



# Integrated Approaches to Testing and Assessment (IATA) for Safety of Cosmetics and Personal Care Products

# 10

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## Abstract

Cosmetics and personal care products induce skin sensitization, and allergies are very common skin-related issues in people worldwide. Therefore, dermal safety assessment is a mandatory requirement before marketing these products. After the ban on animal testing for cosmetics, the safety assessment of these products is now very challenging. Integrated approaches to testing and assessment are the best option and can be used for the prediction of the toxicity or safety of chemicals based on the integration of multiple pieces of information generated via non-testing and testing methods for regulatory purposes. Moreover, along with traditional tools (in vivo and in vitro), IATA is widely including high-throughput screening, and computational approaches as new approach methods (NAM) for data generation, interpretation, and integration. Identifying the AOP for skin allergy also aids in the development of IATA for regulatory

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decision-making. This chapter describes the role of IATA in the safety and toxicity prediction of cosmetics and personal care products.

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**Keywords**

IATA · In chemico · New approach methods and adverse outcome pathway

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## 10.1 Introduction

### 10.1.1 Cosmetics and Personal Care Products

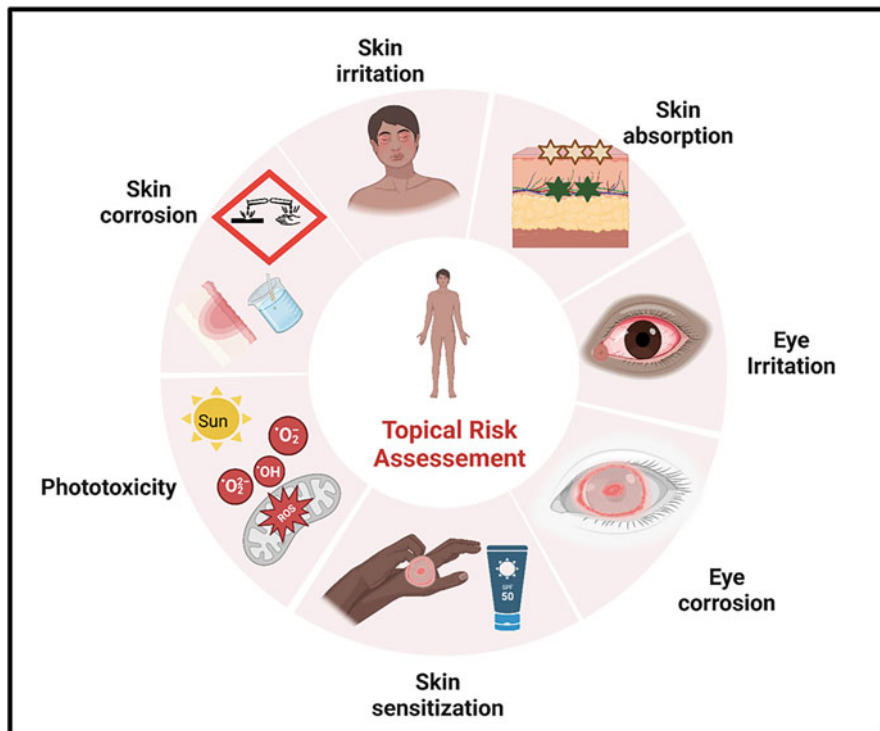
Personal care products and cosmetics use are very common everywhere in the globe. It has a long list of chemicals such as soaps, hair dyes, emulsifiers, fragrances, ultraviolet absorbers, and preservatives (Hamilton and de Gannes 2011). Cosmetics and personal care products contain various ingredients such as colorants, fragrances, and preservatives to make them attractive and safe for consumers. However, these ingredients are a major cause of skin sensitization and skin allergy (Tan et al. 2014). Generally, dermal and ocular safety testing of cosmetics and personal care products is sufficient for commercial use. Therefore, before getting regulatory approval skin irritation, corrosion, phototoxicity, skin sensitization, eye irritation, corrosion, and skin absorption testing are compulsory (Fig. 10.1). If any chemical has deep penetration and is reaching systemic circulation, then systemic toxicity evaluation is important to avoid any organ-specific toxicity.

Carcinogenicity, genotoxicity, developmental toxicity, reproductive toxicity, and endocrine disruption testing are necessary to prevent systemic toxicity of cosmetics and personal care products and their constituents (Fig. 10.2).

The animal-based study was the gold standard for skin sensitization assessment of cosmetics and personal care products. However, after the ban on animal use for cosmetics and personal care product safety in 2013 by European Union and in 2014 by the Indian government, it was very difficult to assess the safety of these products. To overcome this, different alternative models were developed and approved by OECD to assess the skin sensitization/skin allergy of these products. The individual method was not sufficient to draw any regulatory decision. Therefore, integrated approaches are most appropriate in testing and safety assessment of cosmetics and personal care products.

#### 10.1.1.1 IATA

IATA is used to combine various existing statistics and properties including physical and chemical properties, non-testing (QSAR), and testing methods (in vivo and in vitro and in chemico) based on information for regulatory decision (Browne et al. 2017, 2020; Sakuratani et al. 2018). Chemical regulation authorities are confronted due to intensive testing approaches including expensive, utilization of a large number of chemicals, time-consuming, and use of live animals to evaluate all chemicals in the development of personal healthcare products (Tollefsen et al.

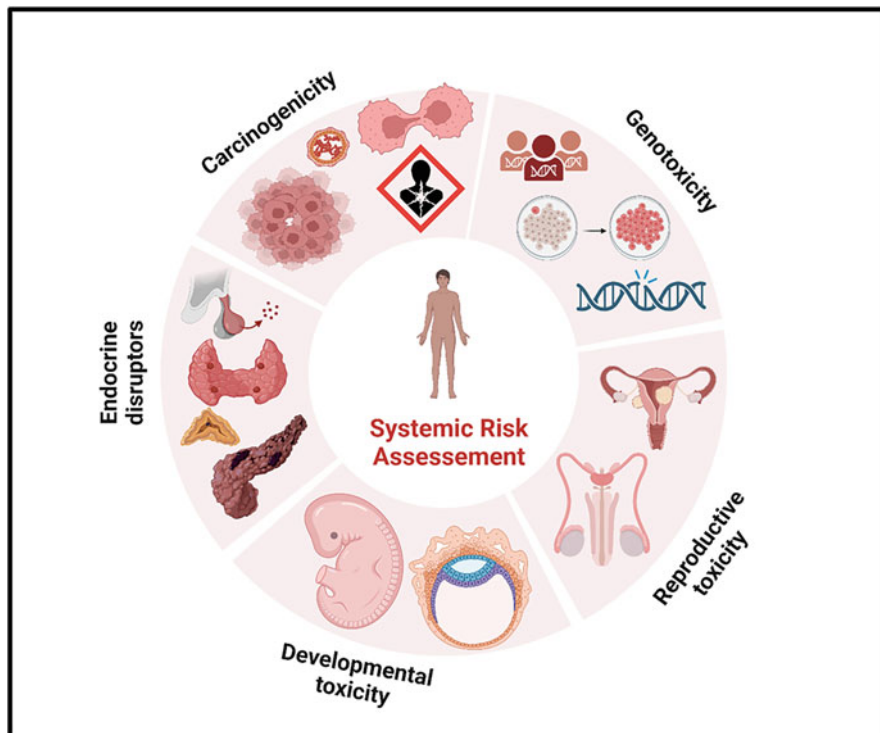


**Fig. 10.1** Cutaneous and ocular risk assessment

2014). The need for robust and effective strategies for the evaluation of threats was imposed by the chemicals in humans via different routes including dermal, inhalation, and systemic exposure (Abd et al. 2016; Wills et al. 2016; Shah et al. 2018; Conway et al. 2020). Though the number of methods are existing for safety assessment, the single method for the prediction of toxicity/safety of chemical is not sufficient for regulatory decision (Pfuhrer et al. 2020, 2021; Tollefsen et al. 2014). Therefore, considering the need for a combined approach via the use of IATA is more reliable for the prediction of toxicity of any chemical. Additionally, to evaluate proper risk assessment, there are progressive approaches to substituting methods for animal use in toxicology and refining to incorporate new approach method (NAM) (Brannen et al. 2016; OECD 2016a, b, 2017). Applying NAM as a solution to toxicological endpoints is included in IATA, e.g., defined approaches for testing and assessment and integrated testing strategies (Casati 2018; Eskes 2019). With acceleration, the artificial intelligence is imparting to incorporate and mix various streams (Fig. 10.3).

#### 10.1.1.2 Non-Testing Methods

In silico approaches (QSAR, read across) are used to assess the safety/toxicity of cosmetics and personal care products.



**Fig. 10.2** Systemic risk assessment

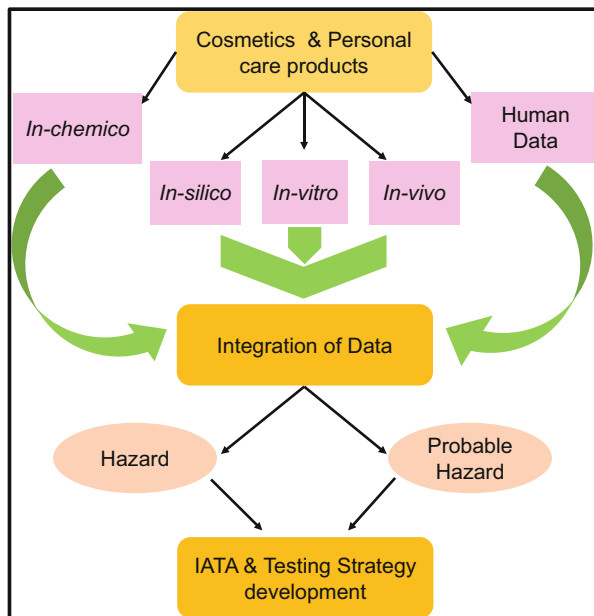
### 10.1.1.3 Testing Methods

There are a variety of testing methods that can serve as important components of an IATA, including *in vivo*, *in vitro*, and *in chemo* experiments. IATA needs to move away from relying on *in vivo*/animal-based data and test components such as toxicogenomic and high-content/high-throughput screening (HC/HT) to address one or more adverse outcomes.

## 10.2 New Approach Methods

Various alternative methods such as omics technology (genomics, proteomics, and metabolomics), *in silico* models, and other advanced biotechnological and computational models can be considered as new approach methods. These new approach methods support the IATA in the exact prediction of the toxicity of chemicals.

**Fig. 10.3** Integrated risk assessment approaches



### 10.2.1 IATA in Skin Sensitization

Skin sensitization has been a regulatory endpoint, needed in various chemical sectors like industrial chemicals, cosmetics, and pesticides, being the center of concerted efforts for replacing animal testing over the years (Henning et al. 2009; Casati 2018 ; de Ávila et al. 2019; Kandarova and Hayden 2021). Various guinea-pig assay was migrated to reduced and distinguished LLNA, to demonstrate the dominance of in vitro and in silico methods (Basketter 2016). EURL organization for alternatives to animal models for testing has implemented strategies for skin sensitization. It has been of key importance in the assurance of the translation of the customary non-animal methods for skin sensitization into the internationally approved test guidelines (European Parliament and the Council of the European Union 2009; Rauscher et al. 2012; Chapman 2015). Consequently, from 2015 to 2017, in vitro and in chemico models and mechanisms are approved by the OECD under the first three crucial events of adverse outcome pathway for skin sensitization (Kandárová et al. 2006; Hecker et al. 2011; OECD 2022a, b). The current test methods cannot fulfill all regulatory requirements regarding skin sensitization potential and chemical potency in comparison with those that are provided by regulatory animal tests. LLNA (OECD TG 429) (OECD 2010a, b) or non-radioactive variants, like LLNA: BrdU-ELISA (OECD TG 442B) (OECD 2018), and LLNA: DA (OECD TG 442A). Considering this reason, data from the direct peptide reactivity assay, the ARE-Nrf2 luciferase assay, and the three protocols of dendritic cell activation (h-CLAT, interleukin-8, and Luc assay) must be considered for IATA. Moreover, combining other relevant information like physical-chemical properties,

facts for other important measures of skin sensitization adverse outcome pathways along with non-testing methods, which includes the read across from chemical analogs (OECD 2022a, b).

In recent years, several defined approaches integrating information and facts from many non-animal methods and other information are developed for skin sensitization hazard assessment, or/and potency categorization. EURL ECVAM gave a project proposal to OECD to develop guidance for harmonized reporting of the defined approaches facilitating their application and assessment in IATA for regulatory purposes, on behalf of the European Commission (Hartung et al. 2004, 2013; Kinsner-Ovaskainen et al. 2009). OECD task force on hazard assessment reported in OECD guidance documents (GD-255 and GD 256, OECD 2016a, b, c) describes defined approaches. This provides a consistent format for describing a defined approach for regulatory purpose (OECD 1997, 2015, 2016a, b).

### 10.2.2 IATA Methodologies

The discrepancy between IATA and the defined approach is a key concept from the OECD. IATA is known as approaches, which are used in the prediction of risk or chemical hazard assessment by integrating the existing information and new information generated by the testing strategies. IATA is an iterative approach for answering a question in a defined regulatory context. The total evaluation process within the IATA mainly depends on weight of evidence, essentially implying an expert judgment for evaluating different pieces of information (OECD 2019, 2020, 2021a, b).

The intended design of IATA renders adaptability for particular regional requirements or regulatory statutes. The defined approaches can be considered a comparable alternative for the *in vivo* data if a similar kind of information is considered within the decision context of the IATA. As per the EURL ECVAM workshop, collaborated with ICATM, it was aimed to enrich the regulatory considered and adopted individual test methods, with the acceptance of defined approaches (although recognized for requirement differences in several sectors and jurisdictions) as an alternative for non-animal methodologies to skin sensitization evaluation by the chemicals used in several areas (Blaauboer et al. 1999; Clothier et al. 1999; Spielmann et al. 2006; Daniel et al. 2018; Strickland et al. 2019). This followed a consensus to maximize regulatory acceptance of data in defined approaches, for which international harmonization and standardization were necessary. This could be accomplished by developing an evaluation outline that allows an independent assessment of the defined approaches, wherein the reproducibility, relevance/predictive capacity, providing sufficient and equivalent information, mechanistically and biologically relevant, transparently described comparable to the reference animal test. Moreover, independent assessment by third parties and conflicting results and uncertainty *in vivo* data and defined approaches should also be considered, with predictions in the context of IATA (OECD 2016a, b).

### 10.3 International Cooperation in the Development of Alternative Test Methods

ICATM was promoting the use of DAs in the field of skin sensitization, and a framework was (Hoffmann 2015; Dumont et al. 2016; Roberts et al. 2016) defined based on the aforementioned criteria. Recent publications that evaluated the variability in the recorded animal datasets could be added to a meta-analysis (Kleinstreuer et al. 2018). Furthermore, the human data will be assembled and LLNA enactment against human data will be matched based on chemical data and variables (Basketter et al. 2014; Bell et al. 2017). The decision of definitions and a clear understanding of defined approaches and IATA were made to create information that brought all who were involved in the related area to a similar understanding. Many stakeholders were identified as important for progress in the field of DAs for skin sensitization assessment. Several scientists from research institutions, industry, and NGOs experienced with *in vitro* and *in silico* methods were also noted to form the building blocks of DAs. The US EPA, and other partners, has initiated many data-sharing pilots for encouraging industry stakeholders and other testing laboratories for easy access to non-animal methods and *in vitro* methods, respectively, for the areas related to toxicology and the broader scientific community, by the availability of such internal resources (<https://www.aahp-abhp.org/node/1224>). CAAT commissioned report suggests utilizing the existing data and monitoring future testing in toxicology by integrated testing strategies (Jaworska and Hoffmann 2010). OECD workshop and previous work (Jaworska et al. 2010) outlined the conceptual requirements as transparent, consistent, and hypothesis-driven (Jaworska et al. 2010).

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### 10.4 Conclusion

IATA has the ability to reduce the usage of animal testing for safety studies of cosmetics and personal care products by utilizing testing and non-testing methods with integration with new approach methods.

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