The Toxicologist in Cosmetics...

Ensuring Safety for All!

THE EXPERTS



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The use of chemical substances is a practice that predates modern advances in chemistry, dating back to periods preceding the first alchemists. In contemporary times, the exploration and use of chemicals in the cosmetic industry have seen exponential growth, marked by significant advancements in understanding their composition and applications. Discoveries in chemistry have been at the core of numerous technological, medical, environmental, and industrial advancements. Over the past two centuries, countries such as France have played a major role in chemical research, paving the way for the synthesis of high-performance chemicals at more affordable costs and offering an increasingly diverse range of choices. This era was characterized by the rise of the chemical industry, which had a major impact on daily life, from pharmaceuticals to energy production, agriculture, and many other fields. This is also true for the use of cosmetics, with the scientific study of their composition, including the chemicals they contain.

To ensure consumer safety amid this increasing exposure to chemical substances, numerous regulations have been implemented. This is the case with the European regulation on chemicals "REACH" (Registration, Evaluation, and Authorization of Chemicals), which, as stated in its first article, *"aims to ensure a high level of protection of human health and the environment [...] for the assessment of hazards associated with substances [...]"*, including those used in cosmetics. REACH thus imposes obligations on manufacturers and importers of chemicals concerning the registration, evaluation, and authorization of chemical substances, thereby contributing to strengthening chemical safety.[1]

Article 10 of the European Cosmetic Regulation states that: *"Before placing a cosmetic product on the market, the responsible person shall ensure, in order to demonstrate that the product complies with Article 3, that its safety is assessed based on appropriate information and that a cosmetic product safety report is drawn up in accordance with Annex I..."* Additionally, Article 3 of the European Cosmetic Regulation stipulates that *"a cosmetic product made available on the market is safe for human health when used under normal or reasonably foreseeable conditions of use,..."*[2] However, the marketing of a cosmetic product does not require prior authorization or CE marking but must meet certain regulatory requirements, particularly that of being non-harmful to consumer health.[3]

Risk assessment by the toxicologist is multifactorial. From exposure to hazard, the elements characterizing risk are numerous. The assessor must continuously analyze risk based ▶▶▶

▶▶▶ on the environmental context, potential material transfer, concentrations involved, the exposed area(s), and, of course, the affected population. Combined with risk factors, investigative tools fortunately play a key role. The evolution of knowledge through R&D and the advancement of techniques used in toxicology encourage the expert to continuously question their findings, maintain the necessary humility in their expertise, and approach each case individually.[4] Moreover, in the context of a toxicological dossier for the marketing of a substance, finished product, or packaging, the expert must be clear and precise in their conclusions, which will lead to the authorization or rejection of the product in question based on numerous parameters to be considered.

In general, in toxicology, the study of harmful, undesirable, or toxic effects depends on several factors. In most cases, the responsible compounds either do not naturally exist in the body and are therefore described as xenobiotics or act at concentrations higher than physiological levels. The study of these effects is thus distinguished by the concept of threshold, which induces toxicity. Some compounds act only above a certain threshold, while others produce an effect immediately upon entering the body (threshold-free effect).

Other external factors, known as environmental factors, contribute to exposure assessment. The toxicologist studies the causes of exposure; these may be directly related to the usual use of a compound or product or, conversely, to unusual, accidental, or illicit use (misuse). The expert then evaluates the hazards and determines the associated risks.

Exposure is indeed the primary criterion, as it determines the approach and evaluation of the case. External exposure refers to the toxic action emanating from the environment (water, air, soil) or consumer products. The toxicant must first be released from a matrix, often a mixture of substances, and then dissolve. This release, through solvation, is influenced by the respective solubility of the toxicant in the surrounding substrates. The physicochemical parameters intrinsic to the substrate and the compound of interest will be crucial in evaluating permeability and transmembrane passage. Subsequently, external exposure is followed by the study of toxicokinetics, namely the absorption, distribution, metabolism, and elimination of the toxicant in the body.



These studies are influenced by the presence or absence of physicochemical or microbiological interactions between the xenobiotic and its environment. The toxicologist also adapts them to the different possible routes of exposure (oral, dermal, pulmonary...) while considering another variability criterion: intra- and inter-individual polymorphism. The evaluation of a compound's toxicity will therefore depend on human factors such as age, sex, genetic profile across populations, and specific physiological states such as pregnancy or lactation, or known pathological conditions.

For most toxicants, it is accepted that hazard corresponds to the presence of a dangerous substance in a well-defined exposure situation. The measured effects depend on the duration of action and the concentrations involved. Risk analysis results from hazard through exposure. It expresses the probability per unit of time, based on exposure and toxicant absorption data, that harmful effects will occur. Thus, depending on the duration of toxic exposure, the expert evaluates acute toxicity (a single exposure dose) or chronic toxicity (multiple doses over time). Numerous specific tests serve to characterize these phenomena. In general, toxicological studies assess carcinogenicity, mutagenicity, reproductive toxicity, local toxicity

(irritation, sensitization, cytotoxicity, phototoxicity...) or systemic toxicity (toxicokinetics-toxicodynamics studies, general behavioral observations, LD50 studies, developmental studies, or target organ toxicity: hepatotoxicity, immunotoxicity, cardiotoxicity, nephrotoxicity, neurotoxicity...). Naturally, depending on the studied 'matrix' and its regulatory context, certain tests are no longer permitted (such as in Cosmetics, since animal testing was banned in 2013).

It is worth recalling that some mainstream media or the emergence of certain new applications on smartphones or tablets, or even some pre-programmed software, present not the risk, but the hazard. Presenting hazard to the general public without contextualizing exposure would be akin to citing the danger of a tiger facing someone without mentioning that it is actually locked in a secured and verified cage, thus making exposure and risk null.

Who spoke of zero risk? For the toxicologist, and if they effectively convey their science to their professional and personal circles, zero risk does not exist. It may tend towards the infinitely low but never zero, as everything is a matter of dose and exposure scenarios. As Paracelsus reminded us: *"Nothing is poison, everything is poison, it is the dose that makes the poison."*

The toxicologist is therefore responsible for studying a compound's (or associations) toxicity on a target organism. They can determine a toxicological profile or general risk only if all previously described factors are considered. Exposure and hazard define the risk, which must be determined within a well-defined and described human context, often with exposure thresholds extrapolated from in vitro, in vivo, or clinical study results.

The toxicologist often has their own databases, allowing them to manage and update their scientific and regulatory data.[5]

To complete their evaluation, the toxicologist assesses the safety of a so-called complex mixture (or finished product) by evaluating three major intersecting and complementary domains:

a) Stability and physicochemical quality in terms of the purity of each substance and the finished product, as well as migration tests related to content/container interactions.
b) Microbiology, which includes the quality of the product in terms of bacterial, yeast, and fungal load, as well as the ability of a formula to "resist" induced contamination.
c) Tolerance tests.

Thus, the toxicologist serves everyone: Consumers or end-users, by ensuring a sufficient level of safety for the use of their products.

Industry professionals, by assisting them in producing within the framework of good manufacturing practices and providing necessary recommendations regarding labeling for product safety and clarity of use.

Official authorities, by ensuring compliance and relaying the enforcement of rules and regulations applicable to all market participants.[6]

In addition, with the increasing concern for environmental sustainability, the toxicologist also evaluates the potential environmental impact of cosmetic products. This includes assessing ecotoxicity, ensuring that products and their ingredients do not harm ecosystems or biodiversity when they enter the environment. This step is becoming essential in the formulation of cosmetics for both human and environmental health.[7] ●

References

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