skin, non-comedogenicity tests are essential to confirm claims that products will not clog pores. These tests help R&D teams ensure suitability for users with acne-prone skin.

Skin Reactivity and Allergic Reactions to Cosmetic Ingredients

Contact dermatitis, which accounts for 2-4% of dermatology cases, may actually be more prevalent, as many consumers stop using products without seeking medical advice. Differentiating between irritant and allergic reactions is essential for accurately labeling products and advising consumers on safe use. Common reactions include irritant contact dermatitis, allergic contact dermatitis, phototoxic responses, and contact urticaria. Differentiating these reactions provides valuable insights for product development, ensuring that products meet consumer needs without compromising skin health.

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Tolerance and Safety evaluation with the C-Cube

Sébastien Mangeruca
Pixience

Consumer safety is a priority, so assessing the tolerance of cosmetic products is a crucial step to ensure that they don't cause any adverse reactions, especially for sensitive skin.

Dermatological testing, which is both rigorous and innovative, aims to ensure that each product meets current safety standards. This is all the more important with the increase in allergies and reactive skin, which requires adapted and carefully studied products.

The C-Cube is a state-of-the-art imager designed to facilitate the clinical evaluation of the effects of dermocosmetic products. It allows to capture ultra-precise images (with a margin of error of 0.1%) of the skin at a micro-dermatoscopic level, thus providing a detailed view of skin changes following the use of a product.

Thanks to its **CIE L*a*b*** measurements, it allows to image and measure the **degree of effectiveness** of your active ingredients on skin and scalp. The data contained in each pixel and the placement of ROIs in the image ensure control and accuracy in your studies.
Its unique format makes it the only system capable of performing full-body measurements without special lighting conditions.

C-Cube 3 - Precise, versatile and ergonomic

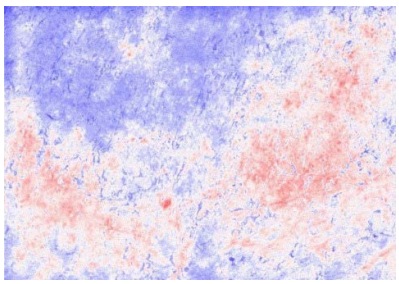
The role of C-Cube in assessing safety and tolerability

During clinical studies to evaluate the safety and tolerability of a product, the C-Cube measures key parameters that attest to the absence of adverse effects and the suitability of the product for sensitive skin.

Thanks to its microdermoscopic imaging capabilities, the C-Cube provides objective and reliable data, ensuring that the products are not only effective, but also perfectly tolerated, even by the most sensitive skin.

Measurement of Inflammatory Response – Erythema

The inflammatory response is a way for the body to defend itself against external aggressions. It intervenes in particular during contact with an intolerant product. To assess the impact of these products on the skin, especially on sensitive skin, it is essential to accurately measure **erythema**.



Artificial Renderings - Erythema color map

Observe the presence of erythema with C-Cube. It is possible to obtain an **erythema index**, which quantifies the intensity of redness in the image, at different stages of the clinical study. You also get the variance corresponding to the homogeneity of the erythema.

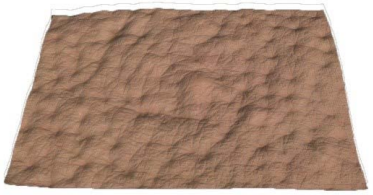
At the same time, our Clinical Research software generates a **skin color map**, highlighting more or less irritated areas.
These measures are crucial for assessing the **safety of cosmetic products.** They make it possible to check if a product causes irritation in volunteers, thus ensuring that it is tolerated even by sensitive skin. This precision offered by the C-Cube ensures that laboratories can scientifically validate that their products are non-irritating to the skin.

Texture Analysis – Roughness Parameters

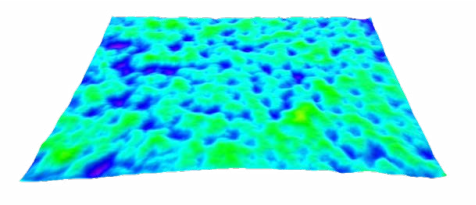
Reactive or irritated skin can develop a rougher surface, with a loss of smoothness and softness, often linked to an inflammatory response or dehydration.

The **C-Cube** can analyze this roughness through precise **3D measurements**, in accordance with the **ISO 25178** standard. Unlike simple grayscale relief maps, the C-Cube captures true three-dimensional data, providing a true picture of skin texture. Roughness parameters such as **Sa**, **Sq**, and **Sdr** allow for accurate quantification of skin irregularities, revealing any alteration after a product has been applied.

These measurements can detect whether a product causes an undesirable skin response, such as increased roughness, or if, on the contrary, it helps to maintain a smooth texture, thus indicating good tolerance.



3D image captured with the C-Cube



Artificial Renderings - Roughness altitude map

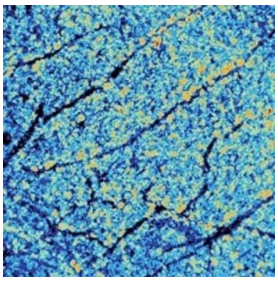
Scaling

Desquamation is an interesting parameter for assessing the tolerance of a cosmetic product, especially on sensitive skin, which is prone to abnormal or accelerated cell renewal. The C-Cube can measure desquamation both in-vivo and ex-vivo.

In-vivo, the C-Cube analyzes the L* component of the Lab*color model, which measures the luminosity of the skin. An increase in white in the images indicates an accumulation of dead cells, reflecting excessive flaking. This data is transformed into a desquamation index, allowing the skin response to be assessed after the application of a product.

Ex-vivo, skin patches (Corneofix® or D-squame®) are used to capture the scales, which the C-Cube then analyzes to generate a desquamation index. Scales are classified into **5 categories according to their thickness.**

Patch Image Capture with the C-Cube



Artificial Renderings - Scaling Classification

These methods make it possible to detect the presence of adverse effects such as an abnormal increase in dead skin, a sign of intolerance to the product.

Conclusion

The Clinical Research C-Cube is a relevant tool for evaluating the tolerance and safety of cosmetic products, especially for sensitive skin. Thanks to its microdermoscopic analysis capabilities, it offers unparalleled precision in the study of parameters such as erythema, roughness, or desquamation. These objective measurements allow to detect any adverse reactions, ensuring that the products tested respect the most fragile skin. By combining technological innovation with scientific rigor, the C-Cube provides laboratories with accurate and reliable validation of the safety of their products.

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PIXIENCE
HEALTHCARE TECHNOLOGY SOLUTIONS

Assess your cosmetic products in complete Safety with a claim adapted to your request

Jean-Robert Campos

IEC

It is essential that a cosmetic product presents no risk to the consumer, and to ensure this, safety tests proposed by our experts are carried out before the product is placed on the market, enabling to assess its tolerance.

Several tolerance evaluation tests are proposed, such as compatibility tests, acceptability tests and immunotoxicity tests, detailed later.

But prior to clinical studies, IEC proposes in vitro methods for assessing the primary ocular tolerance of finished products [*Hen's Egg Test Chorion-Allantoic Membrane*, J.O.R.F. of 26 December 1996], [*Neutral Red Releasing Test*, J.O.R.F. of 30 December 1999], [*Bovine Corneal Opacity and Permeability*, BCOP] and ingredients, [BCOP, OECD guideline n° 437], [*MTT test on three-dimensional system*, OECD guideline n° 492].

Primary cutaneous tolerance is assessed by the *MTT conversion assay on Reconstructed Human Epidermis* for both finished products and ingredients [OECD guideline n° 439].

The *3T3 NRU*, OECD guideline n° 432 is used to determine the phototoxic potential of ingredients.

To assess skin compatibility on subjects, IEC proposes Skin Compatibility tests [48-hour single patch test, "Elbow fold" Test, Repeated Open Application test on the forearm, Repeated patch test for one, 2, or even 3 weeks].

No claims are associated with these tests.
For the Ocular compatibility test, IEC can conduct Ocular projection test on rinsed, leave-on and solar products which claim "***Does not sting or irritate the eyes / no tears*** (formulated in order its foam does not sting or irritate the eyes)" if coupled with a test of use under ophthalmological control (in the sun for a sunscreen product).

Acceptability tests correspond to In-Use tests performed under medical control: Dermatological control for the claims **"tolerance tested under Dermatological control"**, **"suitable for sensitive skins", "suitable for delicate skins", "suitable for reactive skins", "suitable for sensitive lips"**, if at least 20 subjects with the corresponding criterion and no intolerance signal appearing on this subpopulation.

Acceptability tests can be performed with cosmetic products on subjects presenting with skin conditions such as acne, atopic dermatitis, eczema or lucitein the subsidiary of IEC South Africa.

"Non comedogenic" can be claimed if at least 20 subjects from 18 to 40 years old, with oily or combination oily and prone to acne skin, with no statistically significant increase at the end of the study (in comparison with D0) in the number of retentional and inflammatory elements on face.

Under Ophthalmological control we claim **'tolerance tested under Ophthalmological control',** and **'suitable for sensitive eyes', 'suitable for lenses wearers'** if at least 15 subjects with the corresponding criterion and no intolerance signal appearing on this subpopulation.

Studies under Dental surgeon control are proposed in our Bulgaria and South Africa subsidiaries and enable to claim **'tolerance tested under Odontological control', 'suitable for sensitive teeth', 'suitable for sensitive gums',** if at least 20 subjects with the corresponding criterion and no tolerance signal appearing on this subpopulation, **'whitening effect'** (6-week test period required) by scoring and self-evaluation of teeth shade, **'prevents the appearance/formation of plaque'** by scoring he dental plaque, **'care for sensitive gums'** by evaluation of the effect on modified gingival index.

Gynecological control can be carried out in IEC Bulgaria in order to claim **'tolerance tested under Gynecological control',** in at least 20 subjects.

Very specific studies can be carried out **'under supervision of an allergist'** in South Africa.

Studies with a Pediatrician can be performed in IEC Bulgaria and IEC South Africa in order to support the claim **'Tolerance tested under Pediatric control',** combined with a Dermatological control. To be able to test on these sensitive and fragile populations, preliminary safety data are mandatory such as in vitro ocular irritation test (Het Cam , BCOP or 3D skin models), 48 hour-Single patch test. As well as an In Use Test under Dermatological (and Ophthalmological also if required by the product) in adult subjects with at least 20 with a sensitive skin and 20-40% with history of atopy for 3 or 4 weeks) (or, if the product does not allow an in-use testing: Repeated Open Application test - ROAT) and Final clinical Safety Test (TCFS PSC) in at least 100 adult subjects to confirm the lack of cutaneous sensitization.

We also propose Immunotoxicity Tests on finished products in IEC Bulgaria : Sensitization Test (T.C.F.S.-P.S.C. according to ANSM recommendations of 2009), to determine skin primary and cumulative irritation, sensitization (type IV) potential, in at least 100 subjects.

- Photo-irritation (T.C.F.S.-P.T. according to ANSM recommendations of 2009) in 20 (or 25 if coupled to photo-sensitization test) subjects,
- Photo-sensitization Test (I.E.C. protocol or Sponsor's specific protocol) in 25 subjects in standard.

No claims are associated with these tests.

Our subsidiaries located in Asia (Japan, Singapore, Korea and China) allow to test the products on Asian skins taking into account the specificities of each country in term of environmental conditions, culture, beauty routine and skin typology.

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Hybrid diffuse reflectance spectroscopy: the (near) future of sun protection evaluation

Jade Beaumont

Weneos

The solar irradiation that reaches the Earth can be classified into 3 areas: Ultra-Violet (UV), Visible and Infrared lights. In the cosmetic industry, it is considered that UV light is located between 100 and 400 nm and is the most harmful. It can also be categorized into the 3 following types of rays: UVA (320-400 nm), UVB (290-320 nm) and UVC (100-290 nm). [1,2]

Sunscreens are one of many ways to protect ourselves from the sun light. Their performance is rated according to three criteria: the Sun Protection Factor, the UVA Protection Factor and the Critical Wavelength.
The Sun Protection Factor (SPF) indicates the level of protection offered against mainly UVB rays. [3] The UVA Protection Factor (UVA-PF) measures the protection against UVA rays. The Critical Wavelength (CW) provides an overall assessment of the protection against both UVA and UVB rays. It is the smallest wavelength at which at least 90% of the area under the curve between 290 and 400 nm is absorbed. [4]

Currently, sun protection is still mainly evaluated by exposing volunteers to either UVB (ISO 24444:2019) [5] or UVA (ISO 24442:2022) [6] radiations. These methods, also known as *in vivo* methods, face several ethical and methodological challenges. Therefore, for the last decade, global efforts from scientists and the industry have led to the development of alternative and non-invasive *in vitro* methods [7,8]. Two new promising innovations to mainly evaluate the UVB protection should be published by the ISO committee in 2025 with an *in vitro* method for SPF (ISO 23675) [9] and a hybrid method (ISO 23698) for SPF, UVA-PF and CW [10].

As mentioned, one of the alternative methods is the Hybrid Diffuse Reflectance Spectroscopy (HDRS). Its uniqueness stems from the fact that it shares characteristics and principles of both *in vivo* and *in vitro* sun protection testing. The first part is the Diffuse Reflectance Spectroscopy technology, conducted on volunteers. Then, an *in vitro* evaluation of the sun protection and photostability is carried out. At the moment, this method will only be applied to emulsions and one-phase products for official claiming purposes. [11]

The current version of the ISO 23698 allows only two DRS technologies: a monochromatic or a polychromatic system. The DRS technique measures the remitted light, first by the unprotected skin, and then by the protected skin after spreading the product. Those measurements are performed between 320 and 400 nm, which is the range of the UVA rays.
The monochromatic spectrophotometer quantifies the amount of remitted light at each wavelength, to obtain a curve of light intensity depending on the wavelength. The measurements using a polychromatic system are faster (1-5 seconds) and indicate a value of the intensity of light reflected. [12,13]
In both cases, the DRS part results in an initial UVA-PF, also referred to as UVA-PFDRS. Contrary to *in vivo* SPF testing, there is no exposition to UV of the volunteers. As a result, this stage does not provide any information on the photostability of the product or the protection in UVB.
The goal of combining the DRS technique with in vitro testing is to provide the missing information from the first part. This step can only be conducted once the product has been tested on 10 volunteers.

The *in vitro* process is based on the same principles as the ISO 24443:2021 (in vitro UVA-PF). The product is spread on PMMA Molded or Sandblasted plates at either 1.3 or 1.2 mg/cm² respectively and left to dry at a controlled temperature.An initial *in vitro* UVA-PF is calculated through spectrophotometric measurements of the plates. The *in vitro* absorption curve is then readjusted to the UVA-PFDRS, using a correction factor.
An irradiation dose is calculated from the UVA-PFDRS and the spectral irradiance curve from ISO 24444. Once the irradiation step completed, the plates are measured again to obtain the post irradiation absorption curve and UVA-PF. These are readjusted using the same correction factor as previously. For the monochromatic device, a hybridization wavelength between 310 and 350 nm is calculated. This wavelength will allow the integration the DRS and *in vitro* spectra effectively.
Lastly, the final SPF, UVA-PF and CW are calculated. For valid results, (i) the 95% Confidence Interval (CI) shall be ≤ 17% of the mean and (ii) the different Reference Standard results shall fall within the respective acceptance limits in terms of SPF and UVA-PF.

In conclusion, while HDRS addresses many of the challenges faced by *in vivo* evaluation (non-invasive, less time-consuming, more cost-effective), it is not a universal solution and requires a certain level of experience and expertise to ensure high reliability. The other upcoming alternative method published as ISO 23675 offers a fully in vitro approach that appears to be more universal and inclusive.

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Evaluating Tolerance and Safety in cosmetics and personal care products

Jane Tervoorem
Validated Claim Support

When it comes to cosmetics and personal care products, most of us want to look good and feel confident without worrying about what's in the bottle. Whether it's your daily moisturizer or your favorite makeup, ensuring these products are safe and gentle on the skin is essential. That's where the concepts of tolerance and safety come in. These aren't just buzzwords in the beauty industry—they're crucial factors in determining whether a product is suitable for everyday use. So, how are tolerance and safety evaluated in cosmetics, and why does it matter?

In the world of cosmetics, tolerance refers to how well your skin, hair, or body handles a product without irritation or other negative reactions. Think about it: some people can use the same soap for years without any issues, while others might experience redness, itching, or dryness after just one use. This variability is a key reason why tolerance should be tested before a product ever hits the shelves.

Safety is More Than Skin-Deep

While tolerance focuses on how the skin responds to a product, **safety** is about ensuring that the product doesn't cause harm, either in the short term or with long-term use. This means not only preventing immediate reactions like rashes or breakouts but also ensuring that there are no harmful effects from repeated use over time.

Cosmetic safety evaluations start with ingredient safety. Regulatory agencies like the FDA in the US or the EU's Cosmetics Regulation provide guidelines for which ingredients can be used and in what amounts. In addition to following these guidelines, companies conduct safety testing on the final product. This usually involves:

- **Patch testing or HRIPT**: Small amounts of the product are applied to the skin to check for irritation or allergic reactions.
- **Eye safety tests**: For products like mascara or eyeshadow, testing is done to ensure they don't irritate the eyes or surrounding area.
- **Use tests**: People use the product as intended over time to monitor for any adverse reactions.

It's easy to confuse tolerance and safety when it comes to cosmetics, but they're not quite the same. Tolerance is all about how well your skin, hair, or body handles a product in day-to-day use. If a product makes your skin feel dry or causes redness, it might not be well-tolerated, even if the product is technically safe.

On the other hand, safety is the concept of ensuring that the product doesn't cause harm, either immediately or over time. A product might be safe to use (meaning it won't cause serious harm or contain harmful chemicals) but still cause minor irritation in some people with sensitive skin. In a perfect world, we want products that are both well-tolerated and safe.

Factors That Affect Tolerance and Safety in Personal Care Products

There are many variables that can impact how a product is tolerated and how safe it is. Skin type plays a huge role, people with sensitive or allergy-prone skin are more likely to experience issues with certain ingredients, like fragrances or preservatives. This is why many cosmetic brands offer fragrance-free or hypoallergenic versions of their products.

Another factor is the formulation of the product. Even small changes in ingredient concentrations can make a product more irritating or less effective. While a small amount of salicylic acid in a face wash can help with acne, higher concentrations might dry out the skin or cause irritation.

Frequency of use matters. A product that's safe when used occasionally might cause problems with daily use.That's why cosmetics are tested not just for one-time application but for prolonged use as well.

The Push for Clean and Safe Beauty

In recent years,there's been a growing demand for «clean» beauty products—cosmetics that are free from controversial ingredients like parabens,phthalates,and sulfates.Consumers are becoming more educated about what's in their products and are pushing for more transparency from brands.

While clean beauty is trending, it's important to remember that natural doesn't always mean safer. Some natural ingredients can be irritating or even harmful, depending on how they're formulated. That's why both natural and synthetic ingredients need to go through the same rigorous safety and tolerance testing.

Why Do Tolerance and Safety Matter?

At the end of the day, the evaluation of tolerance and safety in cosmetics and personal care products is about protecting consumers. We want products that not only make us look and feel good but also keep our skin, hair, and bodies healthy. By testing for tolerance and safety, companies can ensure that their products are effective, gentle, and safe for long-term use.

As consumers, it's important to stay informed and choose products that are both safe and well-tolerated for our unique needs. With a growing focus on clean beauty and ingredient transparency, we can all feel more confident in the products we use every day, knowing that they've been carefully tested to meet the highest standards.

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Complife global approach for Safety evaluation

Complife Group

Complife is an international group that provides consulting and testing services for different markets. With a long history dedicated to the cosmetics market, the **Complife team can boast high expertise, especially in safety assessment, based on a wide range of safety tests.**

According to European Cosmetics Regulation 1223/2009, a cosmetic product should be safe for human health when used under normal or reasonably foreseeable conditions of use. Consequently, the responsible person shall ensure that, before placing a cosmetic product on the market, it has undergone a safety assessment based on the relevant information and that a safety report is drawn up in accordance with Annex I of this regulation.

A full cosmetic safety assessment needs to be performed and included in a Product Information File (PIF) kept at the company. This file also includes a description of the product, the product safety report, information about the manufacturing methods, and proof of effects claimed.

The **Cosmetic Product Safety Report (CPSR)** is the key component of the PIF. It is divided into two sections: Part A, which contains information about the safety of the cosmetic product, and Part B, which includes the safety assessment itself. The latter, which is intended to demonstrate the product's safety, is a requirement in the EU, and is also widely requested by different regulatory authorities. There are various cosmetic toxicology and safety tests, tailored to evaluate specific potential hazards while adhering to the Cosmetics Regulation, which prohibits animal testing.

Although there are no enforceable industry-wide standards specifying which tests must be performed for assessments of cosmetic products, respected authorities such as the Scientific Committee on Consumer Safety (SCCS) and the Organisation for Economic Co-operation and Development (OECD) provide guidance on recommended tests and methodologies.

Our experts can assist with drafting the Product Information File (PIF) and preparing a toxicological **pre-assessment** report, advising on the necessary safety tests to complete the cosmetic formulation's safety assessment.

Some of the most common tests include:

- **Ocular irritation tests**
- **Phototoxicity tests**
- **Skin sensitization tests**
- **Skin irritation tests**

Complife can conduct these tests on individual ingredients, mixtures, and final products using *in vitro* or **clinical** methods that meet both Good Laboratory Practice **(GLP)** principles and compliance standards.

Ocular irritation tests are essential for evaluating the safety of products that may come into contact with the eyes. Complife offers in vitro alternative methods, including the Chorioallantoic Membrane **(HET-CAM)** Test and the Macromolecular Test Method **(OECD 496)**. The latter utilizes a complex macromolecular matrix that closely mimics the composition of the cornea. But also in vitro methods based on **cytotoxicity assessment,** such as the Neutral Red Uptake **(NRU)** assay, **Agarose diffusion** and reconstructed human cornea-like epithelium **(RhCE)**, which can effectively assess the potential for ocular irritation and serious eye damage while meeting regulatory requirements.

Phototoxicity and **Photo-Sensitization testing** are essential for products applied to sun-exposed areas. Complife's laboratory offers the **3T3 Neutral Red Uptake (NRU) Phototoxicity Test**, which evaluates cytotoxicity, as well as the **Reconstructed Human Epidermis Phototoxicity Test (RhE PT)**, which identifies the phototoxic potential of chemicals applied topically to reconstructed human epidermis (RhE) tissue with and without simulated sunlight exposure **(OECD 498).** Additionally, we conduct **photo-sensitization analysis** which evaluates markers involved in the photosensitization response of cells, using fluorescence-based methods.

For cosmetic products that are primarily intended for skin contact, assessing their potential for **skin irritation and sensitization** is of paramount importance. Our laboratories provide a battery of in vitro solutions for **skin sensitization** testing. These include in chemico skin sensitization assays **(OECD 442C)**, tests for keratinocyte activation **(OECD 442D)**, and assays targeting dendritic cell activation in the Adverse Outcome Pathway for skin sensitization **(OECD 442E)**. Additionally, we offer the Reconstructed Human Epidermis (RhE) Assay **(OECD 439)**, which measures cell viability, providing a reliable assessment of potential **skin irritation.**

In addition to *in vitro* testing, our team also offers **clinical testing** services such as:

- **Human Patch Tests:** Designed to detect contact irritation **(48 hours patch test)** or allergies **(Human Repeat Insult Patch Test (HRIPT))**
- **Use Tests:** Under medical expert control (dermatological, ophthalmological and gynaecological).These tests evaluate both the safety and the efficacy of products by testing them in real conditions by a panel of volunteers and by analysing their properties by a group of specialists.

Finally, our experts could also support testing on Beauty Devices, to evaluate their safety and usability when used alone or in combination with formula(s). These tests are inspired from standard methods applied to Medical Device testing that are transposed and customized accordingly to body contact and intended use of the purposed beauty device. They ensure a high safety level to customer and study volunteer before in vivo tests.

Complife offers all its expertise's to be the best partner to support your pre-clinical and clinical product's development.

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