



## TOXICOLOGY ET REGULATION

We are glad to share with you the **1st FOCUS**, a new publication of Skinobs. This edition is dedicated to the Toxicology & the regulation. 8 articles, 8 views of the today evolutions which follow the latest changes for personal care, the actives, the ingredients and the medical devices. These modifications have consequences on the claim substantiation and evolve rather quickly all over the world. In Europe, the latest change in July 2019 have impacted the testing evaluation activities.

Here are the subjects we will talk about :

- **BIODEGRADABILITY AND ECOLOGICAL LABEL** by [Expertox](#)
- **COMPATIBILITY CONTAINER-CONTENT AND PRODUCTS SAFETY** by CCA GRoup - [Cosmepar](#)
- **SAFETY ASSESMENT OF PLANT EXTRACTS: CONSTRAINTS, CHALLENGES AND SOLUTIONS** by [Eurofins Cosmetics & Personal care](#)
- **REGULATION OF RESEARCH ON MEDICAL DEVICES: BOON OR BANE?** by [CIDP](#)
- **UNDERSTANDING THE SAFETY ASSESMENT OF COSMETICS PRODUCTS** by [Reg&Safe](#)
- **FOCUS ON OMNIBUS REGULATION, CMR SUBSTANCES AND COSMETIC PRODUCTS IN EUROPEAN UNION** by [Institut Scientis](#)
- **THE ENDOCRINE DISRUPTORS: WHERE ARE WE?** by [Equitox](#)
  - **IMPLEMENTATION OF INTERVENTIONAL STUDIES** by [Dermatec](#) (CPP initiatives)

## **BIODEGRADABILITY AND ECOLOGICAL LABEL**

Dr Stéphane PIRNAY - Toxicologist Expert

According to the OECD definition, biodegradability is: "the alteration of the chemical structure of a substance resulting from a biological action and resulting in the loss of specific properties of that substance". Biodegradation in the presence of oxygen (aerobiosis) is to be distinguished from degradation in the absence of oxygen (anaerobiosis) by the nature of the degrading microorganisms and degradation products.

Biodegradability is one of the criteria for the EU Ecolabel. The requirements for the assessment and verification of this criterion are described on ANNEX of the "COMMISSION DECISION of 9 December 2014 establishing the ecological criteria for the award of the EU Ecolabel for rinse-off cosmetic products". [notified under number C (2014) 9302 (2014/893 / EU)]".

The theoretical evaluation of Biodegradability is based on the calculation of the following values:

- ONBDa: Total content of the product of organic substances used in the composition of the product which are not biodegradable under aerobic conditions (not easily biodegradable).
- ONBDan: Total content of the product of organic substances used in the composition of the product which are not biodegradable under anaerobic conditions.

The glossary is finally published! Official Journal of the European Union [COMMISSION DECISION (EU) 2019/701 of 5 April 2019 establishing a glossary of common ingredient names for use in the labelling of cosmetic products] Article 33 of the EU 1223/2009 Regulation states that the labelling cosmetic products should refer to the glossary. This one, has just been published! For reminder, the glossary shall take account of internationally recognized nomenclatures including the International Nomenclature of Cosmetic Ingredients (INCI). That glossary shall not constitute a list of the substances authorized for use in cosmetic products. The common ingredient name shall be applied for the purpose of labelling cosmetic products placed on the market at the latest twelve months after publication of the glossary in the Official Journal of the European Union.

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*The Expertox laboratory is specialized in the analysis of traces, impurities, content/container interaction and quality control of raw materials and finished products. It is also involved in the certification of cosmetics, agri-food products, medical devices and chemical substances and preparations*

## COMPATIBILITY CONTAINER-CONTENT AND PRODUCTS SAFETY

Gaël GERVAIS PhD in Chemistry, Laboratory Manager

**During manufacturing, packaging or storage, physical and chemical exchanges can take place between the product and its packaging. These exchanges can impact the quality, efficiency and safety of the product.**

Determining the compatibility of content with its container is therefore a major challenge imposed on all marketers. This information, which requires particular expertise, enable the coexistence of several approaches:

**1. Under the aegis of Cosmetics Europe**, a European Task Force has been set up.

A work to define an evaluation protocol is underway and results are **not expected until 2025**. The work carried out so far is moving towards a **food approach**, finally far removed from our cosmetic realities: Which simulants are representative of cosmetics & personal care? How to compare oral toxicity and dermal toxicity?

**2. The "Worst case" approach** is to maximize everything. Look for and list the "extractables", i.e. all substances (or almost) present in the material of the pack, and then measure in personal care products the possible presence of multitudes of substances.

The denaturation of the material necessary to measure "extractables" generates a number of chemicals for which the probability of occurrence in even extreme ageing conditions is zero. The risk is therefore to focus on substances of no interest at the expense of the "real culprits" in much smaller quantities but with very real effects.

3. The third, more pragmatic track, **proposes to follow the simultaneous evolution of cosmetic formulas** in bulk and in their final container **during accelerated ageing study** (stability-compatibility). It is thus possible to measure the changes induced by the interactions between the formula and its packaging. Among these developments, it is possible to highlight the migration of different undesirable substances from the pack that could impair the safety of the product. The aim is therefore to get as close as **possible to the actual exposure of the consumer**.

The MSP (Migration Stability Pack) coupled with a simultaneous analysis of 41 plasticizers **at the heart of the formula** was developed to provide concrete **useful information** for the Product Safety Assessment.

\*Phtalates, bisphenols, alkylphenols, perfluorés organophosphates, Tosylamides, adipates , citrates.

"The *goal for us is to take advantage, for example, of the time it takes to conduct stability tests to perform interaction and migration tests,*" explains Dr. Gael GERVAIS of ANALYTEC. *We check the rules for the migration of hazardous substances from the container to the contents in an expedited manner to ensure a safer product.*"

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*COSMEPAR brings together the technical expertise of 3 laboratories (microbiology, analytical chemistry, clinical) designed to offer a global and concerted offer on cosmetic evaluation.*

## SAFETY ASSESMENT OF PLANT EXTRACTS: CONSTRAINTS, CHALLENGES AND SOLUTIONS

Valériane Levelut, Safety assessor and ERT Toxicologist - Eurofins | Evic

Plant extracts are among the first extracts to have been used in cosmetics, and grow increasingly popular every year. Nowadays, **"natural" is synonymous with "safety"** in the minds of consumers, but plants can contain substances that are more or less active and potentially dangerous to human health. As with any cosmetic ingredient, their safety for use in cosmetic products must be established and demonstrated through a risk assessment process, in accordance with the **requirements of Regulation (EC) No 1223/2009**.

The main difficulty in assessing the risk of plant extracts lies in their **complexity and variability, unlike "classic" cosmetic ingredients**, which have a defined and unchanging chemical composition. The composition of a plant extract can vary according to many environmental factors, such as its geographical origin or the harvesting period in which the plant was gathered. In addition, the extraction processes used by manufacturers are increasingly innovative and can isolate or concentrate certain molecules, making each new extract unique in its composition.

The first essential step in the development of the **toxicological profile** of a plant extract is its characterisation, in order to correctly identify the substances present in the extract and to evaluate their content. A number of physico-chemical analyses are recommended to determine the main components in the extract as well as potentially dangerous components present. This data then allows a safety evaluator to assess the risks associated with the extract's usage, **based on the bibliographic data available** on its components. **Risk assessment** can also include traditional and established uses of the plant, such as in food or traditional medicine. However, the extracts studied may vary considerably from those traditionally used, making it difficult to extrapolate data.

Thus, when the safety evaluator considers that the available data is not sufficient enough to conclude on the safety of the plant extract, or when alerts have been identified in literature, it may be necessary to generate **new data by conducting toxicological tests** on the final extract.

The *in vitro* tests which have available to date to test for plant extract safety cover skin irritation, eye irritation, sensitising potential and phototoxicity and genotoxicity of plant extracts. However, it is necessary to determine in advance of conducting these tests that they are technically appropriate to successfully test the extract, particularly in regards to its solubility and composition.

Our teams of experts support and advise you in the various stages of plant extract safety assessment: from toxicological profile to physico-chemical analyses, *in vitro* safety tests, and clinical tolerance assessment.

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*Le réseau des 200 laboratoires Eurofins offre une large gamme de services pour l'évaluation de la sécurité et de l'efficacité de vos produits en analytique, microbiologie, essais in vitro et cliniques et expertise toxicologique.*



## REGULATION OF RESEARCH ON MEDICAL DEVICES: BOON OR BANE?

Dr Reshma RAMRACHEYA - Director of Pharmaceutical Operations

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The recent EU Regulation 2017/745 seeks to protect public health and overhaul how medical devices are regulated in the European Union. While this Medical Device Regulation (MDR) enforces stricter control, it has important implications for the cosmetic industry. From gels and emulsions to cosmetic lenses, breast implants, dermal fillers, liposuction and lipolysis equipment, and lasers, all devices entering the European market will have to comply with this regulation, including the **CE marking process by May 2020**. Considering that the existing capacity within the few handful notified bodies is extremely strained, is the system ready to handle this onslaught of devices?

Under amendments proposed to the **MDR on the 25th November 2019**, manufacturers of certain lower risk medical devices, for instance reusable **Class I medical devices** and **Class I software**, will be given a four-year transitional period **until May 26, 2024**, before they are required to meet the new regulation standards. This grace period will relieve the pressure on the notified bodies and also allow the manufacturers to prepare their technical documentation supported by tests and clinical data, set up their Quality and Risk Management Systems and also improve their market surveillance. These devices would still need to meet certain conditions such as sustained compliance with the relevant directive and ensuring no significant changes in the design and intended purpose of the device. Nonetheless, the MDR requirements for market surveillance, post-market surveillance, vigilance, registration of economic operators and of devices will be applicable instead of the **corresponding regulations in the current Directives**.

The implementation of the MDR 2017/745 may lengthen the time taken for devices to enter the European market. However, it has the best interest to safeguard health and ensure safety of the public, which would increase the credibility of devices in the long run. It was previously believed that the US market entry process was lengthier than the European one. This may no longer be the case. There are new players in this arena and countries like Mauritius are now emerging as a fresh clinical research hub, with a **comprehensible regulatory framework for the conduct of medical device trials**. Following the amendment to the Clinical Trial Act in 2019 incorporating research on medical devices, Mauritius has opened up new avenues for testing a diverse category of sophisticated products. Due to its growing popularity, a number of leading manufacturing companies from Europe have set base. Mauritius has gained recognition as the best place to do business in the whole of Africa for the 3<sup>rd</sup> consecutive year and ranks 13<sup>th</sup> currently for the ease of doing business, globally. In addition to implementing local regulations in line with the EU and FDA guidelines, the ease of doing medical device research in Mauritius stems from the regulatory consideration given to previous market surveillance reports or history of safe use of the device.

From a commercial, product portfolio, research and development process and organizational perspective, it cannot be denied that medical device companies will be impacted upon at different levels. A deeper understanding of the regulatory landscape for medical devices and its implication on the business is crucial to enable companies to effectively and proactively design a strategy for bringing their products to market.

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*CIDP, founded in 2004, is a pioneering international group in the field of pharmaceutical and cosmetic research and development in Mauritius, with the aim of evaluating ingredients, raw materials and drug or cosmetic assets on 5 continents (Maurice, Brazil, Romania, India, Singapore) around 5 activities: R and I, in vitro preclinical, clinical research, data management and regulatory affairs.*



## UNDERSTANDING THE SAFETY ASSESMENT OF COSMETICS PRODUCTS

Françoise Perrodin - Safety Assessor - EUROTOX Registered Toxicologist

### A thorough assessment that covers long-term impacts on health

Always one step ahead in defending the safety of its citizens, the European Union was the first, back in 1993, to introduce the requirement for a Safety Assessment based on the toxicological properties of cosmetic ingredients and the exposure of users.

In 2013, the EU went one step further, by clarifying the information required in what is now called the **Cosmetic Product Safety Report (CPSR)**, the need to assess traces and impurities brought by the raw materials and packaging, the chemical interactions between all the entities in presence, the history of adverse reactions reported by users, and last but not least, the **assessment of the systemic effects** (long-term effects on the general health) further to the potential penetration of substances from the skin to the blood flow.

This assessment is made by identifying for each ingredient the dose/quantity absorbed that has no observed toxicological effect (NOAEL) on the organism. Then, taking into account the actual dose to which the user will be exposed by his daily use of the cosmetic product—the most conservative/worst-case scenario is always taken, a **Margin-of-Safety (MoS)** is calculated for each substance.

For a cosmetic product to be safe, the MoS has to be **at least 100**, meaning that the dose to which the user is exposed is 100-fold less than the dose that did not have any adverse effect in the most sensitive species in which the substance was tested.

The MoS of 100 **embraces the differences in the population**: ages, weight, health conditions, etc, **and differences between species**. When the NOAEL comes from **human data**, a **MoS of 10** is used, and if the human sample is **large/representative enough**, a **MoS of 1** is sufficient.

### A highly demanding regulation, inspiring other regions

*Did you know that the regulation of cosmetic products in the European Union stems from the very strict French legislation that was established in the 1970's, right after the dramatic accident of talc Morhange ? More than 200 young children and babies were intoxicated, 36 dead, by a talc containing an excessive amount of hexachlorophene further to a mistake in production. Since, the EU authorities have developed a strong and effective cosmetic regulation that is now being transposed in many regions of the globe like the Mercosur and Asean.*

### How does the Safety Assessment affect products ?

The Safety Assessor uses the information intended to be labeled—or otherwise communicated by the manufacturer, to calculate consumer exposure.

If the conclusion of the CPSR is that the product is not safe in normal and reasonably foreseeable conditions of use, the product cannot be sold as is. Then, it is the marketing company's duty to enforce the conclusions of their Toxicologist. Most of the times **when MoS are not fully satisfactory**, the Safety Assessor will reverse calculations and find out the maximum dose to which the user can be exposed without risk for his/her health. Based on this, **the Safety Assessor will**

**propose risk elimination measures** that can be:

- different/adapted **use prescriptions or product indications** that reduce the exposure of the user —e.g. reduce advised frequency of application, reduced area of exposure, different target population (exclude infants for instance)
- **precautionary warnings**—e.g. advices on good sun care practices, avoidance of most sensitive zones such as the eye contour area, recommendations to reduce frequency of application if irritation symptoms occur, alerts to pregnant or lactating women, etc.

### **The No Effect Dose (NOAEL)**

*This is the lowest dose at which no adverse toxicological effect has been observed. It is generally coming from studies on animals. However, in the EU and other regions of the world, cosmetics cannot be tested on animals anymore. To calculate MoS, Toxicologists have access to animal data generated before the testing ban or for other purpose than cosmetic use. When data are not available, they can proceed by chemical structure analogy and sophisticated prediction tools. In-vitro methods are also developing fast, under the lead of the cosmetic industry that was forced by Regulators to develop alternatives, hence benefitting all sectors.*

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*Reg and Safe® Cosmetic Solutions assists companies in their research and development projects, technical, scientific and regulatory missions, necessary to market cosmetic products in Europe. By delegating all or part of the tasks related to safety assessment, regulatory compliance and product development, you benefit from more than 25 years of experience in cosmetic research and development from major international companies.*





## FOCUS ON OMNIBUS REGULATION, CMR SUBSTANCES AND COSMETIC PRODUCTS IN EUROPEAN UNION

Corinne BENOLIEL - Toxicologue ERT

The cosmetic products marketed in European Union must comply with requirements of Regulation (CE) n°1223/2009. The article 15 of cosmetics regulation is particularly shifting towards carcinogenic, mutagenic and/or toxic substances for reproduction (CMR), divided in **3 categories** according to their classifications harmonised within the **Regulation CLP (CE) n°1272/2008**, related to classification, labelling and packaging of substances and commingling (CMR 1A, 1B et 2). **The substances CMR are usually prohibited ingredients in cosmetics.**

Yet, a substance **CMR 1A or 1B** can be used, exceptionally, if it meets in full the following requirements : compliance with food safety requirements, absence of any more appropriate alternative substance, advice of the **European Scientific Committee for the Consumers Safety (CSCC)** judging it is safe for defined use in cosmetic products, taking into account exposition considered as global, including particular attention to vulnerable populations.

A substance CMR 2, on the other hand, can be used in exceptional circumstances if the CSCC ensures the safe use in the cosmetics.

In order to integrate all the CMR substances whose classification had been harmonised since 2010, but which had not been considered by the European cosmetics regulation, the Regulation [\(UE\) n°2019/831](#), called « Omnibus Regulation » has entered into force since June, 12th 2019 and has consequently clarified the use of the CMR substances. This regulation makes the connection with the article 15 of the cosmetics regulation.

The annex II, III et V of the regulation (CE) n°1223/2009, related respectively to the prohibited, limited and preservatives substances have consequently been updated.

From now on, cosmetics products non-compliant to this first version of the Omnibus Regulation must not be on the market anymore.

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*INSTITUT SCIENTIS is a scientific service provider, specialized in the fields of regulation, formulation and scientific marketing of products such as cosmetics, detergents and biocidal products. The main activity is the evaluation of the safety of cosmetic products. The company globalizes the scientific projects of professionals in the agri-food, cosmetics, pharmaceutical and parapharmaceutical industries, hospitals, medical and dental sectors, and communities.*



## THE ENDOCRINE DISRUPTORS: WHERE ARE WE?

Stéphanie MOULIN - Toxicologist

In 2002, the World Health Organization (WHO) proposed a **definition of endocrine disruptors** (EDs). An ED is an exogenous substance that alters the functions of the endocrine system with the result that adverse effects on the health of an organism, its offspring or its (under) populations. Based on this definition, European chemical regulations have strengthened their regulatory network to consider PEs with the **aim of protecting people and the environment**. For example, various regulations put in place processes for identifying and characterizing PEs. This task is complex because it relies on a robust set of data to prove whether or not a substance meets the definition of an ED.

In 2017, the scientific criteria for determining the **disruptive properties** of the endocrine system were adopted at European level for biocides, followed by phytopharmaceuticals (April 2018), and cosmetics (November 2018). Under the REACH regulation, the identified PEs are considered to be substances of extreme concern (SVHC), with a level of concern equivalent to carcinogens, mutagens or reproductive toxicants. To date, **16 substances** are SVHC because PE has been reversed. Some of these substances are already subject to the REACH authorization process. **82 other substances** are suspected to be PEs. They are being evaluated to clarify this concern.

In addition, the **Scientific Committee on Consumer Safety (SCCS)** has also established priority lists of PEs not yet covered by the cosmetic regulations. A data call was opened by the **European Commission in May 2019**. 14 substances are being evaluated by the SCCS to prohibit or restrict their use in cosmetics.

Once the substance is identified as PE, the question arises, **depending on its exposure, of the characterization of risk to humans and/or the environment**. Traditionally, the safety of a chemical is determined by the basis of a **"safety threshold" that** corresponds to the dose below which no adverse effects should occur. Today, there is no consensus that a "threshold" approach should or should not be adopted for EDs.

The current guidelines do not take into account certain stages of life, the search for certain critical PE effects and the possibility of adverse effects below the conventional NOAEL or NOEC values, which calls into question the adoption of a threshold approach when assessing ED risks.

For the time being, it is often appropriate to refer to the expert judgment when assessing the risks of these particular substances. The European Commission has planned for mid-2020 a "fitness check" to assess whether the current regulatory framework is adequate to protect human health and the environment by reducing overall exposure to the ED.

*Source : Agence Européenne des produits Chimiques (ECHA).*

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*Equitox is composed of 7 experts in toxicology, ecotoxicology and physio-chemistry. These experts share the will to practice their job within a responsive team, gathered around the same values of scientific and ethical quality, and guided by listening the customer service.*



## IMPLEMENTATION OF INTERVENTIONAL STUDIES

Agnès Lavoix - Manager for cosmetics projects

### What are RIPH studies?

**Framed by the Jardé Law**, these interventional studies are carried out through prospective research involving the follow-up of healthy patients or volunteers in order to develop biological or medical knowledge. They are of three orders:

- **so-called Category 1 interventional research** that involves an intervention not without risk to the participants and not justified by their usual care. This is most often research involving drugs but also on surgical procedures, medical devices or cell therapies.
- **risk and minimally constrained interventional research category 2** that involves minimal intervention or minimal action. Their exhaustive list is set by an order. Studies may focus on health products or drugs under their usual conditions of use if and only if they are not the subject of research.
- **category 3 searches** that are risk-free. It can be adherence to treatments, tolerance to a drug after it is put on the market, practices of one health center compared to another...

### Complementarity centers of expertise, support of the RIPH studies

**DERMATEC by CPPi** (Center of Partnership Projects - Initiatives) was born out of a desire to pool knowledge, skills, expertise and initiatives. CPP initiatives thus give all the tools to its expert poles, to carry out their **monocentric and multi-center projects, interventional, non-interventional, mixed, in hospital**, outpatient and home. One of the major strengths of this initiative center is to rely on the **regulatory support** of the **CRO Partners** platform for the conduct of **RIPH** interventional clinical studies and the 20 years of experience of the association **LyREC** (Lyon Research Clinique), specializing in the design and execution of industrial and academic clinical studies. CPPi now **has two internal clinical investigation centers** to meet client needs. The first is located in Tassin-la-Demi-Lune for perfect synergy with the Centre Laser Médical Ouest (CLMO). PIC, the second center, is located in the Centre Hospitalier Lyon Sud (CHLS), partner of allergology, clinical immunology and rheumatology services through LyREC which hold the Regional Health Agency authorization as a research site for Research Involving the Human Person (RIPH) Category 1.

**CPPi** incorporates two other centers of expertise to carry out interventional studies. It includes **MCP** (Medical Creative Partners), which offers Human Factors tests for the **management of the risks of Medical Devices**; Food and Drugs Administration (FDA) tests. **HUMÂNAN** proposes **to evaluate the effectiveness of support care in the management of severe chronic conditions** such as cancers. In synergy with DERMATEC, it is now possible to evaluate cosmetic support and integrative/global cosmetic care in the context of intervention studies. **DERMATEC** is an expert in interventional clinical studies and brings together actors with **over 20 years of experience**. It can provide advice, writing, submission and management adapted to the simplest tests (e.g. dermal exploration without products) to the most complex, medical CE marking, in accordance with the new european medical devices regulation.

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**DERMATEC** has a solid foundation of skills and knowledge acquired over the last 20 years to conduct RIPH studies (mainly level 1), via **LyREC** in particular. This association of law 1901 led by David Bottiglioli is located in the heart of the Lyon Sud hospital. This implementation allows the use of all hospital technical platforms: biology laboratories, imaging services, pharmacy for indoor use